

Converting Labeling for Older Drugs from the Old Format to the PLR Format

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Disclaimer



- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.

Overview



- Physician Labeling Rule (PLR)
- Voluntary PLR conversions
- Converting labeling approved in old format (non-PLR) to PLR format for older drugs
 - General principles
 - Selected sections from the full prescribing information (FPI)
 - Developing other parts of the prescribing information (PI)

Definitions for this presentation:

- “PLR format” refers to labeling that meets the requirements at 21 CFR 201.56(d) and 201.57.
- “Old format” (i.e., non-PLR format) refers to labeling that meets the requirements at §§ 201.56(e) and 201.80.
- “Drug” refers to both human prescription drug and biological products.
- “Older drug” refers to those drugs not subject to the implementation schedule described at § 201.56(c).

General Principles Pertaining to All Labeling¹



Labeling must:

- Contain a summary of the essential scientific information needed for the safe and effective use of the drug
- Be informative and accurate and neither promotional in tone nor false or misleading in any particular
- Be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading

Labeling is NOT static

¹ §§ 201.56(a)(1) and (2)

Physician Labeling Rule (PLR) (1 of 2)



- Final rule, commonly referred to as the *Physician Labeling Rule* (PLR), published on January 24, 2006¹
- PLR regulations: 21 CFR 201.56(b), (c), and (d), and 201.57
- Revised content and format requirements of labeling for human prescription drugs

¹ See final rule (PLR) “Requirements on Content and Format of Labeling For Human Prescription Drug and Biological Products” 71 FR 3922 (January 24, 2006)

Physician Labeling Rule (PLR) (2 of 2)



- Applies to all NDAs/BLAs and efficacy supplements (ESs) approved on or after June 30, 2001
- NDAs/BLAs approved from 1938 to June 29, 2001 (without an ES approved on or after June 30, 2001) are not required to have labeling in PLR format – can voluntarily convert to PLR format at any time

Efforts to Increase Number of PLR Labeling (Voluntary PLR Conversions) (1 of 2)



FDA has publicly encouraged voluntary PLR conversions since the 2006 final rule¹

- PLR labeling *“will enhance safe and effective use of prescription drug products and reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information”*
- *“Manufacturers of older products that voluntarily elect to (PLR convert) may submit a supplement with proposed (PLR) labeling at any time”*

¹ See final rule (PLR) “Requirements on Content and Format of Labeling For Human Prescription Drug and Biological Products” 71 FR 3922 (January 24, 2006)

Efforts to Increase Number of PLR Labeling (Voluntary PLR Conversions) (2 of 2)



In 2013, FDA publicly stated – best interest of public health to increase number of PLR labeling¹

- *“PLR format represents a more useful and modern approach for communicating accurate and up-to-date information on the safe and effective use of drugs and makes prescription information more accessible for use with electronic prescribing tools and other electronic information resources”*
- *“FDA strongly encourages all applicants to voluntarily convert the labeling of their drug products to the PLR format, regardless of the date of approval”*

¹ See 78 FR 8446 (February 6, 2013)

Prioritizing Voluntary PLR Conversions of Older Drug Labeling



Consider voluntarily PLR converting labeling of older drugs with:

- **High drug use**
- Complex safety issues
- Reports of medication errors related to misunderstood or incorrectly applied labeling information



Implementing the PLR Content and Format Requirements Guidance



Guidance for Industry

Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2013
Labeling

Provides recommendations for:

- Developing new PLR labeling
- Developing Highlights
- Formatting labeling
- **Revising labeling already approved in old format to PLR**

PLR Conversion of Labeling for Older Drugs: General Principles



General PLR Conversion Principles

(1 of 3)



- Identify information in old format labeling that is pertinent to prescribing decisions
 - Omit clearly inapplicable or inappropriate information¹
- Distribute and reorganize information into appropriate PLR format labeling sections and subsections²
 - Place important clinical information pertinent to prescribing decisions in the section that most appropriately communicates the information
 - Other labeling sections may briefly describe or refer to the topic, but not repeat the same level of detail
 - Order information within a section based on the content's importance and relative public health significance

¹ § 201.56(d)(4)

² [Implementing the PLR Content and Format Requirements](#) guidance

General PLR Conversion Principles

(2 of 3)



- Revise labeling to clarify text, eliminate redundancies, and update terminology^{1,2}
- Unapproved indications or uses or dosing regimens must not be implied or suggested in labeling³
- Remove unsubstantiated claims and remove or revise outdated information^{1,2,4}

¹ [Implementing the PLR Content and Format Requirements](#) guidance

² § 201.56(a)

³ §§ 201.57(c)(2)(iv), (c)(2)(v), and (c)(3)(ii)

⁴ 21 CFR 314.70(c)(6)(iii)(D) and 21 CFR 601.12(f)(2)(i)(D)

General PLR Conversion Principles

(3 of 3)



- Generally, no new data analyses of the information in the old format are required if the labeling is truthful and accurate¹
- Major labeling updates may not be appropriate for a PLR conversion labeling supplement (e.g., adding a new dosing regimen, revising indication statement(s) in a manner that expands the population in whom the drug is indicated)^{1,2}

¹ [Implementing the PLR Content and Format Requirements](#) guidance

² [Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees](#) guidance

Selected Full Prescribing Information (FPI) Sections

In the slides that follow:

- The labeling examples are fictitious. Given space constraints and aim of emphasizing specific issues, the examples may not include all regulatory/statutory requirements or guidance recommendations for each section/subsection.
- “DRUG-X” represents the proprietary name and “drugoxide” represents the active moiety.

Focus of Discussion

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 DRUG ABUSE AND DEPENDENCE
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

INDICATIONS AND USAGE (I&U) Section



- Update the indication statement(s) to reflect current terminology and ensure that the statement(s) is:^{1,2}
 - Clinically relevant
 - Scientifically valid
 - Understandable to health care practitioners
- Delete generalized discussions or move information that is not appropriate for the INDICATIONS AND USAGE section to other more appropriate sections of the labeling^{3,4}

¹ § 201.56(a)(2)

² [Implementing the PLR Content and Format Requirements](#) guidance

³ § 201.57(c)(15)

⁴ [Clinical Studies Section of Labeling](#) guidance

Old Format Text

INDICATIONS AND USAGE

DRUG-X is indicated for the relief of symptoms in adults with acute and recurrent **diabetic gastric stasis**.

The **effectiveness** of DRUG-X was **established in two 12-week clinical trials** in adults with a diagnosis of diabetic gastric stasis.

The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) **responded to DRUG-X within different time intervals** (see CLINICAL STUDIES).

I&U Section – Example

Information not appropriate for I&U section

Old Format Text

INDICATIONS AND USAGE

DRUG-X is indicated for the relief of symptoms in adults with acute and recurrent diabetic gastric stasis.

The effectiveness of DRUG-X was established in two 12-week clinical trials in adults with a diagnosis of diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g., nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) responded to DRUG-X within different time intervals (see CLINICAL STUDIES).

Revised/Improved with PLR Conversion

1 INDICATIONS AND USAGE

DRUG-X is indicated for the relief of symptoms in adults with acute and recurrent **diabetic gastroparesis**.

Updated terminology

DOSAGE AND ADMINISTRATION

(D&A) Section (1 of 2)



Ensure information is clear and accessible:^{1,2}

- Develop subsections to organize the information
- Create tables, flowcharts, or diagrams for complex dosage or administration schemes

¹ [Implementing the PLR Content and Format Requirements](#) guidance

² [Dosage and Administration Section of Labeling](#) guidance

D&A Section (2 of 2)

DOSAGE AND ADMINISTRATION Section

Old Format Regulation (§ 201.80(j))

This section of the labeling shall state the recommended usual dose, the usual dosage range...

PLR Format Regulation (§ 201.57(c)(3)(i))

This section must state the recommended dose, and as appropriate:
(A) The dosage range...



- State the *recommended* dosage (as opposed to the *usual* dosage)¹
- Consider using active voice (i.e., command language)

¹ § 201.57(c)(3)(i)

D&A Section – Example



Old Format Text

DOSAGE AND ADMINISTRATION

The **usual dosage** of DRUG-X is 20 mg orally once daily.

In patients with mild hepatic impairment (Child-Pugh Class A), the dosage of DRUG-X **should be decreased by 25%**. In patients with moderate hepatic impairment (Child-Pugh Class B), the dosage of DRUG-X **should be halved**. In patients with severe hepatic impairment (Child-Pugh Class C), the dosage of DRUG-X **should be decreased by 75%**.

In patients who develop diarrhea (3 or more loose bowel movements daily) on DRUG-X, the dosage **should be reduced** to 10 mg once daily. If diarrhea persists greater than 7 days after dosage reduction, DRUG-X **should be discontinued**.

D&A Section – Example



Old Format Text

DOSAGE AND ADMINISTRATION

The usual dosage of DRUG-X is 20 mg orally once daily.

In patients with mild hepatic impairment (Child-Pugh Class A), the dosage of DRUG-X should be decreased by 25%. In patients with moderate hepatic impairment (Child-Pugh Class B), the dosage of DRUG-X should be halved. In patients with severe hepatic impairment (Child-Pugh Class C), the dosage of DRUG-X should be decreased by 75%.

In patients who develop diarrhea (3 or more loose bowel movements daily) on DRUG-X, the dosage should be reduced to 10 mg once daily. If diarrhea persists greater than 7 days after dosage reduction, DRUG-X should be discontinued.

Revised/Improved with PLR Conversion

2 DOSAGE AND ADMINISTRATION

Three subsections developed to organize information; subsection titles identify the content

2.1 Recommended Dosage

The recommended dosage of DRUG-X is 20 mg orally once daily.

Active voice

2.2 Dosage Modifications Because of Diarrhea

In patients who develop diarrhea (3 or more loose bowel movements daily) on DRUG-X, reduce the dosage to 10 mg once daily. If diarrhea persists greater than 7 days after dosage reduction, discontinue DRUG-X [see *Warnings and Precautions (5.3)*].

2.3 Dosage Modifications in Patients with Hepatic Impairment

Table 1 provides recommended dosage modifications in patients with hepatic impairment [see *Use in Specific Populations (8.6)*].

Table 1. Dosage Modifications of DRUG-X in Patients with Hepatic Impairment

Degree of Hepatic Impairment	Recommended Dosage
Mild (Child-Pugh Class A)	15 mg once daily
Moderate (Child-Pugh Class B)	10 mg once daily
Severe (Child-Pugh Class C)	5 mg once daily

• Table to present dosage modification scheme
• Actual dosage in mg rather than “halve” or “decrease by 50%”

CONTRAINDICATIONS Section (1 of 2)



Include only known contraindications^{1,2,3}

- Remove theoretical possibilities

CONTRAINDICATIONS Section	
Old Format Regulation (§ 201.80(d))	PLR Format Regulation (§ 201.57(c)(5))
These situations include...continued use of the drug in the face of an unacceptably hazardous adverse reaction.	Those situations include use of the drug in patients...for whom no potential benefit makes the risk acceptable.



- Reclassify risk if appropriate – if certain clinical situations are listed in the CONTRAINDICATIONS section and the drug can be used safely in practice in these situations, then move this information to an appropriate section (e.g., WARNINGS AND PRECAUTIONS)

¹ § 201.57(c)(5)

² [Implementing the PLR Content and Format Requirements](#) guidance

³ [Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling](#) guidance

CONTRAINDICATIONS Section (2 of 2)

As appropriate,* ensure each contraindication includes a:^{1,2}

- Brief description of the contraindicated situation
- Description of the type and nature of reaction(s)
- Cross-reference to a more detailed discussion elsewhere in the PI

* If description of the adverse reaction(s) is lengthy or if there are many contraindications, could consider including the description of the contraindicated use in another section (e.g., WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS), and only including a cross-reference in the CONTRAINDICATIONS section.

¹ [Implementing the PLR Content and Format Requirements](#) guidance

² [Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling](#) guidance

Old Format Text

CONTRAINDICATIONS

DRUG-X is contraindicated in patients who have demonstrated a previous hypersensitivity to it. **Continued use** of DRUG-X is contraindicated in patients with severely depressed bone marrow function.

WARNINGS

Depression of Bone Marrow Function

DRUG-X can severely depress bone marrow function. Neutropenia is the major dose-limiting toxicity with DRUG-X...

PRECAUTIONS

Laboratory Tests

Complete blood counts should be monitored prior to each dose of DRUG-X...

CONTRAINDICATIONS Section – Example

Old Format Text

CONTRAINDICATIONS

DRUG-X is contraindicated in patients who have demonstrated a previous hypersensitivity to it. Continued use of DRUG-X is contraindicated in patients with severely depressed bone marrow function.

WARNINGS

Depression of Bone Marrow Function

DRUG-X can severely depress bone marrow function. Neutropenia is the major dose-limiting toxicity with DRUG-X...

PRECAUTIONS

Laboratory Tests

Complete blood counts should be monitored prior to each dose of DRUG-X...

Revised/Improved with PLR Conversion

Included brief description and cross-reference

4 CONTRAINDICATIONS

DRUG-X is contraindicated in patients with prior serious hypersensitivity reactions to drugoxide or any other components of DRUG-X. Anaphylaxis has been reported [see *Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

Risk with severely depressed bone marrow function reclassified from a contraindication; known risk mitigation strategies added

5.1 Myelosuppression

DRUG-X can cause myelosuppression. Neutropenia is the major dose-limiting toxicity with DRUG-X...

Monitor complete blood counts prior to each dose of DRUG-X. Withhold DRUG-X treatment in patients with an absolute neutrophil count (ANC) <1,000 cells/mm³. Base dosage adjustment of DRUG-X on the ANC obtained on the day of treatment [see *Dosage and Administration (2.2)*].

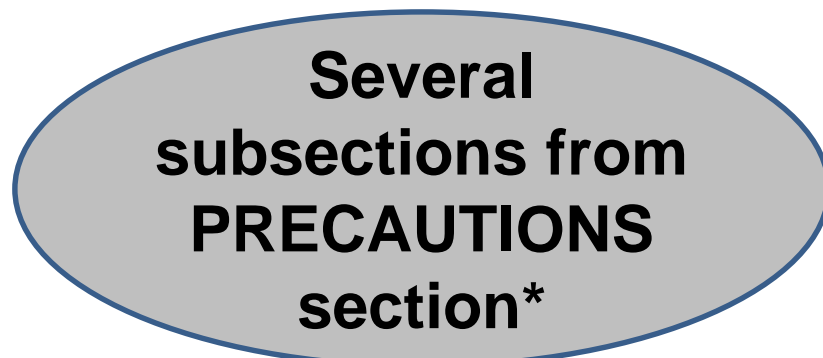
5.2 Serious Hypersensitivity Reactions Including Anaphylaxis

Serious hypersensitivity reactions including anaphylaxis have been reported with DRUG-X...

WARNINGS AND PRECAUTIONS (W&P) Section (1 of 2)



Old
Format



PLR Format



* Appropriate risk information from the *General*, *Laboratory Tests*, and *Drug/Laboratory Test Interactions* subsections of the old format PRECAUTIONS section is incorporated into the PLR format WARNINGS AND PRECAUTIONS section (see [Implementing the PLR Content and Format Requirements](#) guidance). Risk information from other sections of the old format PI may also contribute to the content of the WARNINGS AND PRECAUTIONS section.

W&P Section (2 of 2)



- Update or add information as appropriate (e.g., description of the risk or adverse reaction (AR), known risk factors for the AR, steps to prevent, mitigate, monitor for or manage the AR)¹
- Avoid subsection headings that are not useful for signaling the content of the subsection (e.g., *General* or *Miscellaneous*)^{2,3}
- Avoid ambiguous and uninformative statements (e.g., “Use with caution”) and terminology that implies a contraindication (e.g., “DRUG-X should not be used” or “Do not use”)^{2,3}

¹ § 201.57(c)(6)(i)

² [Implementing the PLR Content and Format Requirements](#) guidance

³ [Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling](#) guidance

W&P Section – Example



Old Format Text

CONTRAINDICATIONS

None known.

PRECAUTIONS

General

DRUG-X has been reported to cause severe constipation.

DRUG-X **should be used with caution** in patients with a history of constipation. DRUG-X **should not be used** in patients with severe constipation.

W&P Section – Example



Old Format Text

CONTRAINDICATIONS

None known.

PRECAUTIONS

General

DRUG-X has been reported to cause severe constipation. DRUG-X should be used with caution in patients with a history of constipation. DRUG-X should not be used in patients with severe constipation.

Revised/Improved with PLR Conversion

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

...

5.4 Severe Constipation

Severe constipation has occurred with DRUG-X administration. Institute a prophylactic bowel regimen to mitigate potential constipation, considering adequate dietary fiber intake, hydration, and use of stool softeners.

Discontinue DRUG-X if severe constipation occurs during treatment.

Rather than “should be used with caution,” provided known strategies to mitigate risk of the AR

Subsection title characterizes the risk

Revised to remove language that infers a contraindication

ADVERSE REACTIONS Section

(1 of 2)



- Dosing regimens not described in D&A section must not be implied or suggested in other sections of the labeling¹
- Review to ensure appropriate description of AR:^{2,3}
 - Rates expressed in percentages should ordinarily be rounded to the nearest integer
 - Remove redundancies and events not likely related to the drug (e.g., events for which placebo rate equals or exceeds rate for the drug)

¹ § 201.57(c)(3)(ii)

² § 201.57(c)(7)

³ [Adverse Reactions Section of Labeling](#) guidance

ADVERSE REACTIONS Section

(2 of 2)



- Where possible, ensure that AR that occurred in clinical studies are separated from those identified from domestic and foreign spontaneous reports¹
- If the source of AR cannot be determined, consider omitting numbered subsections (e.g., subsections 6.1 Clinical Trials Experience and 6.2 Postmarketing Experience) and including a list of AR preceded by a modified postmarketing caveat statement
- Include management strategies for clinically significant AR in WARNINGS AND PRECAUTIONS rather than ADVERSE REACTIONS section²

¹ § 201.57(c)(7)

² [Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling](#) guidance

ADVERSE REACTIONS Section – Example #1



Old Format Text

ADVERSE REACTIONS

...

Table 1. Adverse Reactions* in DRUG-X-Treated Patients with Condition-Y in Study 1

Adverse Reaction	DRUG-X 50 mg Once Daily (N=237)	DRUG-X 50 mg Twice Daily (N=313)	DRUG-X 100 mg Twice Daily (N=244)	Placebo (N=320)
Asthenia	14.8%	16.3%	13.5%	12.2%
Headache	8.4%	7.3%	10.2%	11.3%
Diarrhea	5.5%	5.1%	5.3%	1.3%

* Incidence at least 5% in the DRUG-X-treated group.

...

Adverse reactions with use of DRUG-X based on spontaneous reports include asthenia, hepatitis, and renal tubular impairment.

DOSAGE AND ADMINISTRATION

The recommended dosage of DRUG-X is 50 mg orally twice daily.

ADVERSE REACTIONS Section – Example #1



Old Format Text

ADVERSE REACTIONS

Table 1. Adverse Reactions* in DRUG-X-Treated Patients with Condition-Y in Study 1

Adverse Reaction	DRUG-X 50 mg Once Daily (N=237)	DRUG-X 50 mg Twice Daily (N=313)	DRUG-X 100 mg Twice Daily (N=244)	Placebo (N=320)
Asthenia	14.8%	16.3%	13.5%	12.2%
Headache	8.4%	7.3%	10.2%	11.3%
Diarrhea	5.5%	5.1%	5.3%	1.3%

* Incidence at least 5% in the DRUG-X-treated group.

Adverse reactions with use of DRUG-X based on spontaneous reports include asthenia, hepatitis, and renal tubular impairment.

DOSAGE AND ADMINISTRATION

The recommended dosage of DRUG-X is 50 mg orally twice daily.

Revised/Improved with PLR Conversion

2 DOSAGE AND ADMINISTRATION

The recommended dosage of DRUG-X is 50 mg orally twice daily.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Only approved dosage arm included

Table 1. Adverse Reactions* in DRUG-X-Treated Patients with Condition-Y in Study 1

Adverse Reaction	DRUG-X 50 mg Twice Daily (N=313)	Placebo (N=320)
Asthenia	16%	12%
Diarrhea	5%	1%

Percentages rounded; "Headache" removed from table

* Incidence at least 5% in the DRUG-X-treated group and greater than placebo

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of DRUG-X...

- Hepatitis
- Renal tubular impairment

AR from spontaneous reports in separate subsection; "Asthenia" removed

Old Format Text

ADVERSE REACTIONS

Infection has occurred with use of drugoxide. If infection occurs, discontinue the infusion, evaluate the patient, and institute appropriate therapeutic countermeasures. Other adverse reactions reported with use of drugoxide included hyperglycemia, phlebitis extending from the site of injection, and peripheral edema.

Did these adverse reactions occur in clinical studies or in another setting (e.g., spontaneous reports)?

ADVERSE REACTIONS Section – Example #2

Old Format Text

ADVERSE REACTIONS

Infection has occurred with use of drugoxide. If infection occurs, discontinue the infusion, evaluate the patient, and institute appropriate therapeutic countermeasures. Other adverse reactions reported with use of drugoxide included hyperglycemia, phlebitis extending from the site of injection, and peripheral edema.

Revised/Improved with PLR Conversion

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Infection [see *Warnings and Precautions* (5.1)]
- Hyperglycemia [see *Warnings and Precautions* (5.2)]

Cross-reference to W&P for management strategies

The following adverse reactions associated with the use of drugoxide were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Infection
- Hyperglycemia
- Phlebitis extending from the injection site
- Peripheral edema

Modified caveat statement because source of AR not clear

OVERDOSAGE Section (1 of 2)



- Ensure that information is accurate and up-to-date
 - Postmarketing experience with overdose may inform the content of this section¹
- Remove animal data when human data are available²
 - Regarding the LD₅₀ (median lethal dose):

OVERDOSAGE Section	
Old Format Regulation (§ 201.80(i))	PLR Format Regulation (§ 201.57(c)(11))
Specific information shall be provided about... (3) Oral LD ₅₀ of the drug in animals...	The following specific information must be provided... (iii) Oral LD₅₀ of the drug in animals...

¹ [Implementing the PLR Content and Format Requirements](#) guidance

² § 201.57(c)(11)

OVERDOSAGE Section (2 of 2)



- Remove unqualified recommendations for which data are lacking for the specific drug or drug class¹
- Avoid describing dosages exceeding the maximum recommended dosage for which signs and symptoms of overdose were not reported²
- Rather than enumerating patients with overdose from spontaneous reports (such enumeration can quickly become outdated), consider focusing on signs/symptoms and other clinically relevant information

¹ § 201.57(c)(11)

² § 201.57(c)(3)(ii)

OVERDOSAGE Section – Example #1



Old Format Text

OVERDOSAGE

Experience with DRUG-X **overdose in humans** is limited. Acute toxic encephalopathy, coma, and methemoglobinemia have been observed in isolated cases.

The **oral LD₅₀** of drugoxide is greater than 2 grams/kg in mice and rats.

Measures that may detoxify the gut include administration of activated charcoal and a cathartic.

For current information on the management of overdose, contact the National Poison Control Center.

OVERDOSAGE Section – Example #1

Old Format Text

OVERDOSAGE

Experience with DRUG-X overdose in humans is limited. Acute toxic encephalopathy, coma, and methemoglobinemia have been observed in isolated cases.

Remove animal data when human data available

The oral LD₅₀ of drugoxide is greater than 2 grams/kg in mice and rats.

Measures that may detoxify the gut include administration of activated charcoal and a cathartic.

Remove unqualified treatment recommendations for which data are lacking for the specific drug/drug class

For current information on the management of overdose, contact the National Poison Control Center.

Revised/Improved with PLR Conversion

10 OVERDOSAGE

Reported symptoms of overdose following ingestion of DRUG-X ranging from 1.5 to 3 grams (30 to 60 times the approved recommended dose) included acute toxic encephalopathy, coma, drowsiness, memory loss, and methemoglobinemia.

For current information on the management of overdose, contact the National Poison Control Center.

Updated information on overdose range and signs/symptoms

OVERDOSAGE Section – Example #2

Old Format Text

OVERDOSAGE

DRUG-X overdose has been reported in four subjects. Two subjects who received DRUG-X orally at a dosage of 60 mg daily over multiple days did not report any adverse outcomes. There have been two spontaneous reports of subjects who received a single oral dose of 80 mg. One subject reported abdominal pain, nausea, and diarrhea, and the other developed asthenia, orthostatic hypotension, and diarrhea.

DOSAGE AND ADMINISTRATION

The recommended oral dosage of DRUG-X is 20 mg once daily.

OVERDOSAGE Section – Example #2

Old Format Text

OVERDOSAGE

DRUG-X overdose has been reported in four subjects. Two subjects who received DRUG-X orally at a dosage of 60 mg daily over multiple days did not report any adverse outcomes. There have been two spontaneous reports of subjects who received a single oral dose of 80 mg. One subject reported abdominal pain, nausea, and diarrhea, and the other developed asthenia, orthostatic hypotension, and diarrhea.

DOSAGE AND ADMINISTRATION

The recommended oral dosage of DRUG-X is 20 mg once daily.

Remove information that implies safe use of unapproved dosages

Revised/Improved with PLR Conversion

2 DOSAGE AND ADMINISTRATION

The recommended oral dosage of DRUG-X is 20 mg once daily.

10 OVERDOSAGE

Following a single oral dose of 80 mg (4 times the approved recommended dosage) of DRUG-X, signs and symptoms of overdose included abdominal pain, nausea, diarrhea, asthenia, and orthostatic hypotension.

Focused on signs/symptoms of overdose rather than listing number of spontaneous reports of overdose

CLINICAL STUDIES Section

- Move clinical study information that appears in other sections of the old format labeling (e.g., CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE) to the CLINICAL STUDIES section^{1,2}
- Ensure that unapproved indications or uses and unapproved dosing regimens are not implied or suggested^{1,3}
- For older drugs that do not contain a CLINICAL STUDIES section in the old format PI, should generally not create a CLINICAL STUDIES section if efficacy data that supported approval are not readily available or do not provide useful information about safe and effective use of the drug⁴

¹ § 201.57(c)(15)

² [Clinical Studies Section of Labeling](#) guidance

³ §§ 201.57(c)(2)(iv), (c)(2)(v), and (c)(3)(ii)

⁴ [Implementing the PLR Content and Format Requirements](#) guidance

PATIENT COUNSELING INFORMATION Section



- Unless it is clearly inapplicable, create and develop this section even if the corresponding subsection in the old format PI (*Information for Patients*) does not exist^{1,2,3}
- If the old format PI includes the *Information for Patients* subsection, review content and determine what information to retain, add, or remove³

¹ § 201.57(c)(18)

² [Implementing the PLR Content and Format Requirements](#) guidance

³ [Patient Counseling Information Section of Labeling](#) guidance

Developing Other Parts of the PI



Once FPI Has Been Developed



- Develop Highlights
- Ensure that accurate cross-references to the appropriate sections or subsections are included throughout the labeling
- Develop Contents



Summary



- Voluntary PLR conversions are encouraged
- Consider prioritizing labeling of drugs with highest use or complex safety issues for voluntary PLR conversion
- PLR conversion involves more than moving information from an old format section/subsection to the corresponding PLR format section/subsection
- PLR conversion provides an opportunity to review all parts of the labeling to ensure the labeling is truthful and accurate

