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Labeling Considerations for Product Quality Information in the Prescribing Information

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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.
- Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the FDA.

Format of Proprietary Name in PI

- Proprietary name should appear in UPPER CASE letters in ≥ 3 places in PI[1]
  - Twice in Highlights Limitation Statement
  - Once in product title

- In other parts of PI, proprietary name can appear in other cases (e.g., UPPER CASE, Title Case)
  - Recommend consistency in use of letter case in other parts of PI (e.g., always UPPER CASE or always Title Case)

1 Implementing the PLR Content and Format Requirements guidance

Highlights of Prescribing Information (Highlights)

Highlights: Product Title[1]

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

[1] 21 CFR 201.57(a)(2)

Format of Product Title (PT)

- Must bold text in PT[1]
- Proprietary name is in UPPER-CASE and rest of PT is in lower case[2]
  - **MYDRUG (drugozide) capsules, for oral use**
- If there is no proprietary name, chemical proportion of nonproprietary name (or proper name) is in UPPER-CASE and rest of PT is in lower case (parentheses are omitted)[2]
  - **DRUGOZIDE capsules, for oral use**
- Comma precedes ROA[2] (if ROA not part of nonproprietary name)

ROA = route of administration

[1] 21 CFR 201.57(d)(5)

[2] Consider having all items in PT appear in lower case with some limited exceptions (e.g., proprietary name, controlled substance symbol, acronyms for radioisotopes)

Consider Avoiding Following in PT

- Additional descriptors (e.g., avoid film-coated)
- Methods of intravenous infusion (e.g., infusion)
- Abbreviations (e.g., IV for intravenous, HCl for hydrochloride)
- Drug's origin information[1]
- Slash marks when displaying name of fixed combination drug products
- Repetition of ROA if ROA precedes dosage form
  - DRUG (drugozide) topical solution~~, for topical use~~

[1] Consider avoiding including information about drug's origin (e.g., rDNA) unless it is required by regulation, it is part of the nonproprietary name, or it is clinically relevant (e.g., human)

Avoid Use of Following Terminology in PT

- "USP"
- "Powder" as a dosage form for injectable products requiring reconstitution
  - e.g., avoid "lyophilized powder", instead use "for injection"[1]
- "Solution" as a dosage form for injectable drug products[2]
- "Only" (e.g., for topical use only)

[1] USP General Chapter <1121> Nomenclature for additional information on the nomenclature of injectable drug products

Product Title Examples: Products With a Proprietary Name

CADUET (amlodipine besylate and atorvastatin calcium) tablets, for oral use

LEVITRA (vardenafil hydrochloride) tablets, for oral use

ZOMIG-ZMT (zolmitriptan) orally disintegrating tablets

FENTORA (fentanyl buccal tablets), CII

REVATIO (sildenafil) for oral suspension

OXYTROL (oxybutynin transdermal system)

ADASUVE (loxapine) inhalation powder, for oral inhalation use

SIMPONI (golimumab) injection, for subcutaneous use

BOTOX (onabotulinumtoxin A) for injection, for intramuscular, intradetrusor, or intradermal use

Product Title Examples: Products Without a Proprietary Name

CYCLOPHOSPHAMIDE tablets, for oral use

PHENYLEPHRINE HYDROCHLORIDE injection, for intravenous use

GLUCAGON for injection, for intravenous or intramuscular use

DOXORUBICIN HYDROCHLORIDE for injection, for intravenous use

DOXORUBICIN HYDROCHLORIDE injection, for intravenous use

Format of Elements in PT in Highlights vs. Carton/Container Labeling

Product information in product title and on carton/container labeling should be as consistent as possible, but acceptable differences

	Carton/Container Labeling	Product Title in Highlights of Prescribing Information
Format of proprietary name	Title Case	UPPER CASE
Number of lines	Many lines (e.g., dosage form and ROA can be presented beneath drug name)	Present on one line if space permits
Strength	Strength present	Strength generally should not appear
ROA	May include word "only"	Avoid word "only"
Methods of intravenous administration (e.g., intravenous infusion)	May appear	Avoid

Highlights: Dosage Forms and Strengths (DFS) Heading

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See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

Highlights: DFS Heading

- Include a concise summary:[1]
  - Dosage form(s) (e.g., tablets, capsules, injection)
  - Strength or potency of dosage form in metric system (e.g., 10 mg)
- Use bullets if a product has more than one dosage form[2]
- May include limited packaging information to facilitate prescribing (e.g., 15 and 30 gram tubes)[2]
- Multiple strengths should be listed on one line if possible[2]
- Should not include identifying characteristics of dosage forms (e.g., tablet color, shape, embossing)[2]

[1] 21 CFR 201.57(a)(8)

[2] Implementing the PLR Content and Format Requirements guidance

Highlights: DFS Heading - Scoring[1]

- If product meets guidelines and criteria for a scored tablet, state “functionally scored”
- If product does not meet guidelines and criteria for a scored tablet and was approved:
  - On or after March 2013 remove the term “scored”
  - Before March 2013 may retain the term “scored” unless there is a safety or efficacy issue with splitting the tablet

[1] Tablet Scoring – Nomenclature, Labeling, and Data for Evaluation guidance

Highlights: DFS Heading – Package Terms[1]

Appropriate labeling terms for describing containers for injectable drugs for parenteral administration (e.g., intravenous use)

	Characteristics
Single-dose	• For a single patient use as a single injection • Entire contents of container may not be a full dose (e.g., may need more than one container for full dose) • Some patients may not require entire contents of container (e.g., pediatric patients)
Multiple-dose[2]	• For multiple use (e.g., single patient or multiple patients) • Contains more than one dose of drug • Generally has a maximum volume of 30 mL • Cannot be used beyond 28 days after needle puncture (unless sufficient data allows longer use)
Single-patient use[2]	Used multiple times for a single patient

[1] Selection of Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient Use Containers guidance

[2] Multiple-dose must pass antimicrobial testing; single-patient use containers may require antimicrobial testing

Highlights: DFS Heading – Examples

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 5 mg (functionally-scored) (3)
- Orally disintegrating tablets: 2.5 mg and 5 mg (3)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 50 mg of drugoxide as a lyophilized powder in a single-dose vial for reconstitution (3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/2 mL (50 mg/mL) in single-patient use autoinjector (3)

Full Prescribing Information

Full Prescribing Information (FPI)

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

DOSAGE FORMS AND STRENGTHS Section (Section 3) of FPI

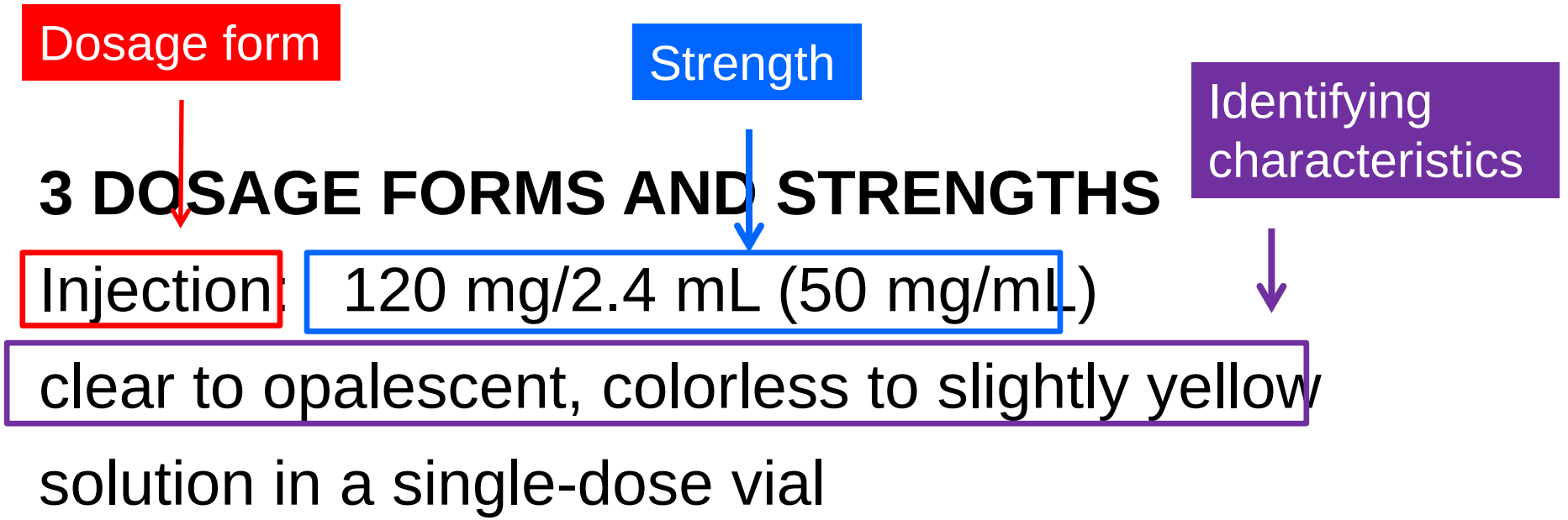
DFS Section of FPI

- Must include:[1]
  - Dosage form(s) (e.g., tablets, capsules, injection)
  - Strength or potency of dosage form in metric system (e.g., 10 mg)
  - Description of identifying characteristics of dosage forms:
    - Solid dosage forms: shape, color, coating, size, scoring, flavor, and imprinting
    - Parenteral dosage forms: color and other identifying characteristics
- Should include functionally scored or scored when appropriate[2]
- Include limited packaging information to facilitate prescribing (e.g., 15 and 30 gram tubes)

[1] 21 CFR 201.57(c)(4)

[2] Tablet Scoring – Nomenclature, Labeling, and Data for Evaluation guidance

Considerations for Order[1] of Required[2] Elements in DFS Section of FPI



[1] Consider order of elements for consistency across labeling
[2] 21 CFR 201.57(c)(4)

DFS Section of FPI

If appearance of a parenteral dosage form (e.g., injection, for injection) is visible to the healthcare provider consider including identifying characteristics:

- Information about color (e.g., colorless to slightly pale yellow solution), and
- Clarity (e.g., clear to slightly cloudy)

DFS Section of FPI: Packaging Information

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/2.4 mL (50 mg/mL)

clear to opalescent, colorless to slightly yellow solution in a single-dose vial

Although not required in this section, may include package term[1] and limited package information

Should include functionally scored when appropriate[2]

[1] Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use draft guidance

[2] Tablet Scoring – Nomenclature, Labeling, and Data for Evaluation guidance

DFS Section Examples

- For injection: 50 mg, 100 mg, or 200 mg of drugozide as a white lyophilized powder in single-dose vial for reconstitution
- Injection: 90 mg/0.75 mL clear solution in single-patient-use autoinjector
- Injection: 300 mg/3 mL (100 mg/mL) clear solution in multiple-dose vial
- Cream: 70 mg of lidocaine per gram (7%) and 70 mg of tetracaine per gram (7%) of white to off-white cream in 30 gram and 60 gram tubes
- Implant: 68 mg of etonogestrel, pre-loaded in needle of disposable applicator

Alternative Format for DFS Section: Multiple Strengths

3 DOSAGE FORMS AND STRENGTHS

REXULTI tablets are available in 6 strengths (see Table 2).

Table 2: REXULTI Tablet Strengths and Identifying Features

Tablet Strength	Tablet Color/Shape	Tablet Markings
0.25 mg	Light brown; Round; shallow convex; bevel-edged	"BRX" and "0.25"
0.5 mg	Light orange Round; shallow convex; bevel-edged	"BRX" and "0.5"
1 mg	Light yellow Round; shallow convex; bevel-edged	"BRX" and "1"
2 mg	Light green Round; shallow convex; bevel-edged	"BRX" and "2"
3 mg	Light purple Round; shallow convex; bevel-edged	"BRX" and "3"
4 mg	White Round; shallow convex; bevel-edged	"BRX" and "4"

FDA-approved PI for REXULTI (2/23/2017)

DESCRIPTION Section (Section 11) of FPI

DESCRIPTION Section of FPI Must Include:[1]

- Proprietary name
- Established name or proper name
- **Dosage form(s)**
- **Route(s) of administration**
- **Pharmacologic or therapeutic class**
- Qualitative and quantitative ingredients
- Statement product is sterile (if product is sterile)
- Chemical name and structural formula (for drug products)
- If radioactive, important nuclear physical characteristics
- Other important chemical or physical information (e.g., pH)

Sometimes missing from proposed labeling

[1] 21 CFR 201.57(c)(12)

Information that Generally Does Not Belong in DESCRIPTION Section

- "Drugoxide sublingual tablets are intended to be placed under the tongue where they will **dissolve in about two minutes to allow disintegration and absorption of drugoxide across the oral mucosa**"

- "DRUG contains drugoxide, an inhibitor of transporter X, **the transporter responsible for reabsorbing the majority of glucose filtered by the kidney**"

- "DRUG, **a therapy for Condition-Y**"

HOW SUPPLIED/STORAGE AND HANDLING Section

(Section 16) of FPI

HOW SUPPLIED/STORAGE AND HANDLING Section of FPI Must Include:[1]

- Dosage form(s)
- Strength or potency in metric system (e.g., 10 mg)
- Units in which dosage form is ordinarily available for prescribing by practitioners (e.g., bottles of 100)
- Description of identifying characteristics of the dosage forms
  - Solid dosage forms: shape, color, coating, size, scoring, flavor, and imprinting
  - Parenteral dosage forms: color and other identifying characteristics
- National Drug Code (NDC) number(s)

[1] 21 CFR 201.57(c)(17)

Storage Instructions for Supplied vs. Reconstituted/Diluted Products

Supplied Product

Special handling and storage conditions must be in HOW SUPPLIED/STORAGE AND HANDLING section[1]

- Protect from light, do not shake, do not freeze, refrigerate

Reconstituted or Diluted Products

- Detailed description of storage conditions in D&A section[2]
- May also summarize storage conditions in HOW SUPPLIED/STORAGE AND HANDLING with a cross-reference to D&A section
  - "Store reconstituted solutions of DRUG-X at Y temperature *[see Dosage and Administration (2.x)]."*

D&A = DOSAGE AND ADMINISTRATION

[1] 21 CFR 201.57(c)(17)

[2] 21 CFR 201.57(c)(3) and Dosage and Administration Section of Labeling guidance

HOW SUPPLIED/STORAGE AND HANDLING Section of FPI: Latex

- If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex:[1]
  - State: “Not made with natural rubber latex”
  - Avoid statements such as "latex-free" or "does not contain latex“
- If certain components of product are not made with latex, may include statement:[1]
  - “The vial cap is not made with natural rubber latex.”

[1] Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex guidance

HOW SUPPLIED/STORAGE AND HANDLING Section: Avoid Passive Language

- Instead of “Unopened bottles should be stored at room temperature”, state “Store a room temperature”

- Instead of “Vials should be refrigerated at …”, state “Refrigerate at …”

Avoid the Following Items in HOW SUPPLIED/STORAGE AND HANDLING Section of FPI

Avoid including statements that are not applicable to special handling and storage conditions for health care provider, such as:

- “Keep out of the reach of children.”
- “Do not use if seal over bottle opening is broken or missing”

Manufacturing Information at End of Labeling

Manufacturing Information in PI for Drug Products (1 of 2)

- Manufacturing information is required [e.g., name and location of business (street address, city, state and zip code)] and should be located at end of PI
- If a product has FDA-approved patient labeling that:
  - Follows PI (not a separate document), include manufacturing information after FDA-approved patient labeling
  - Does not follow PI (i.e., separate document) include manufacturing information after both Section 17 of FPI and after FDA-approved patient labeling

Manufacturing Information in PI for Drug Products (2 of 2)

For NDAs and ANDAs, either the manufacturer's name, packer's name, or distributor's name is acceptable: For example:

- "Manufactured by …"
- "Manufactured for … "
- "Distributed by …"
- "Packaged by …"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