Regulatory Education for Industry (REdI):

PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES

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Prescribing Information (PI) Potpourri

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Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

The labeling examples included in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended labeling templates.

Labeling Quiz Bowl

The following questions may have one or more appropriate answers

1. All of the following are good labeling practices for developing the PI except:

a. Use active voice as appropriate

b. Order information (e.g., subsection headings, tables, or bullets) based on the content's importance and relative public health significance

c. Use bold print as much as possible

d. Include clear titles and numbers for all tables and figures

Question 1 Answer:

c: Use bold print as much as possible.

<u>Rationale</u>: Unnecessary bolding throughout labeling could minimize important bolded information. The other responses (i.e., a, b, and d) are considered good labeling development practices.

2. *True or False*

The PI headings must be underlined; while subheadings are italicized as exemplified ….

8.1 Pregnancy

<u>Data</u>

Human Data

Animal Data

Question 2 Answer:

False

<u>Rationale</u>: Although a consistent approach for formatting headings and subheadings throughout the PI is recommended (e.g., underlining for headings and italics for subheadings) either formatting approach (e.g., using underlining or italics for headings) is acceptable).

3. All of the following are required headings in Highlights except:

a. Dosage Forms and Strengths

b. Contraindications

c. Drug Interactions

d. Use in Specific Populations

Question 3 Answer:

c. Drug Interactions

and

d. Use in Specific Populations

Rationale:

- *If there are no clinically significant drug interactions (DI), the DI heading should be omitted from Highlights**
- *If there are no clinically important differences in response or recommendations for use of drug in specific populations, Use in Specific Populations heading should be omitted from Highlights**

* FDA Guidance for Industry: Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements

4. *True or False*

Not all warnings and precautions listed in the Full Prescribing Information must be listed in Highlights.

Question 4 Answer:

True

*<u>Rationale</u>: The most clinically significant safety concerns should be presented in Highlights; however, not all of the safety information from the FPI will always be included in Highlights.**

* FDA Guidance for Industry: Labeling for Human Prescription Drug and Biological Products-Implementing the PLR Content and Format Requirements

5. A description of the identifying characteristics of the dosage form is discussed in which section(s) of the PI:

a) Description

b) Dosage Forms and Strengths

c) How Supplied/Storage and Handling

d) Dosage and Administration

Question 5 Answer:

b) Dosage Forms and Strengths*

and

c) How Supplied/Storage and Handling**

* See 21 CFR 201.57(c)(4)

** See 21 CFR 201.57(c)(17)

6. Recommended statements for the Patient Counseling Information section include which of the following:

a) Inform patients that DRUG is contraindicated for use in patients with severe hepatic impairment.

b) Discuss the risks and benefits of DRUG with the patient.

c) Advise the patient to promptly contact a physician if they develop any toxic reactions.

d) None of the above

Question 6 Answer:

d) None of the Above*

Rationale for why other responses are incorrect:

a) Information that informs prescribing decisions are not included in this section.

b) General recommendations lacking context that would be a standard component of any provider-patient discussion are omitted from this section.

c) General advice that could apply to any drug are omitted from this section.

* See FDA Guidance: *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products-Content and Format*

7. *True or False*

The Adverse Reactions section must list adverse reactions that occur not only with the drug but also with drugs in the same pharmacologically active and chemically related class.

Question 7 Answer:

True*

*See 21 CFR 201.57(c)(7)(i)

8. Bolded text is used for:

a) Boxed Warning in Highlights

b) Boxed Warning in the Full Prescribing Information

c) Product Title in Highlights

d) Initial U.S. Approval in Highlights

Question 8 Answer: (all options are correct)

a) Boxed Warning in Highlights*

b) Boxed Warning in the Full Prescribing Information**

c) Product Title in Highlights*

d) Initial U.S. Approval in Highlights*

*See 21 CFR 201.57(d)(5)

** See FDA Guidance: Warnings and Precautions, Contraindications, and Boxed Warning Section of Labeling for Human Prescription Drug and Biological Products-Content and Format

9. Which of the following should be included in the Clinical Studies section:

a) Studies that provide primary support for effectiveness

b) Studies that prospectively evaluate a safety endpoint

c) Studies that imply effectiveness for an unapproved use

d) Studies that suggest a lack of effectiveness in a clinical situation or lack of effect on a particular endpoint where drug may have been expected to work

Question 9 Answer: (a), (b), and (d)

a) Studies that provide primary support for effectiveness*

b) Studies that prospectively evaluate a safety endpoint*

d) Studies that suggest a lack of effectiveness in a clinical situation or lack of effect on a particular endpoint where the drug may have been expected to work*

Rationale: Option (c) is incorrect because based on 21 CFR 201.57 (c)(2)(iv): "Indications or uses must not be implied or suggested in other sections of the labeling if not included in" the Indications and Usage section.

* See FDA Guidance: *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products-Content and Format*

10. Useful information to provide in the Overdosage section includes all of the following except:

a) A statement that a patient exposed to twice the recommended dose appeared to tolerate the dose without toxic effects

b) Signs, symptoms, and laboratory findings of an overdosage

c) Clinical management of overdosage

d) Complications that occur with an overdosage (e.g., organ toxicity)

Question 10 Answer:

a) A statement that a patient exposed to twice the recommended dose appeared to tolerate the dose without toxic effects

Rationale: All of the other responses are consistent with labeling regulations. Response (a) does not describe signs, symptoms, or lab abnormalities associated with overdosage. Furthermore, the statement may imply a dosage that is not recommended in the Dosage and Administration section***

*See 21 CFR 201.57(c)(11); 21 CFR 201.57(c)(3)(ii)

11. Dosage form(s) and route(s) of administration must be included in which of the following:

a) Product Title in Highlights

b) Description Section

c) Dosage Forms and Strength section

d) How Supplied/Storage and Handling section

Question 11 Answer:

a) Product Title in Highlights*

b) Description Section**

*See 21 CFR201.57(a)(2)

**See 21 CFR201.57(c)12)

12. The sentence, “Keep out of reach of children”, may be appropriate for which of the following section(s) of the PI:

a) Patient Counseling Information

b) Dosage and Administration

c) How Supplied/Storage and Handling

d) None of the Above

Question 12 Answer:

d) None of the Above

<u>Rationale</u>: General advice that could apply to any drug are not included in the PI unless particularly relevant for an individual product (e.g., the need to keep opioid-containing patches away from children and pets).

13. Highlights must (choose the best answer):

a) Have a ½ inch margin on all sides

b) Have a ½ inch margin on all sides and between columns

c) Have a one inch margin on all sides

d) Have a one inch margin on all sides and between major columns

Question 13 Answer:

b) Have a ½ inch margin on all sides and between columns*

*See 21 CFR 201.57(d)(8)

14. *True or False*

When developing the PI for a new molecular entity, the term, "Approval Date" is more appropriate than "Revision Date" and should be used at the end of Highlights (i.e., because this is the first labeling, the term "Revision Date" is not pertinent).

Question 14 Answer:

False

*<u>Rationale</u>: Revision Date must always be used at the end of Highlights for drug and biological product PLR labeling including NME and new biological product labeling.**

See 21 CFR 201.57(a)(15)

15. Studies that evaluate the effects of psychoactive drugs on the ability to operate a motor vehicle are concisely summarized in which section of the PI:

a) Warnings and Precautions

b) Clinical Studies

c) Clinical Pharmacology

d) Patient Counseling Information

Question 15 Response:

b) Clinical Studies*

*See draft FDA Guidance: *Evaluating Drug Effects on the Ability to Operate a Motor Vehicle*

16. Which of the following are true about the Recent Major Changes heading in Highlights:

a) Changes resulting from PLR conversion should be listed

b) Changes to the Boxed Warning, Indications and Usage, Contraindications, Warnings and Precautions and Drug Interactions sections are listed

c) Changes must be listed for at least one year and then removed at the first printing subsequent to the one year period

d) The Recent Major Changes date is the date that the supplement was submitted

Question 16 Answer:

c) Changes must be listed for at least one year and then removed at the first printing subsequent to the one year period*

*See 21 CFR 201.57(a)(5) and FDA Guidance for Industry: *Labeling for Human Prescription Drug and Biological Products-Implementing the PLR Content and Format Requirements*

17. Pregnancy exposure registry information should be included in which of the following:

a) Under the "Use in Specific Populations" heading in Highlights

b) In the Pregnancy subsection

c) In the Patient Counseling Information section

Question 17 Answer:

b) In the Pregnancy subsection*

c) In the Patient Counseling Information section**

Response (a) is incorrect***

*See 21 CFR 201.57(c)(9)(i)

** See FDA draft Guidance: *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*

*** See FDA Guidance for Industry: *Labeling for Human Prescription Drug and Biological Products-Implementing the PLR Content and Format Requirements*

18. Which of the following is the best presentation of information for Dosage Forms and Strengths section:

a) Lyophilized powder in a single-use vial containing 50 mcg of drugoxide, 20 mg of albumin and 2 mg of monobasic sodium

b) DRUG is available as 5mg and 10mg film-coated tablets that are not functionally scored

c) For injection: 300 mg of drugoxide as a white lyophilized powder

Question 18 Answer:

c) For injection: 300 mg of drugoxide as a white lyophilized powder*

Rationale: This presentation concisely describes all of the elements (dosage form, strength, and identifying characteristics of dosage form) and omits unnecessary information.

*See 21 CFR 201.57(c)(4)

19. The proprietary name and nonproprietary name must be included in which of the following:

a) Description section

b) Product Title in Highlights

c) Indications and Usage section

Question 19 Answer

a) Description section*

b) Product Title in Highlights**

* See 21 CFR 201.57(c)(12)

** See 21 CFR 201.57(a)(2)

20. *True or False*:

Adverse reactions that are listed in the Clinical Trials Experience subsection should be repeated in the Postmarketing Experience subsection if they are identified after drug approval.

Question 20 Answer:

False

*<u>Rationale</u>: Clinical information should be located in the section (or subsection) that most appropriately communicates the information to avoid redundancy. Therefore, repeating an adverse reaction in Postmarketing Experience subsection is usually not necessary.**

* See FDA Guidance for Industry: *Labeling for Human Prescription Drug and Biological Products-Implementing the PLR Content and Format Requirements*

21. Which of the following statements is true:

a) Clinical implications and management strategies based on pharmacokinetic data should be discussed in Pharmacokinetics subsection in the Clinical Pharmacology section

b) Management strategies for adverse reactions should be discussed in the Adverse Reactions section

c) None of the above

Question 21 Answer:

c) None of the Above

Rationale:

- *Clinical recommendations are not discussed in the Clinical Pharmacology section. Instead, a cross-reference to appropriate section (e.g., Warning and Precautions section) is included.**
- *The Warnings and Precautions section (as opposed to Adverse Reactions section) discusses risk mitigation strategies.***

* See FDA draft Guidance*: Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products-Considerations, Content, and Format*

** See FDA Guidance: *Warnings and Precautions, Contraindications, and Boxed Warning Section of Labeling for Human Prescription Drug and Biological Products - Content and Format*

22. The text: “Drug X is a cytotoxic drug. Follow applicable special handling and disposal procedures”, is applicable to:

a) Dosage and Administration section

b) How Supplied/Storage and Handling section

c) Dosage Forms and Strengths section

d) (a) and (b)

Question 22 Answer:

d) (a) and (b)

*<u>Rationale</u>: Both the Dosage and Administration and How Supplied/Storage and Handling sections include information concerning special handling of a dosage form where mishandling may have serious consequences.**

*See FDA Guidance: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format and 21 CFR 201.57(c)(17)

23. Information concerning a drug interaction that results in a severe adverse reaction that can be prevented by modifying dosing may be discussed in which section(s) of the PI?

a) Clinical Pharmacology

b) Dosage and Administration

c) Drug Interactions

d) Patient Counseling Information

e) Warnings and Precautions

Question 23 Answer: a, b, c, d, and e are correct*

Rationale:

- *Dosage and Administration section describes dosage adjustments due to drug interactions (DI)*
- *Warnings and Precautions section describes DI with clinically significant outcomes (i.e., serious adverse reactions)*
- *Drug Interactions section includes description of clinical implications of clinically significant DI*
- *Clinical Pharmacology section includes results from DI studies*
- *Patient Counseling Information section includes DI pertinent to patient use such as avoiding grapefruit juice and DI if they include an important risk (e.g., they are mentioned in the Boxed Warning, Contraindications, or Warnings and Precautions sections)*

** See FDA draft Guidance: Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*

24. The risk mitigation strategy: "Avoid use of DRUG in patients with severe hepatic impairment", is most appropriate for which of the following two section/subsection(s) of the PI:

a) Use in Specific Populations/Patients with Hepatic Impairment

b) Warnings and Precautions

c) Clinical Pharmacology

d) Indications and Usage/Limitations of Use

Question 24 Answer:

a) Use in Specific Populations/Patients with Hepatic Impairment*

b) Warnings and Precautions**

Rationale: Use in Specific Populations and Warnings and Precautions sections include risk mitigation strategies for specific populations; while the Clinical Pharmacology section does not and the Limitations of Use heading (or subsection) generally does not.

* See 21 CFR 201.57(c)(9)

** See 21 CFR 201.57(c)(6)

25. All of the following are discussed in the Dosage and Administration section except:

a) Dosing recommendation based on clinical pharmacologic effect (e.g., food effect)

b) PK results in patients with hepatic impairment that provide the rationale for a recommended dosage adjustment

c) Dosage modifications based on drug interactions

d) Directions on dilution

Question 25 Answer:

b) PK results in patients with hepatic impairment that provide the rationale for a recommended dosage adjustment

*Rationale: The Dosage and Administration section provides dosage and administration recommendations and includes a cross-reference to the appropriate section(s) of labeling for a rationale for these recommendations (e.g., PK results - that provide support for dosage adjustments - appear in the Pharmacokinetics subsection of the Clinical Pharmacology section)**

* See FDA draft Guidance*: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations,* and FDA Guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format*

26. A cross-reference to the Nonclinical Toxicology section for a detailed discussion of animal studies is most appropriate for information in which subsection(s):

a) 8.1 Pregnancy

b) 8.2 Lactation

c) 8.3 Females and Males of Reproductive Potential

Question 26 Answer:

c) Females and Males of Reproductive Potential*

* See FDA draft Guidance: *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format*

Thank you!