Regulatory Education for Industry (REdI): PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES

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Challenges and Issues With the INDICATIONS AND USAGE Sections of Labeling

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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 fictitious and are provided only to demonstrate current labeling development challenges.

INDICATIONS AND USAGE (I&U) Section: Resources

Code of Federal Regulations:

- 21 CFR 201.57(c)(2)

Future Labeling Guidance:

- I&U Section of Labeling Guidance (under development)

I&U Section: Example #1

What can be improved?
1 INDICATIONS AND USAGE DRUGOXIDE injection, USP (100 mg/mL) contains drug-x, a pyrophosphate analog CMV DNA polymerase inhibitor / HSV DNA polymerase inhibitor, and is indicated for intravenous use in the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome.
Improved Language
1 INDICATIONS AND USAGE DRUGOXIDE is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome.

I&U Section Example #1: Comments

What can be improved?
1 INDICATIONS AND USAGE DRUGOXIDE injection, USP (100 mg/mL) contains drug-x, a pyrophosphate analog CMV DNA polymerase inhibitor / HSV DNA polymerase inhibitor, and is indicated for intravenous use in the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome.
Improved Language
1 INDICATIONS AND USAGE DRUGOXIDE is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome.

To improve readability of indications statement, recommend removal of dosage form, USP descriptor, strength, FDA established pharmacologic class text phrase, and route of administration

I&U Section: Example #2

What Can Be Improved?
1 INDICATIONS AND USAGE DRUGOXIDE is indicated for the treatment of Disease Y *[see Clinical Studies (14.1)]*. The efficacy of DRUGOXIDE in Disease Y was established in one 8-week and three-10 week trials and one maintenance study in adults. The efficacy of DRUGOXIDE was also established in two 8- to 10-week trials in pediatric patients aged 8 to 18 years; doses greater than 80 mg/day have not been studied in pediatric patients with Disease Y.
Improved Language
1 INDICATIONS AND USAGE DRUGOXIDE is indicated for the treatment of patients 8 years old and older with Disease Y.

I&U Section Example #2: Comments

Recommend **excluding** the following in indications statement:

- Basis of approval
  - Instead efficacy evidence in CLINICAL STUDIES section*
- Study design including dosages
  - Instead describe study design including dosage used in studies in CLINICAL STUDIES section**

* 21 CFR 201.57(c)(15)

** Section III(B)(4) - Clinical Studies Section of Labeling Guidance

I&U Section: Example #3

What Can Be Improved?

1 INDICATIONS AND USAGE

DRUGOXIDE is indicated for the treatment of adults with schizophrenia.

Schizophrenia (DSM-IV) is characterized by having at least two of the following criteria for most of the time at least over a one month period: delusions, hallucinations, disorganized speech, or severely disorganized or catatonic behavior. These signs or symptoms must have an impact on social or occupational functioning for at least six months.

Improved Language

1 INDICATIONS AND USAGE

DRUGOXIDE is indicated for the treatment of adults with schizophrenia.

I&U Section Example #3: Comments

Recommend **excluding** disease definitions and diagnostic criteria in indications statement:

- Instead include important eligibility criteria and baseline disease characteristics in CLINICAL STUDIES section*

* Section III(B)(4) - Clinical Studies Section of Labeling Guidance

I&U Section: Example #4

What Can Be Improved?

1 INDICATIONS AND USAGE

DRUGOXIDE is used in adults during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract. DRUGOXIDE is as effective for this examination as are the anticholinergic drugs. However, the addition of the anticholinergic agent may result in increased side effects. After the end of the diagnostic procedure, give oral carbohydrates to patients who have been fasting, if this is compatible with the diagnostic procedure applied.

Improved Language

1 INDICATIONS AND USAGE

DRUGOXIDE is indicated for use in adults as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract.

I&U Section Example #4: Comments

- I&U "section must state **drug is indicated for"** treatment, relief, prevention, mitigation, cure, or diagnosis of a recognized disease/condition or manifestation of a recognized disease/condition*
  - Recommend starting indications statement with "**DRUGOXIDE is indicated** …"

- Redistribute information, by moving:
  - Efficacy results to CLINICAL STUDIES section
  - Drug interaction information to another section (e.g., WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS)
  - Concomitant medications to DOSAGE AND ADMINISTRATION section (if drug is approved in combination with carbohydrates)

* 21 CFR 201.57(c)(2)

I&U Section: Example #5

What Can Be Improved?
1 INDICATIONS AND USAGE DRUGOXIDE is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure. Studies establishing effectiveness included predominantly patients with chronic heart failure (NYHA Class II-IV). In these studies, all patients received a beta-blocker and mineralocorticoid receptor antagonist. In these studies, 90% and 10% had left ventricular ejection fraction ≤ 35% and > 35%, respectively.
Improved Language
1 INDICATIONS AND USAGE DRUGOXIDE, in conjunction with a beta-blocker and a mineralocorticoid receptor antagonist, is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and left ventricular ejection fraction ≤ 35%.

I&U Section Example #5: Comments

- If a drug is indicated **only** in conjunction with a primary mode of therapy (e.g., another drug, behavioral change), must include a statement that drug is indicated as **an adjunct** to that mode of therapy*
  - Include beta-blocker and mineralocorticoid receptor antagonist in indication statement
- Move study design and baseline disease characteristics to CLINICAL STUDIES section**
- If evidence supports safety and effectiveness only in selected subgroups of larger population, indicate only in subpopulation***

* 21 CFR 201.57(c)(2)(i)(A)
** Section III(B)(4) - Clinical Studies Section of Labeling Guidance
*** 21 CFR 201.57(c)(2)(i)(A)

I&U Section: Example #6

What Can Be Improved?

1 INDICATIONS AND USAGE

1.1 Use as a Diagnostic Aid

DRUGOXIDE is indicated for use in adults as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract.

1.2 Patients with Acromegaly

DRUGOXIDE is indicated for the treatment of adults with acromegaly who have had an inadequate response to surgery or radiation therapy, or for whom these therapies are not appropriate.

Improved Language

1 INDICATIONS AND USAGE

DRUGOXIDE is indicated for:

- Use in adults as a diagnostic aid during radiologic examinations to temporarily inhibit movement of the gastrointestinal tract.
- Treatment of adults with acromegaly who have had an inadequate response to surgery or radiation therapy, or for whom these therapies are not appropriate.

I&U Section Example #6: Comments

Subsection heading should be consistent with information in body of subsection*

- Labeling must be accurate; must not be misleading**
  - "Use as Diagnostic Aid" **is not equivalent to "**diagnostic aid during radiologic examinations to temporarily inhibit movement of GI tract"
- Options:
  - Remove subsection heading that is not consistent with information in body of subsection
  - Modify subsection heading to be consistent with information in body of subsection

Formatting for multiple indications:

- Bulleted list vs. subsection headings

* Best labeling practice; ** 21 CFR 201.56(a)(2)

Limitations of Use (LOU) in I&U Section: Resources

Code of Federal Regulations:

- 21 CFR 201.57(c)(2)

Future Labeling Guidance:

- I&U Section of Labeling Guidance (under development)

LOU in I&U Section (1)

- If there is a common belief that a drug may be effective for a certain use, but preponderance of evidence suggests drug is ineffective or that therapeutic benefits do not generally outweigh its risks, I&U section must state that there is a lack of evidence that drug is effective or safe for that use or condition*
- LOU are uses in which there is a reasonable concern or uncertainty about drug's risk-benefit profile; evidence falls short of a contraindication**
- In contrast, contraindications are situations in which the risks of use clearly outweighs any possible therapeutic benefit***

* 21 CFR 201.57(c)(2)(ii); ** Best labeling practice; *** 21 CFR 201.57(c)(5)

LOU in I&U Section (2)

- Contraindications are not included as LOU
- Not all uses or conditions which are not recommended for drug should be LOU*
  - May be more appropriate for other sections (e.g., WARNINGS AND PRECAUTIONS, USE IN SPECIFIC POPULATIONS)

* Best labeling practice; ** 21 CFR 201.57(c)(5)

LOU: Example #1

1 INDICATIONS AND USAGE

DRUGOXIDE is indicated for the initial treatment of adult women with painful symptoms of endometriosis.

Limitations of Use:
The use of DRUGOXIDE greater than 6 months is not recommended because of concerns about the adverse impact of DRUGOXIDE on bone mineral density *[see Warnings and Precautions (5.1)]*.

Must include information on LOU or uncertainty about anticipated clinical benefits that is relevant to appropriate duration of treatment when such treatment should be limited*

* 21 CFR 201.57(c)(2)(i)(D)

LOU: Example #2

1 INDICATIONS AND USAGE

DRUGOXIDE in combination with other antiretroviral drugs is indicated for treatment of HIV-1 infection in antiretroviral treatment-experienced adults.

Limitations of Use:

The concomitant use of DRUGOXIDE with protease inhibitors and cobicistat is not recommended *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.5 Risk of Loss of Therapeutic Effect and Resistance with Concomitant Use of Protease Inhibitors and Cobicistat

Dosage recommendations for the concomitant use of DRUGOXIDE with protease inhibitors and cobicistat to treat HIV-1 infection have not been established. Concomitant use may result in suboptimal plasma concentrations of the antiretroviral drugs leading to loss of therapeutic effect and development of resistance. Therefore, the concomitant use of DRUGOXIDE with protease inhibitors and cobicistat is not recommended.

LOU: Example #3

What Can Be Improved?
1 INDICATIONS AND USAGE DRUGOXIDE is indicated for the treatment of complicated urinary tract infections (UTI) caused by specific susceptible microorganisms (i.e., Escherichia coli, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Citrobacter freundii, Proteus spp., and Pseudomonas aeruginosa) in adults. Limitations of Use: DRUGOXIDE is not recommended as a first-line or second-line therapy in the treatment of complicated UTI.
Improved Language
1 INDICATIONS AND USAGE DRUGOXIDE is indicated for the treatment of complicated urinary tract infections caused by specific susceptible microorganisms (i.e., Escherichia coli, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Citrobacter freundii, Proteus spp., and Pseudomonas aeruginosa) in adults who have limited or no alternative treatment options.

LOU Example #3: Comments

Information that narrows or further defines a drug's intended use should be incorporated directly into indications statement, rather than a separate LOU*

* Best labeling practice

References

- PLR Requirements for Prescribing Information website: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

Thank you!