

Improving the Accuracy of SPL Submissions: “The Missing LOINC”

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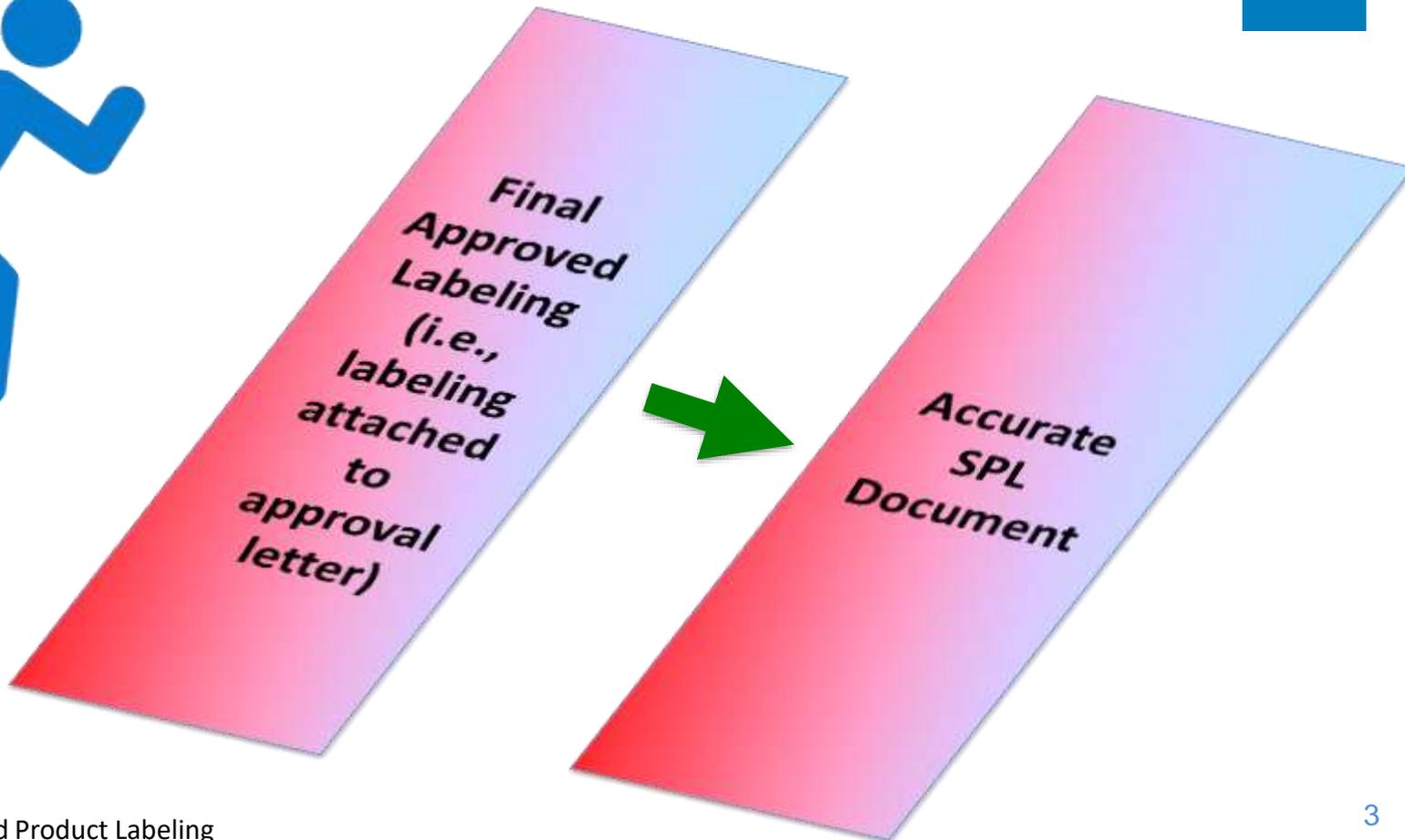
Office of New Drugs, Center for Drug Evaluation and Research, FDA

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.

The Labeling “Finish Line”

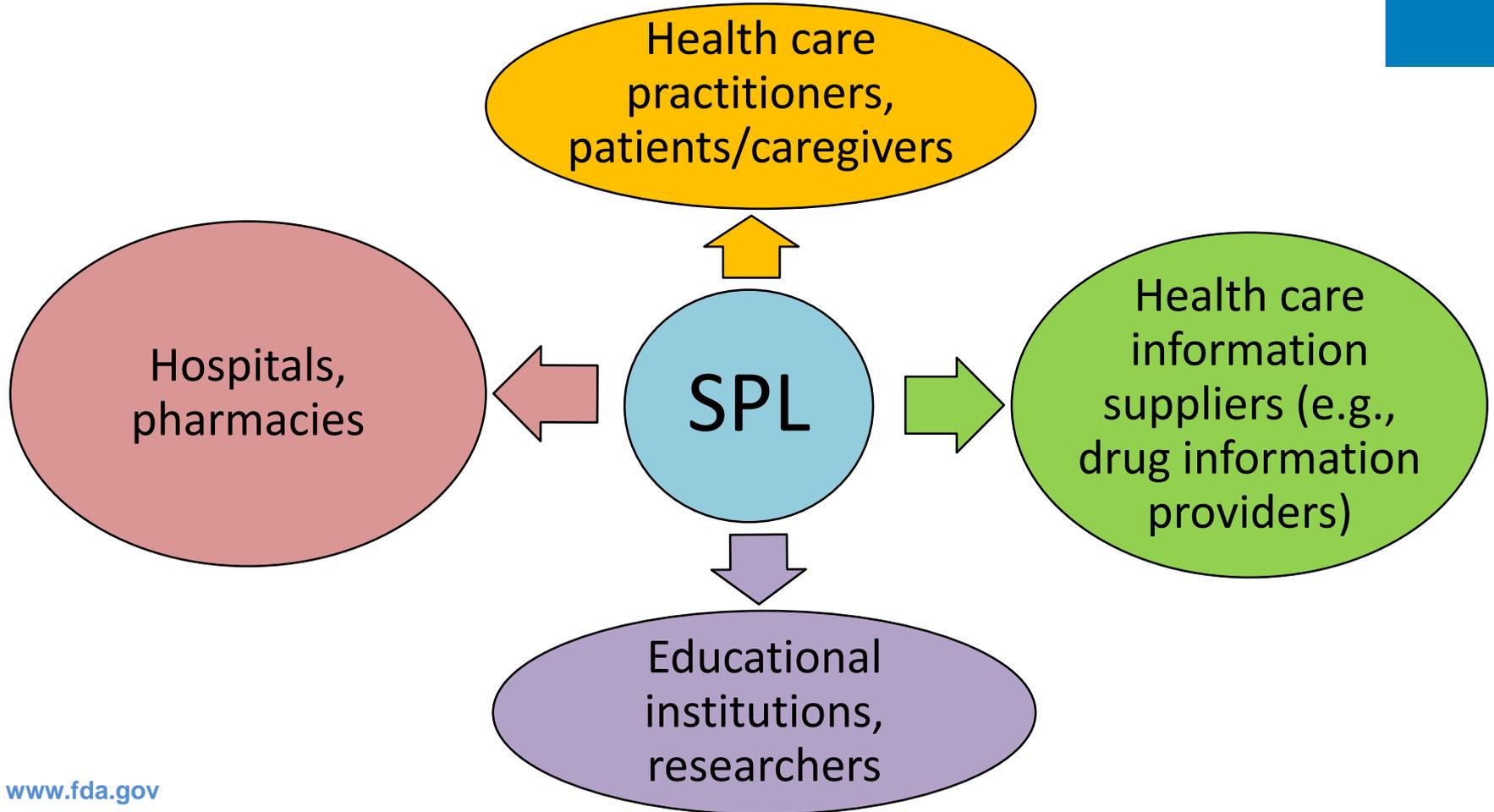


Learning Objectives



- Review downstream users of SPL, accessibility of SPL, and importance of SPL accuracy
- Discuss role of LOINC in SPL accuracy, and why accurate assignment of sections/subsections of the PI in SPL using LOINC is important
- Identify some challenges with accurate LOINC assignment in SPL
- Describe a resource intended to improve accuracy of LOINC assignment in SPL (“the LOINC document”)

Downstream Users of SPL



Accessing SPL



- Online labeling repositories that access SPL include:



- Such repositories allow for specific searches within SPL (e.g., search for text within a specific section/subsection of the PI).

Granularity in Searching for Specific Sections/Subsections in SPL



The screenshot shows the DailyMed Advanced Search interface. A dropdown menu is open, listing various drug label sections. The list includes:

- Index Section (14030-9)
- Adverse Reactions Section (14034-4)
- Animal Pharmacology/Toxicology Section (14035-9)
- Boxed Warning Section (14036-1)
- Carcinogenicity, Mutagenesis, Impairment of Fertility Section (14037-4)
- Clinical Pharmacology Section (14039-1)
- Clinical Studies Section (14042-7)
- Contraindications Section (14070-9)
- Controlled Substance Section (14085-3)
- Experience Section (14087-7)
- Indication Section (14089-3)
- Dosage And Administration Section (14089-7)
- Dosage Forms And Strengths Section (14078-2)



The screenshot shows the FDA Label search results page. The search criteria are: "Labeling Section(s)" with the query "BOXED WARNING (14044 labeling) AND 1 INDICATIONS AND USAGE (14070 labeling) AND 2 DOSAGE AND ADMINISTRATION (14039 labeling)". The results list the following sections:

- BOXED WARNING (14044 labeling)
- 1 INDICATIONS AND USAGE (14070 labeling)
- 2 DOSAGE AND ADMINISTRATION (14039 labeling)

Importance of SPL Accuracy

- Quality of search output from online labeling repositories is directly affected by quality of the source data (i.e., the SPL).
- Accuracy of SPL (e.g., accurate assignment of PI sections/subsections in SPL) can be just as important as the content of labeling.
- Incorrect or inappropriate assignment of PI sections/subsections in SPL impairs ability to accurately search or extract data from those sections/subsections.

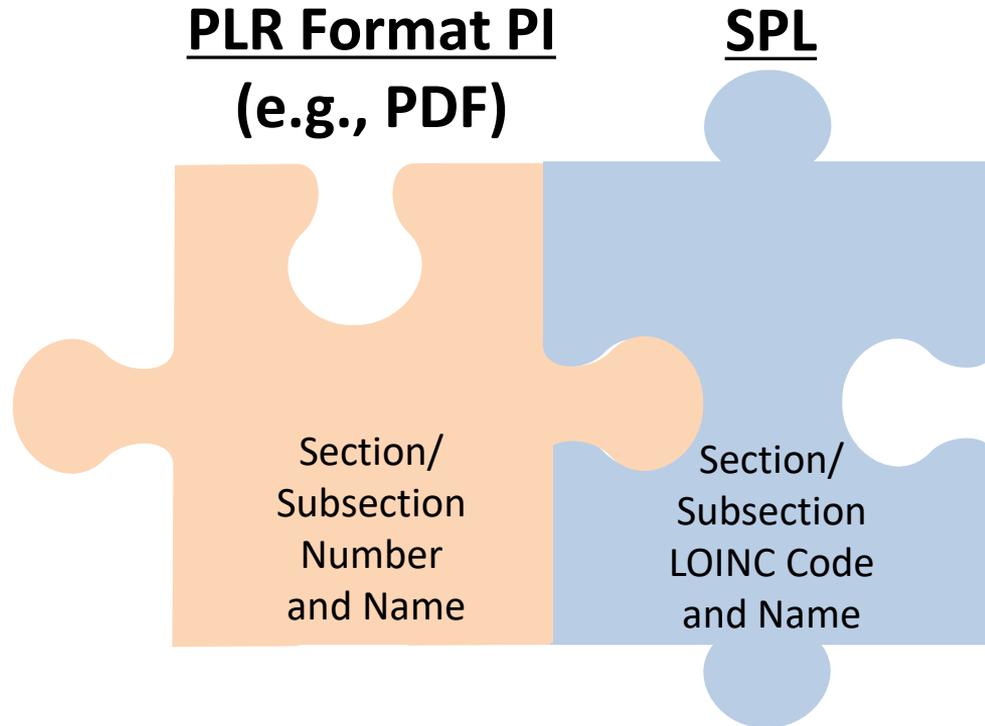
The logo features the word "LOINC" in a bold, orange, sans-serif font with a black outline. It is centered within two overlapping light blue speech bubbles. The bubble in the foreground is slightly larger and positioned to the right of the one behind it.

LOINC

The Role of LOINC in SPL Accuracy

LOINC 101

- LOINC codes: universal codes to identify medical terminology
- SPL section and subsection LOINC codes:
 - Consist of six digits in the format XXXXX-X
 - Match a section or subsection name with the content of the section or subsection (e.g., match a section or subsection of PI to a section or subsection LOINC code/name)





Section/Subsection LOINC Codes – Human Prescription Drug and Biological Products (1 of 2)

Ideally, in the SPL we would have all PI sections and subsections designated by PLR labeling regulations¹ or guidances assigned to specific LOINC codes. For example:

PLR Format Full Prescribing Information Section/Subsection		LOINC	
Number	Name	Code	Name
6	ADVERSE REACTIONS	34084-4	ADVERSE REACTIONS SECTION
9.2	Abuse	34086-9	ABUSE SECTION



When a user searches an online labeling database like DailyMed for text within a PI section/subsection (e.g., *Abuse* subsection), the database uses the LOINC to “decide” whether an SPL contains that section/subsection.

¹ 21 CFR 201.56 and 201.57



Section/Subsection LOINC Codes – Human Prescription Drug and Biological Products (2 of 2)

Any PI sections/subsections *not* designated by PLR labeling regulations¹ or guidances would then be assigned to the LOINC code for “SPL Unclassified Section.” For example:

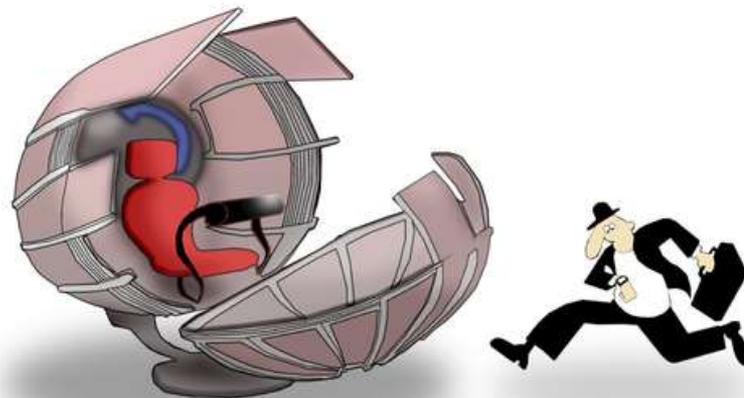
PLR Format Full Prescribing Information Subsection		LOINC	
Number	Name	Code	Name
2.4	Preparation Instructions	42229-5	SPL UNCLASSIFIED SECTION
5.3	Hepatotoxicity	42229-5	SPL UNCLASSIFIED SECTION

Do all PI sections/subsections designated by PLR labeling regulations or guidances have a specific LOINC code?

¹ 21 CFR 201.56 and 201.57

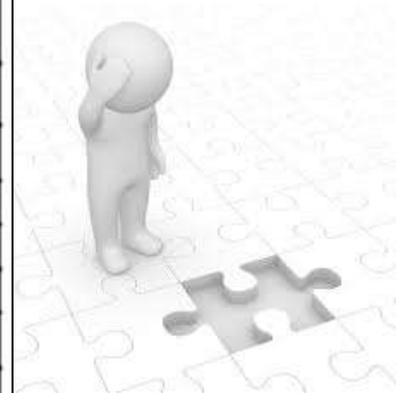
Challenge: Availability of LOINC Codes for PLR Format PI Sections/Subsections

A Brief Trip Back to the 2017 CDER Prescription Drug Labeling Conference



No LOINC Codes for Several Popular Subsections/Sections (PLR format)

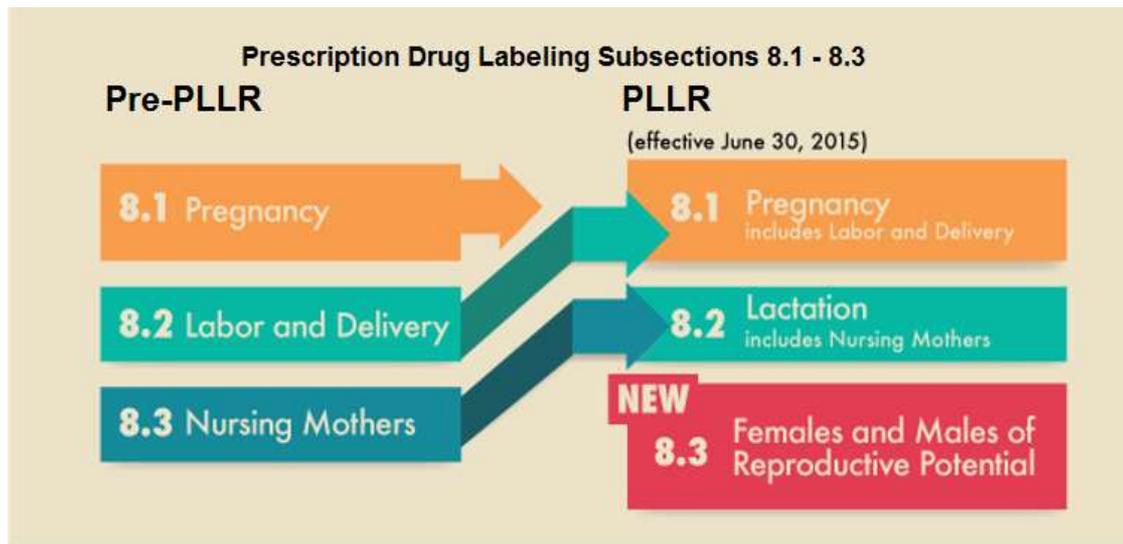
Section/ Subsection	Section/Subsection Name	LOINC Code
PRESCRIBING INFORMATION (PLR format)		
6	ADVERSE REACTIONS section	34084-4
6.1	Clinical Trials Experience subsection	No LOINC Code
6.2	Immunogenicity subsection	No LOINC Code
6.2 or 6.3	Postmarketing Experience subsection	No LOINC Code
8	USE IN SPECIFIC POPULATIONS section	43684-0
Typically 8.6	Renal Impairment subsection	No LOINC Code
Typically 8.7	Hepatic Impairment subsection	No LOINC Code
16	HOW SUPPLIED/STORAGE AND HANDLING section	No LOINC Code
17	PATIENT COUNSELING INFORMATION section	No LOINC Code



Challenge: Uptake of Newer LOINC Codes (for two subsections designated under PLLR)



Subsection Changes Under the Pregnancy and Lactation Labeling Rule (PLLR)



Subsection Number/Name in PLR Format Full Prescribing Information	LOINC Code	LOINC Name
8.2 Lactation subsection	77290-5	LACTATION SECTION
8.2 Labor and Delivery subsection	34079-4	LABOR & DELIVERY SECTION
8.3 Females and Males of Reproductive Potential subsection	77291-3	FEMALES & MALES OF REPRODUCTIVE POTENTIAL SECTION
8.3 Nursing Mothers subsection	34080-2	NURSING MOTHERS SECTION

Uptake of Newer LOINC Codes – Assessment for Subsections 8.2 and 8.3



- Searched for SPL of approved NDAs/BLAs with PLR format labeling
- Excluded SPL from repackers/relabelers and SPL of NDA authorized generics
- Examined LOINC code assignments for subsections 8.2 and 8.3

Uptake of Newer LOINC Codes – LOINC Code Assignment for Subsection 8.2

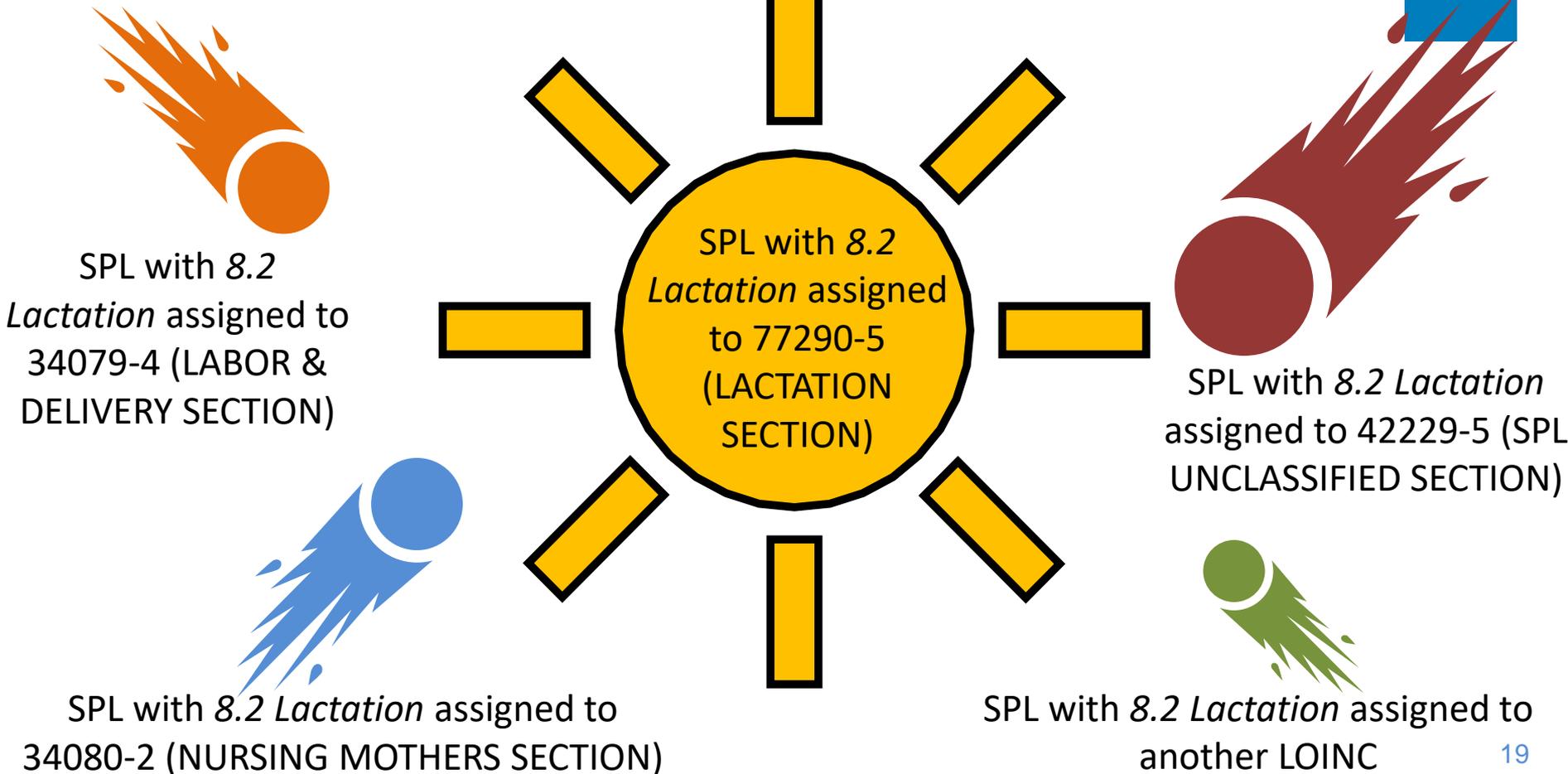


Subsection	Specific Corresponding LOINC Code	LOINC Code (Name) Selected for the Subsection in the SPL (%)
8.2 Lactation	77290-5	<ul style="list-style-type: none"> •77290-5 (LACTATION SECTION): 78% ✓ •42229-5 (SPL UNCLASSIFIED SECTION): 11% ✗ •34080-2 (NURSING MOTHERS SECTION): 5% ✗ •34079-4 (LABOR & DELIVERY SECTION): 5% ✗ •Others: 1% ✗
8.2 Labor and Delivery	34079-4	<ul style="list-style-type: none"> •34079-4 (LABOR & DELIVERY SECTION): 95% ✓ •42229-5 (SPL UNCLASSIFIED SECTION): 3% ✗ •34080-2 (NURSING MOTHERS SECTION): 1% ✗ •Others: 1% ✗

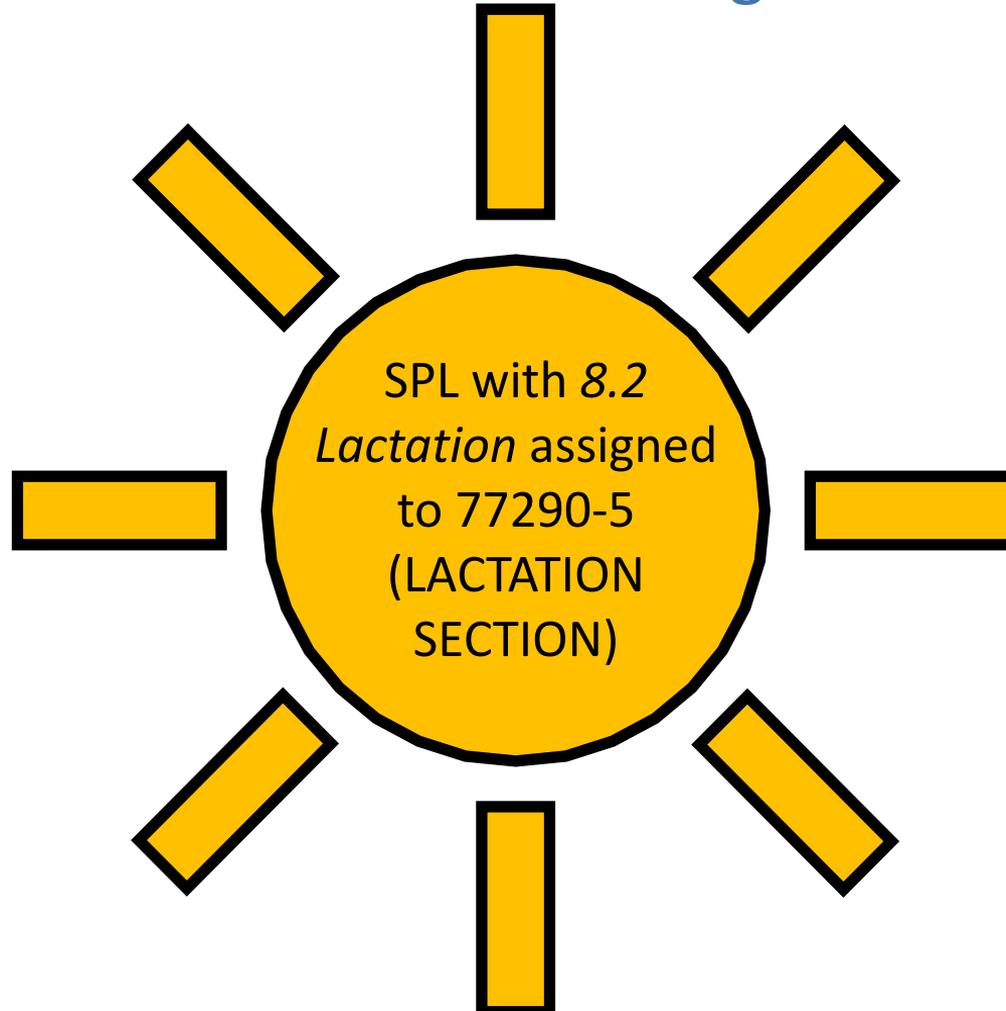
Of the SPL that included a subsection 8.2 Lactation, ~22% assigned a suboptimal or incorrect LOINC code to the subsection 8.2 Lactation.

Data obtained June 22, 2019 and reflect SPL of FDA-approved human prescription drug and biological products under an NDA or BLA with PLR format labeling. Repacker and relabeler SPL were excluded, as were NDA authorized generic SPL. Data are courtesy of the FDALabel team of the National Center for Toxicological Research (NCTR).

Current "Universe" of SPL Containing 8.2 Lactation



Ideal “Universe” of SPL Containing 8.2 *Lactation*



Uptake of Newer LOINC Codes – LOINC Code Assignment for Subsection 8.3



Subsection	Specific Corresponding LOINC Code	LOINC Code (Name) Selected for the Subsection in the SPL (%)
8.3 Females and Males of Reproductive Potential	77291-3	<ul style="list-style-type: none"> •77291-3 (FEMALES & MALES OF REPRODUCTIVE POTENTIAL SECTION): 73% ✓ •42229-5 (SPL UNCLASSIFIED SECTION): 16% ✗ •34080-2 (NURSING MOTHERS SECTION): 7% ✗ •Others: 4% ✗
8.3 Nursing Mothers	34080-2	<ul style="list-style-type: none"> •34080-2 (NURSING MOTHERS SECTION): 95% ✓ •42229-5 (SPL UNCLASSIFIED SECTION): 2% ✗ •77291-3 (FEMALES & MALES OF REPRODUCTIVE POTENTIAL SECTION): 1% ✗ •Others: 2% ✗

Data obtained June 22, 2019 and reflect SPL of FDA-approved human prescription drug and biological products under an NDA or BLA with PLR format labeling. Repacker and relabeler SPL were excluded, as were NDA authorized generic SPL. Data are courtesy of the FDALabel team of the National Center for Toxicological Research (NCTR).



Linking the LOINC

Optimizing LOINC Code Selection – The “LOINC Document”



Recently, a PDF document called “LOINC for Human Prescription Drug and Biological Product Labeling”¹ (i.e., the “LOINC document”) was posted on the Prescription Drug Labeling Resources website.²



¹ [Logical Observation Identifiers Names and Codes \(LOINC\) for Human Prescription Drug and Biological Product Labeling](#) – For questions about this document, please contact the [Labeling Policy Team](#) in the Office of New Drugs in CDER.

² [Prescription Drug Labeling Resources website](#) (previously called “PLR Requirements for Prescribing Information” website)

The “LOINC Document” – Contents¹

1

Describes several specific considerations to optimize appropriate LOINC assignment

2

Lists four tables that correlate LOINC codes/names with the corresponding:

Sections/subsections of PLR format PI (incorporates recently added LOINC codes/names)

Sections/subsections of old (non-PLR) format PI

Type of FDA-approved patient labeling [i.e., Patient Information, Medication Guide (MG), and Instructions for Use (IFU)]

Type of carton/container labeling (principal display panel)

¹ [Logical Observation Identifiers Names and Codes \(LOINC\) for Human Prescription Drug and Biological Product Labeling](#) – For questions about this document, please contact the [Labeling Policy Team](#) in the Office of New Drugs in CDER.

Tables Correlating LOINC with Specific Sections/Subsections of PI – Example



**Table 1: HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS
PLR FORMAT PRESCRIBING INFORMATION***

Full Prescribing Information

LOINC Code	LOINC Name	Section/Subsection Name as Per 21 CFR 201.56(d) and 201.57(c) or by Guidance
34066-1	BOXED WARNING SECTION	BOXED WARNING section
34067-9	INDICATIONS & USAGE SECTION	1 INDICATIONS AND USAGE section
34068-7	DOSAGE & ADMINISTRATION SECTION	2 DOSAGE AND ADMINISTRATION section
43678-2	DOSAGE FORMS & STRENGTHS SECTION	3 DOSAGE FORMS AND STRENGTHS section
34070-3	CONTRAINDICATIONS SECTION	4 CONTRAINDICATIONS section
43685-7	WARNINGS AND PRECAUTIONS SECTION	5 WARNINGS AND PRECAUTIONS section
34084-4	ADVERSE REACTIONS SECTION	6 ADVERSE REACTIONS section
90374-0	CLINICAL TRIALS EXPERIENCE SECTION	6.1 Clinical Trials Experience subsection
88830-5	IMMUNOGENICITY	Immunogenicity subsection
90375-7	POSTMARKETING EXPERIENCE SECTION	Postmarketing Experience subsection
34073-7	DRUG INTERACTIONS SECTION	7 DRUG INTERACTIONS section
43684-0	USE IN SPECIFIC POPULATIONS SECTION	8 USE IN SPECIFIC POPULATIONS section

[Logical Observation Identifiers Names and Codes \(LOINC\) for Human Prescription Drug and Biological Product Labeling](#)

– For questions about this document, please contact the [Labeling Policy Team](#) in the Office of New Drugs in CDER.

Recently Added LOINC for PLR Format PI (1 of 2)

BOXED WARNING	
1	INDICATIONS AND USAGE
2	DOSAGE AND ADMINISTRATION
3	DOSAGE FORMS AND STRENGTHS
4	CONTRAINDICATIONS
5	WARNINGS AND PRECAUTIONS
6	ADVERSE REACTIONS
6.1	Clinical Trials Experience
6.2	Immunogenicity
6.2 or 6.3	Postmarketing Experience
7	DRUG INTERACTIONS
8	USE IN SPECIFIC POPULATIONS
8.1	Pregnancy
8.2	Lactation
8.3	Females and Males of Reproductive Potential
8.4	Pediatric Use
8.5	Geriatric Use
8.6	Renal Impairment
8.7	Hepatic Impairment

90374-0
CLINICAL TRIALS EXPERIENCE SECTION

88830-5
IMMUNOGENICITY

90375-7
POSTMARKETING EXPERIENCE SECTION

88828-9
RENAL IMPAIRMENT SUBSECTION

88829-7
HEPATIC IMPAIRMENT SUBSECTION

Note: *The Immunogenicity* subsection is frequently subsection 6.2, the *Renal Impairment* subsection is typically subsection 8.6, and the *Hepatic Impairment* subsection is typically subsection 8.7.

Recently Added LOINC for PLR Format PI (2 of 2)

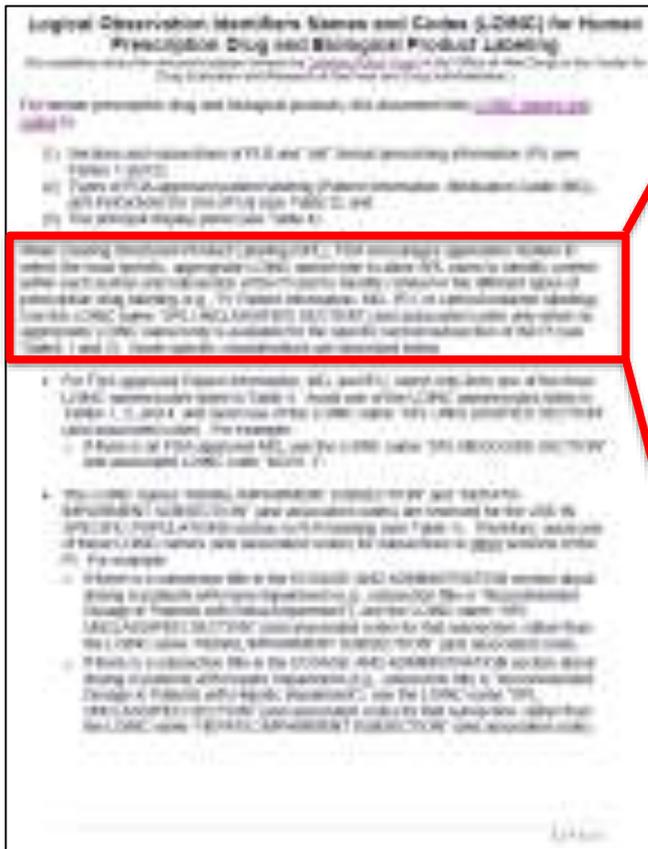


9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

LOINC code and name are being developed

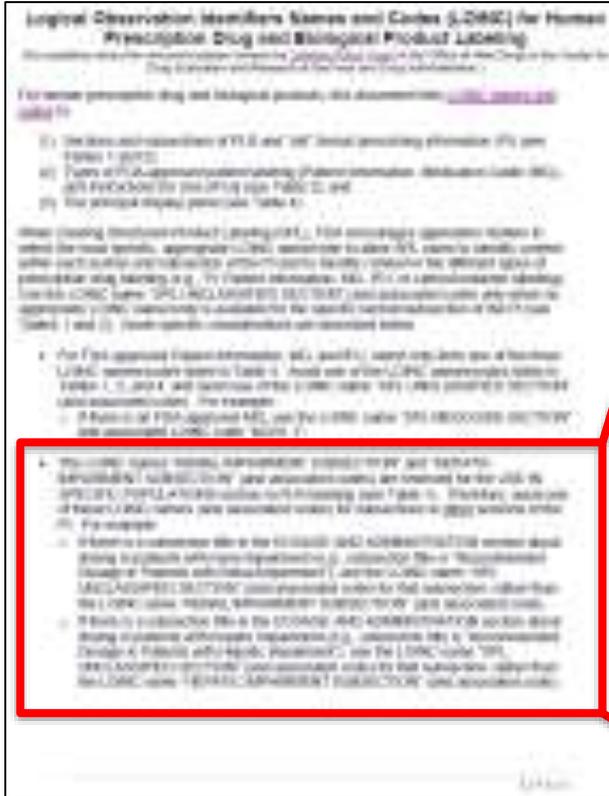
88436-1
PATIENT COUNSELING
INFORMATION

Specific Considerations – LOINC Selection



- Select the most specific, appropriate LOINC code to allow SPL users to identify content within each section/subsection of the PI.
- Use LOINC code for “SPL UNCLASSIFIED SECTION” only when no appropriate LOINC code is available for the specific section/subsection of the PI.

Specific Considerations – Renal Impairment and Hepatic Impairment LOINC



- In PLR labeling, reserve LOINC codes for “RENAL IMPAIRMENT SUBSECTION” and “HEPATIC IMPAIRMENT SUBSECTION” for the USE IN SPECIFIC POPULATIONS section (Section 8).
- Avoid use of these LOINC codes for subsections in other sections of PLR labeling.

Reserving Renal Impairment and Hepatic Impairment LOINC for Section 8 – Example

FULL PRESCRIBING INFORMATION: CONTENTS*

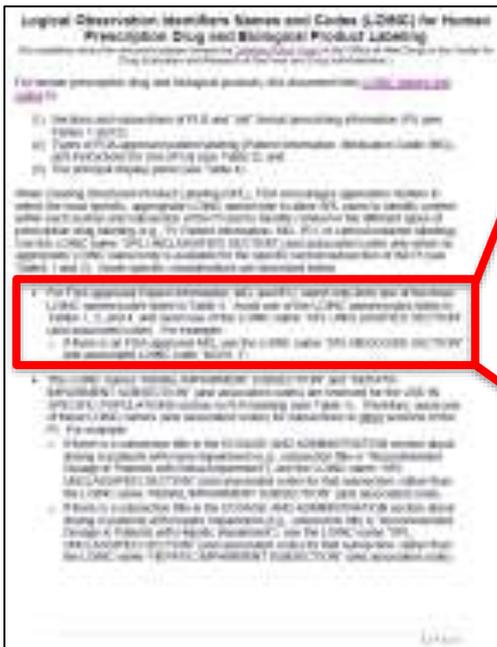
- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Recommended Dosage in Adults
 - 2.2 Recommended Dosage for Renal Impairment
 - 2.3 Recommended Dosage for Hepatic Impairment
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Diarrhea
 - 5.2 Embryo-Fetal Toxicity
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
 - 6.2 Immunogenicity
 - 6.3 Postmarketing Experience
- 7 DRUG INTERACTIONS**
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Lactation
 - 8.3 Females and Males of Reproductive Potential
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Renal Impairment
 - 8.7 Hepatic Impairment

Use 42229-5 (SPL UNCLASSIFIED SECTION) for these subsections

Use 88828-9 (RENAL IMPAIRMENT SUBSECTION) for this subsection

Use 88829-7 (HEPATIC IMPAIRMENT SUBSECTION) for this subsection

Specific Considerations – FDA-Approved Patient Labeling



For FDA-approved Patient Information, MG, and IFU, select only from one of the three LOINC codes in Table 3. Avoid use of other LOINC codes (e.g., “SPL UNCLASSIFIED SECTION”).

Table 3: HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS FDA-APPROVED PATIENT LABELING		
LOINC Code	LOINC Name	Type of FDA-Approved Patient Labeling ^A
59845-8	INSTRUCTIONS FOR USE SECTION	Instructions for Use
42231-1	SPL MEDGUIDE SECTION	Medication Guide
42230-3	SPL PATIENT PACKAGE INSERT SECTION	Patient Information (also called Patient Package Insert)

^A Prescription drug labeling may include either a Medication Guide (or Patient Information), or Instructions for Use, or both.

Accessing the “LOINC Document”



1. Select “Additional Labeling Resources” from the Table of Contents on the Prescription Drug Labeling Resources website.¹

Prescription Drug Labeling Resources

This website provides labeling resources for the Prescribing Information, FDA-approved patient labeling, and carton and container labeling for human prescription drugs, including biological products - see Overview of Website

Highlights of Prescribing Information: Format Sample

Table of Contents

- Overview of Website
- 2019 CDER Prescription Drug Labeling Conference
- Prescribing Information and Application Holder Responsibilities
- Prescribing Information Requirements and Rules
- Prescribing Information Guidelines
- Presentations - Sections of the Prescribing Information
- Presentations - Broad Labeling Content
- Sample Templates and Format Tools for Prescribing Information
- Established Pharmacologic Class (EPC) Resources
- ANDA-Specific Labeling Resources
- Biological Product-Specific Labeling Resources
- Product Quality-Related Labeling Resources
- Carton/Container Labeling Specific Resources
- Patient Labeling Specific Resources
- Labeling Databases
- **Additional Labeling Resources**
- Articles with Labeling Content
- Questions

2. Click to open the document.

Additional Labeling Resources

- Public Availability of Labeling Changes in “Changes Being Effected” Supplements (draft guidance)
- Medical Product Communications That Are Consistent With the FDA-Required Labeling - Questions and Answers (final guidance)
- Best Practices in Developing Proprietary Names for Drugs (draft guidance)
- Safety Labeling Changes - Implementation of Section 505(o)(4) of the FDC Act (final guidance)
- Pregnancy and Lactation Labeling (Drugs) Final Rule: Labeling for use of prescription drugs, including biological products, during pregnancy, during lactation, and in females and males of reproductive potential
- Structured Product Labeling Resource: SPL is the standard format for electronic submission of the content of labeling
- **Logical Observation Identifiers Names and Codes (LOINC) for Human Prescription Drug and Biological Product Labeling: For human prescription drugs, including biological products, this document links LOINC codes and names to (1) sections and subsections of PLR and “old” format labeling, (2) types of FDA-approved patient labeling, and (3) the principal display panel**

¹ [Prescription Drug Labeling Resources website](#) (previously called “PLR Requirements for Prescribing Information” website)

Challenge Question

Use of the LOINC code and name “88828-9 (RENAL IMPAIRMENT SUBSECTION)” is appropriate for which of the following?

- a) Any subsection in the PI that contains information on patients with renal impairment
- b) The *Renal Impairment* subsection in the USE IN SPECIFIC POPULATIONS section
- c) A subsection on dosing in patients with renal impairment in the DOSAGE AND ADMINISTRATION section

Summary



- SPL accuracy can be as important as the content of labeling.
- Accurate assignment of LOINC codes to sections/subsections of PI is critical to SPL accuracy.
- Several new LOINC codes have recently become available for sections/subsections of PLR format PI. Appropriate use of these LOINC codes is encouraged!



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