March 16, 2005
Version 2

Introduction to SPL Changes with the Physician Labeling Rule

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Outline

- Brief overview of SPL
- Introduction to the Physicians Labeling Rule
- Relationship between the Physicians Labeling Rule and the SPL

What is SPL

- A model-derived standard adopted for the exchange of FDA-regulated product information including:
  - Content of labeling
  - Coded information from the content of labeling (‘data elements’)
  - Wrapper for electronic listing elements
- Required with drug submissions since 10/05

SPL Release 1 (2a)

- Adopted by CDER for products as of October, 2005.
- Used to model *existing* labels
- Extremely (exceptionally!) flexible
- Constraints defined by FDA implementation guide (http://www.fda.gov/oc./datacouncil/spl.html)

An Old Example….

SINGULAIR
(MONTELUKAST SODIUM)
TABLETS, CHEWABLE TABLETS, AND ORAL GRANULES

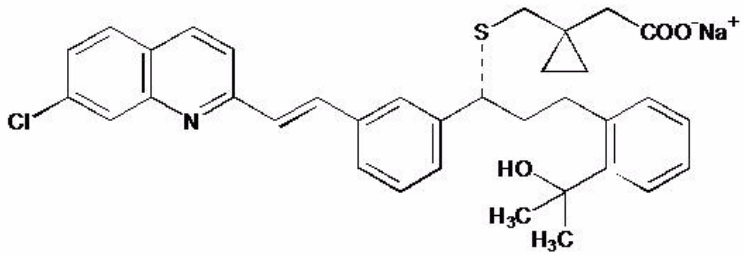
EXAMPLE DOCUMENT- NOT FOR MEDICAL REFERENCE

DESCRIPTION

Montelukast sodium, the active ingredient in SINGULAIR®*, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT$_1$ receptor.

Montelukast sodium is described chemically as [*R*-(*E*)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt.

The empirical formula is $C_{35}H_{35}ClNNaO_3S$, and its molecular weight is 608.18. The structural formula is:



Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Each 10-mg film-coated SINGULAIR tablet contains 10.4 mg montelukast sodium, which is equivalent to 10 mg of montelukast, and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

Each 4-mg and 5-mg chewable SINGULAIR tablet contains 4.2 and 5.2 mg montelukast sodium, respectively, which are equivalent to 4 and 5 mg of montelukast, respectively. Both chewable tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

XML Code Snippet

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  <code code="34090-1" codeSystem="2.16.840.1.113883.6.1"
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    SECTION"/>
  <title>CLINICAL PHARMACOLOGY</title>
  <component>
    <section>
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      <code code="34067-9" codeSystem="2.16.840.1.113883.6.1"
          codeSystemName="LOINC"/>
      <title> Mechanism of Action</title>
      <text>
        <paragraph> The cysteinyl leukotrienes (LTC<sub>4</sub>,
      LTD<sub>4</sub>, LTE<sub>4</sub>) are products of
      arachidonic acid metabolism and are released from various cells,
      including mast cells and eosinophils. These eicosanoids bind to
      cysteinyl leukotriene (CysLT)
```

Three Major Aspects to SPL Rel. 1

- Header
- Body
  - Narrative (+ images)
  - Tables
- ‘Data elements’ within body

Physician Labeling Rule (PLR)

- **The Physician Labeling Rule**
  - FR Notice Vol. 71, No. 15, 1/24/06
  - Revises 21 CFR § 201.57
- Approved labeling now has 3 parts:
  - Highlights
  - Contents
  - Full prescribing information (FPI)
- Identifies and Dates “Recent Major Changes”
  - Captures *Indications, D&A, Boxed Warning, CI and W&P*
  - Referenced in *Highlights*; margin mark in FPI
- Added date of initial US approval

Physician Labeling Rule

- Supporting information available at:

  http://www.fda.gov/cder/regulatory/physLabel/
- Supporting guidance:
  - Labeling content and format (*draft*)
  - Adverse Reactions (*final*)
  - Clinical Studies (*final*)
  - Warning and Precautions, Contraindications and Boxed Warning (*draft*)
- Fictitious labeling examples
- FAQs

Format Innovations

- Reorders and reorganizes sections
- Establishes format requirements
- *Warnings and Precautions* consolidated
- New sections
  - *Drug Interactions*
  - *Dosage Forms and Strengths*
  - *Use in Specific Populations*
  - *Patient Counseling Information*
- Formerly optional, now required
  - *Clinical Studies*
  - *Nonclinical Toxicology*

Contents and Full Prescribing Information (FPI)

- Boxed Warning
- 1 Indications & Usage
- 2 Dosage & Administration
- 3 Dosage Forms & Strengths
- 4 Contraindications
- 5 Warnings & Precautions
- 6 Adverse Reactions
- 7 Drug Interactions
- 8 Use in Specific Populations*
- 9 Drug Abuse & Dependence*
- 10 Overdosage
- 11 Description
- 12 Clinical Pharmacology*
- 13 Nonclinical Toxicology*
- 14 Clinical Studies
- 15 References
- 16 How Supplied/Storage & Handling
- 17 Patient Counseling Information

* Indicates sections with specified numbering of subsections

Sample Highlights Section

Add to a Collection

RESCRIBING INFORMATION

These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (cholinasol) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:

- **Neutropenia/agranulocytosis (5.1)**
- **Thrombotic thrombocytopenic purpura (5.1)**
- **Aplastic anemia (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Coronary Stenting (1.2)	2/200X
Dosage and Administration, Coronary Stenting (2.2)	2/200X

----------INDICATIONS AND USAGE----------

Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:

- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:

- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

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

Capsules: 50 mg (3)

----------CONTRAINDICATIONS----------

- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

----------WARNINGS AND PRECAUTIONS----------

- Neutropenia (2.4 % incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X

Example

SPL and PLR

- What is new for SPL with the implementation of the PLR
  - Recent major changes notation
  - Highlights text
  - Highlights data elements

Recent Major Changes Notation

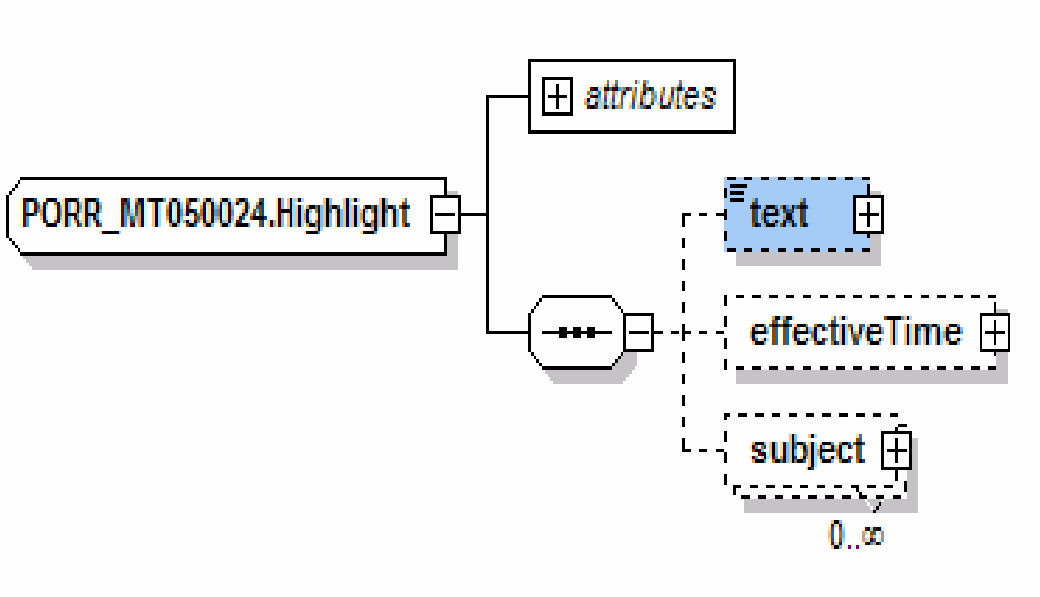
- New labeling information
  - Recent major changes tagged in the labeling text using styleCode text tag
  - <text>This is an example of text that is not changed.<content styleCode="xmChange">This is an example of text that is a recent major change</content>This is an example of changed text that is not considered a recent major change</text>

*This slide has been changed since the presentation

Highlights Text

- Text is provided for each section of the Highlights
- Sections with Highlights text
  - Box Warning
  - Recent Major Changes
  - Indications and Usage
  - Dosage and Administration
  - Dosage Forms and Strengths
  - Contraindications
  - Warnings and Precautions
  - Adverse Reactions
  - Drug Interactions
  - Use in Specific Populations
  - Patient Counseling Information

Highlights Text



Highlights Text

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    <highlight>
        <text></text>
        <effectiveTime></effectiveTime>
    </highlight>
</excerpt>
```

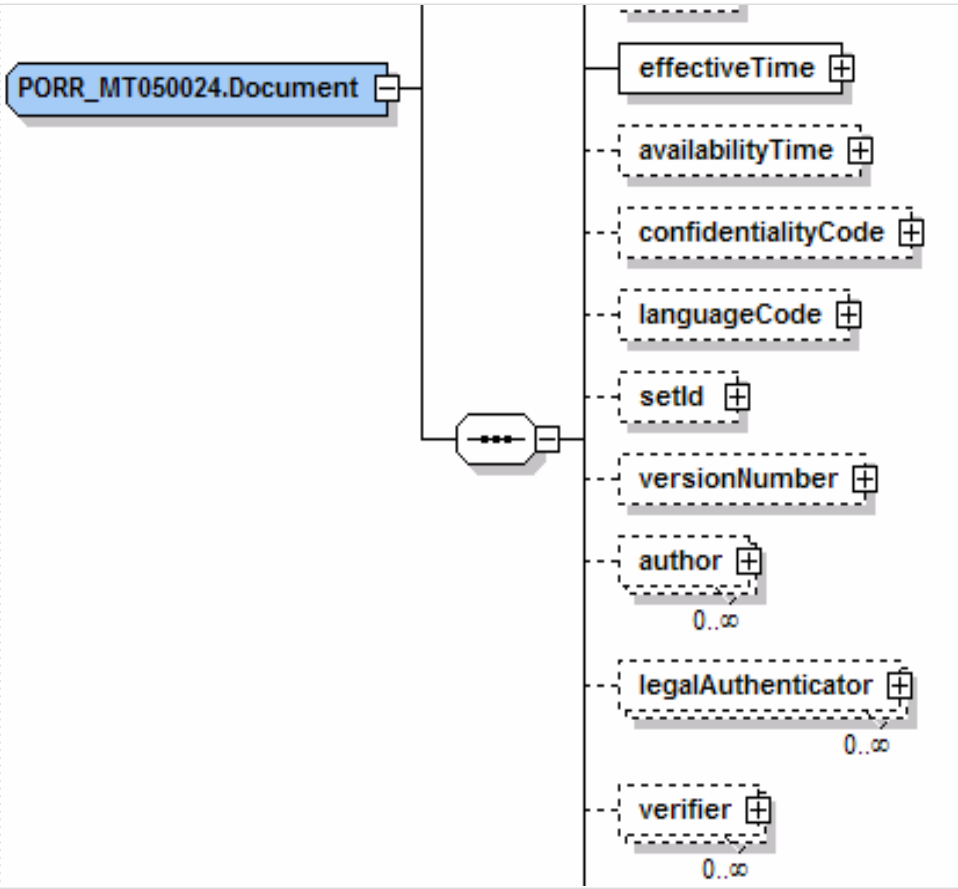
Highlights Data Elements

- Company and approval information
- Indications and usage
- Interactions and adverse reactions

Company and Approval Information

- Company information
  - Company Name
  - Labeler code
  - Phone number for reports
  - Web address for reports
- Approval information
  - Date of initial approval

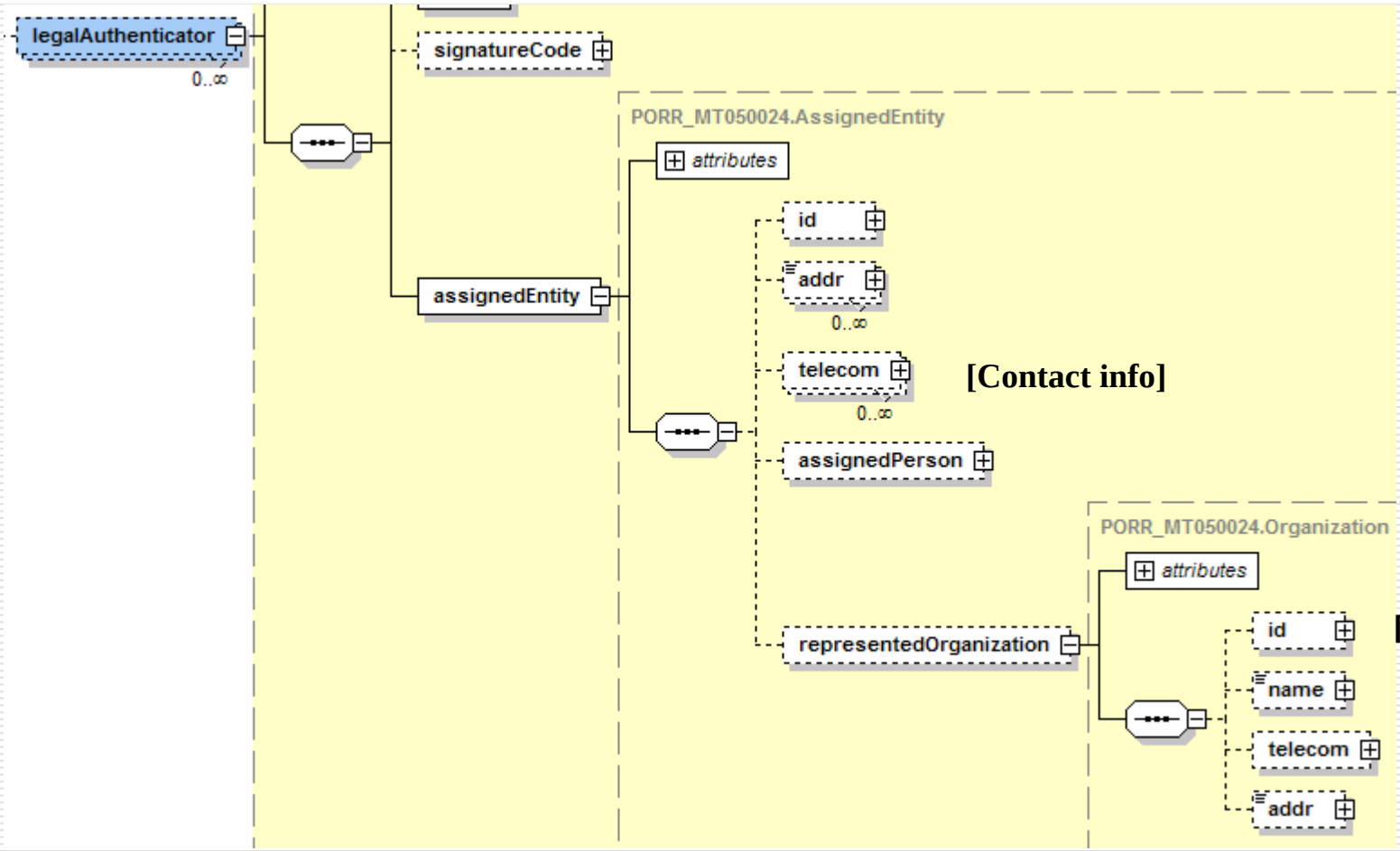
Document Level



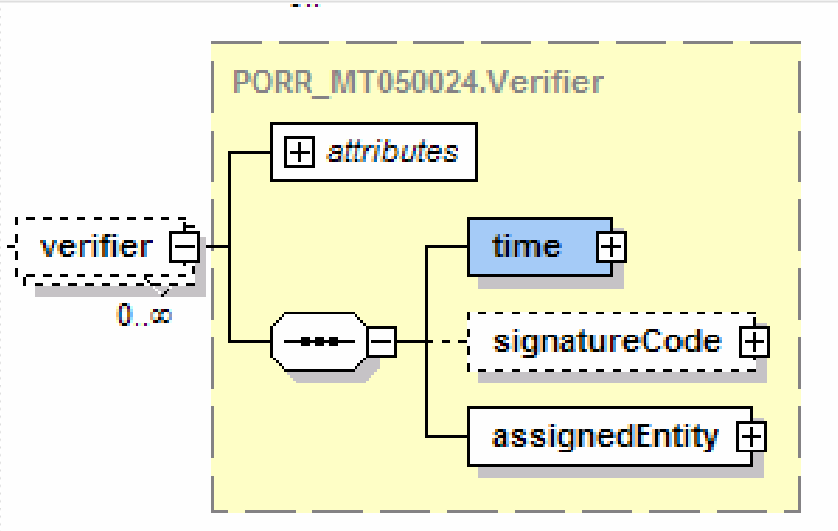
[Company information]

[Approval information]

Company Information



Approval Information



[Initial approval]

Company and Approval Information

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        <telecom>web address here</telecom>
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            <id root="2.16.840.1.113883.6.69" extension="0001" />
            <name>company name here</name>
            </representedOrganization>
    </assignedEntity>
</legalAuthenticator>
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    <assignedEntity/>
</verifier>
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[Contact info]

[Labeler code]

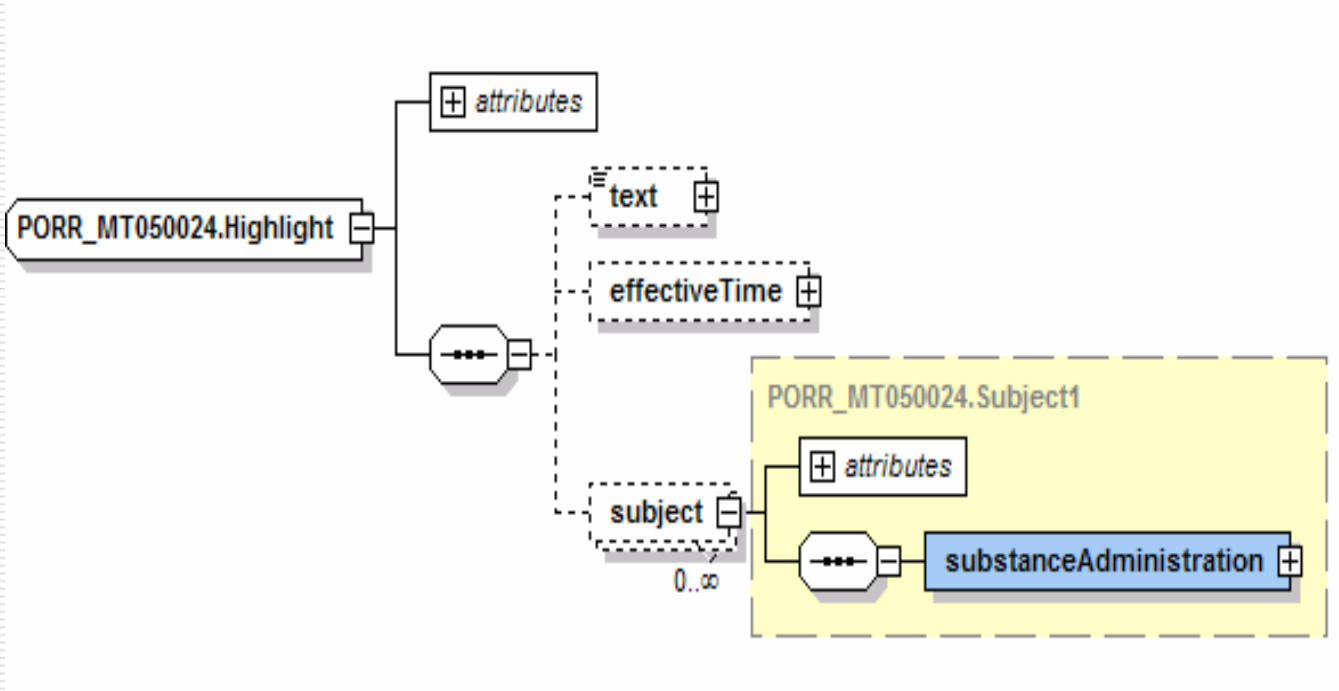
[Company name]

[Initial approval]

Indications and Usage Data Elements

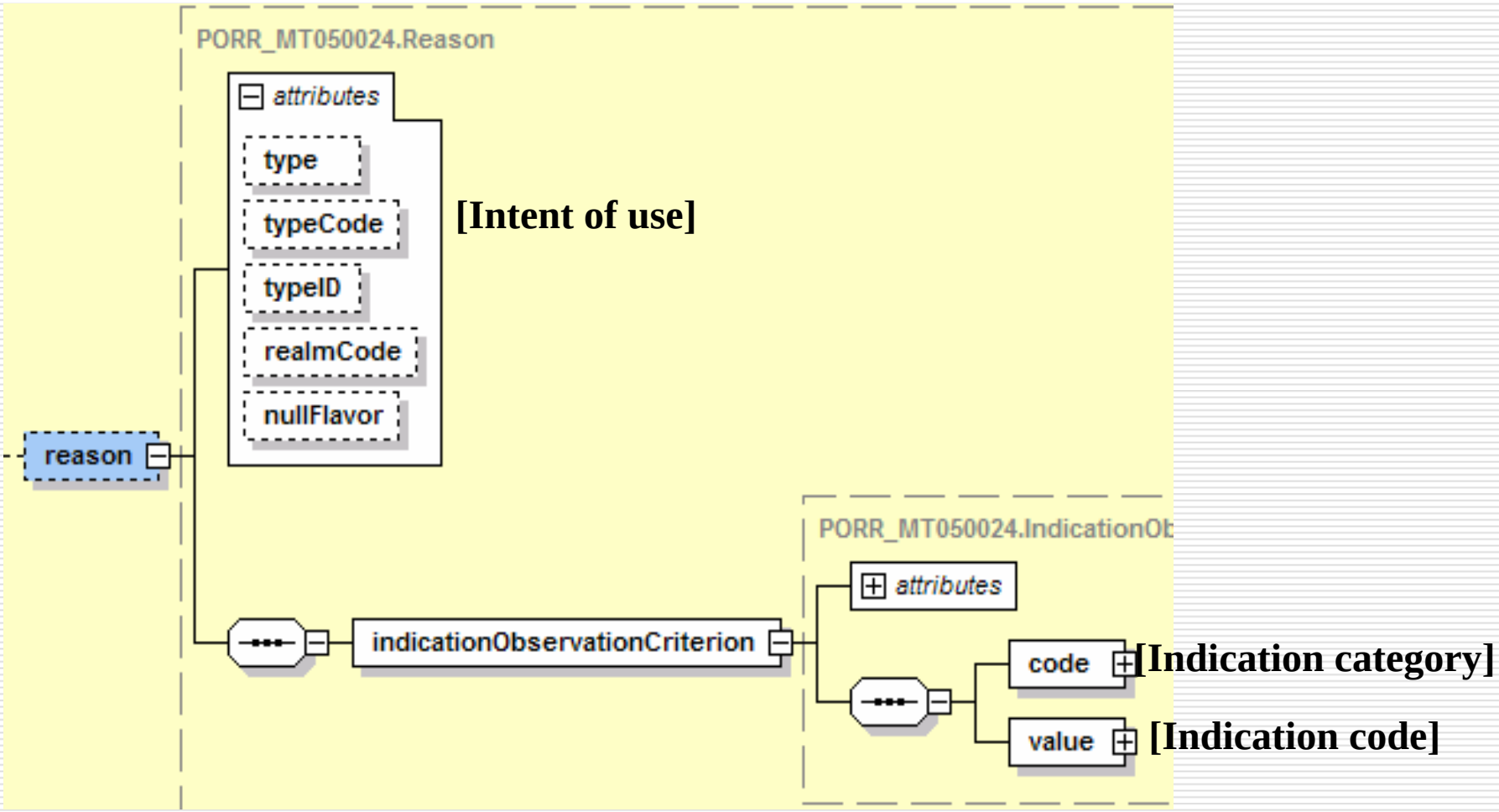
- Indication
  - Highlights text
  - Intent of use
  - Indication code
- Usage
  - Limitation of use
    - Limitation of use category
    - Precondition category
    - Precondition
  - Condition of use
    - Adjunct therapy and Screening/monitoring
    - Precondition category
    - Precondition
  - Maximum dose
    - Amount per time period
- Pharmacological class

Indications and Usage



- **reason**
- **subjectOf**
- **precondition**
- **componentOf**
- **maxDoseQuantity**

Indication


PORR_MT050024.Reason
attributes
type
typeCode
typeID
realmCode
nullFlavor
[Intent of use]
reason
PORR_MT050024.IndicationOb
attributes
indicationObservationCriterion
code
[Indication category]
value
[Indication code]

Indication

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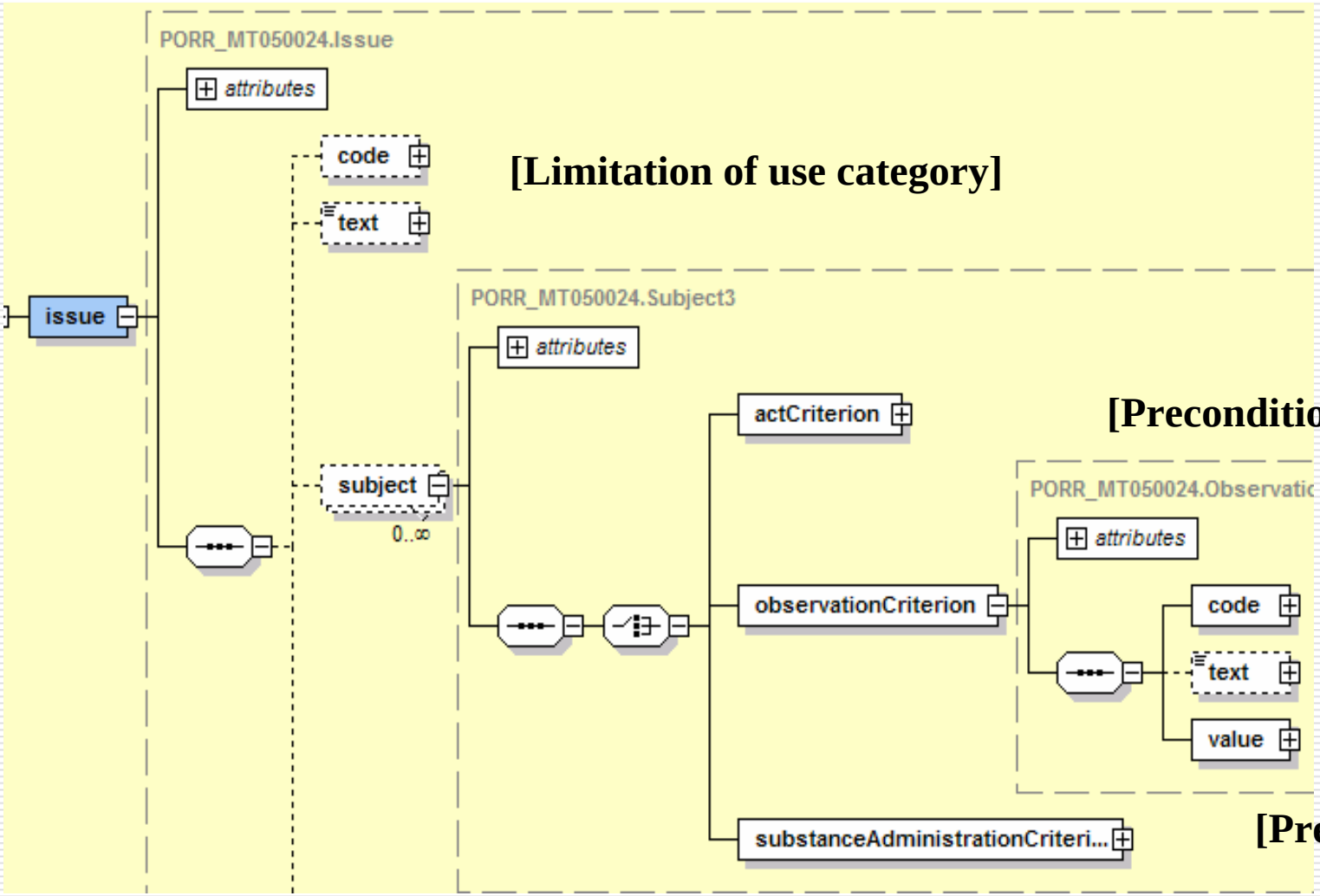
            displayName=“xxxx"/>
    </indicationObservationCriterion>
</reason>
```

[Intent of use]

[Indication category]

[Indication code]

Limitation of Use



Limitation of Use

```
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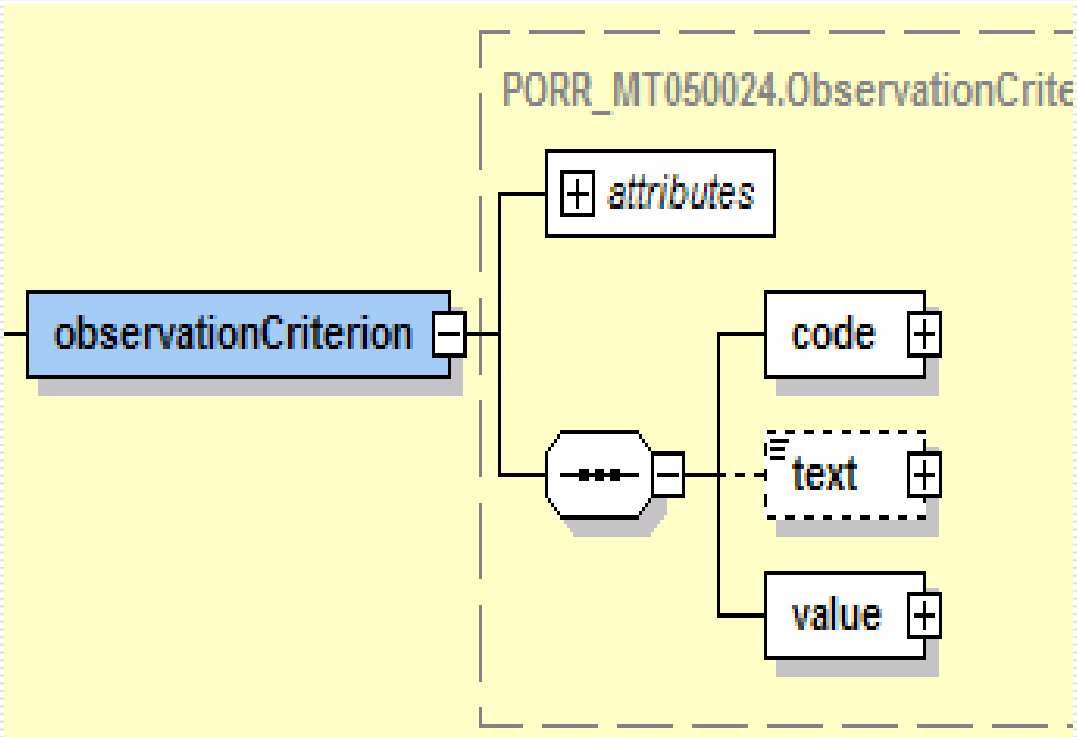
            displayName="xxxx"/>                    [Limitation of use category]
        <subject>
            <observationCriterion>
                <code code="xxx" codeSystem="2.16.840.1.113883.6.1"
                    displayName="xxxx"/>
                <value xsi:type="CE" code="xxx"          [Precondition category]
                    codeSystem="2.16.840.1.113883.3.xx.x"
                    displayName="xxx"/>
            </observationCriterion>
        </subject>
    </issue>
</subjectOf>
```

[Precondition]

Condition of Use



[Precondition category]

[Precondition]

Condition of Use

```
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            displayName="xxx"/>
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            codeSystem="2.16.840.1.113883.3.xxx"
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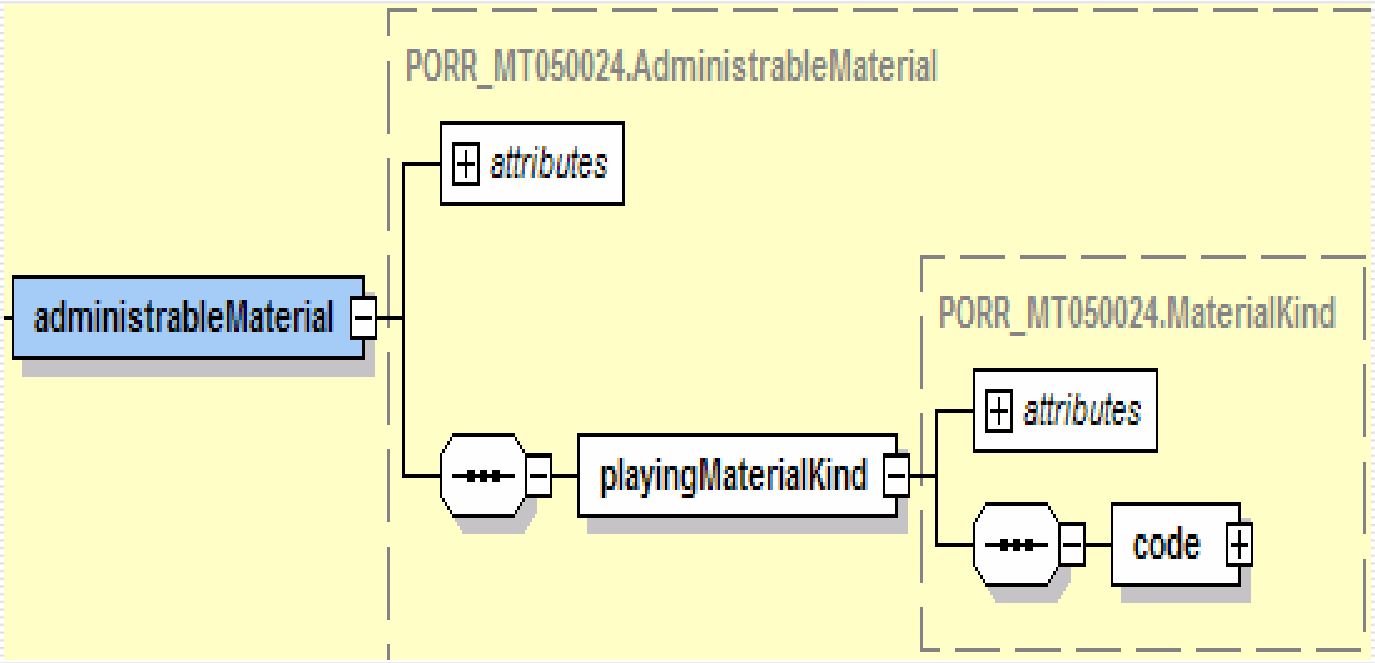
</precondition>
```

[Precondition category]

[Precondition]

Adjunct Treatment



Adjunct Treatment

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                    displayName=“xxx"/>
                </playingMaterialKind>
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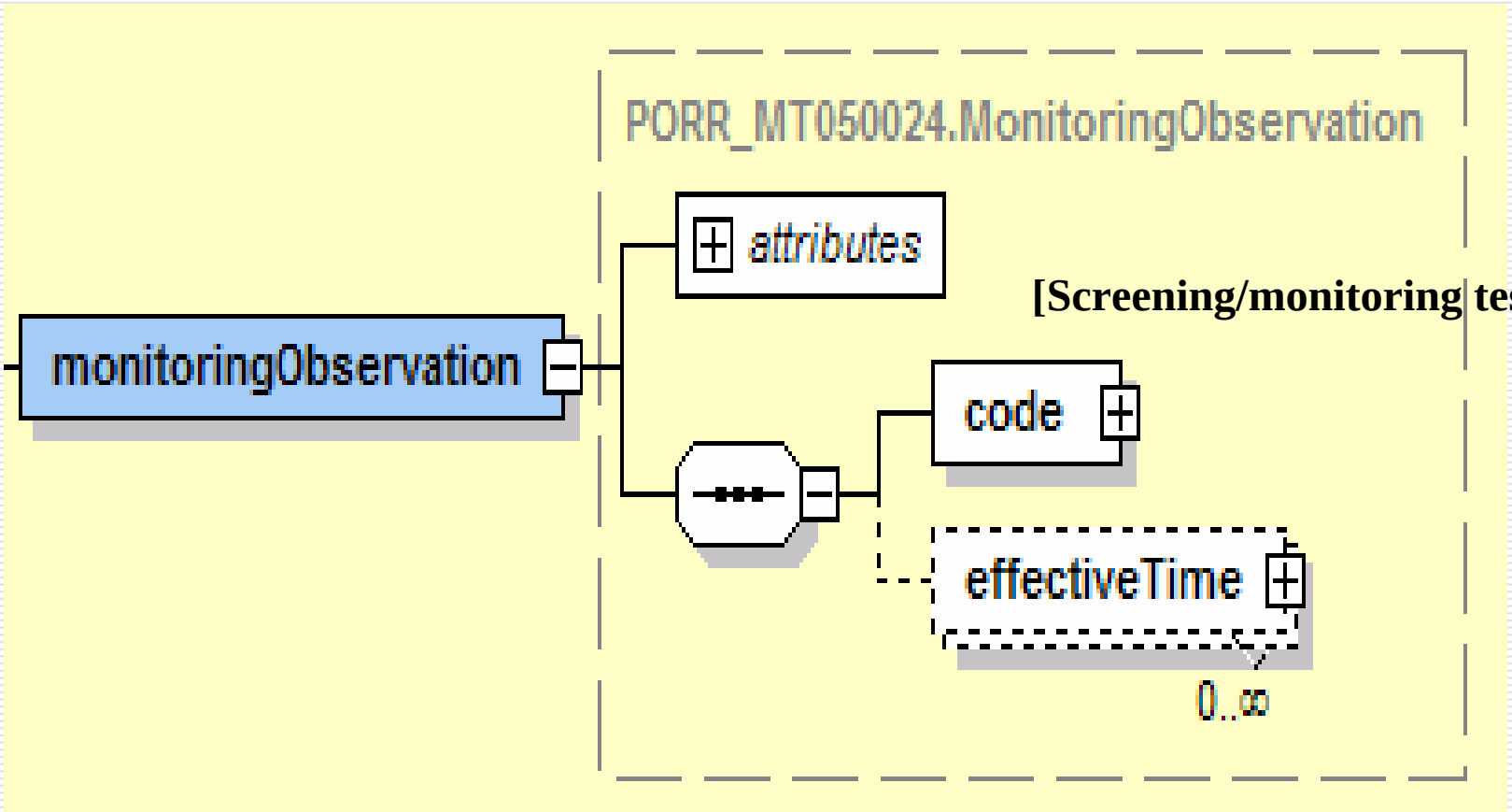
[Adjunct treatment]

Screening/Monitoring Test



Screening/Monitoring Test

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    <protocol>
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        </component>
    </protocol>
</componentOf>
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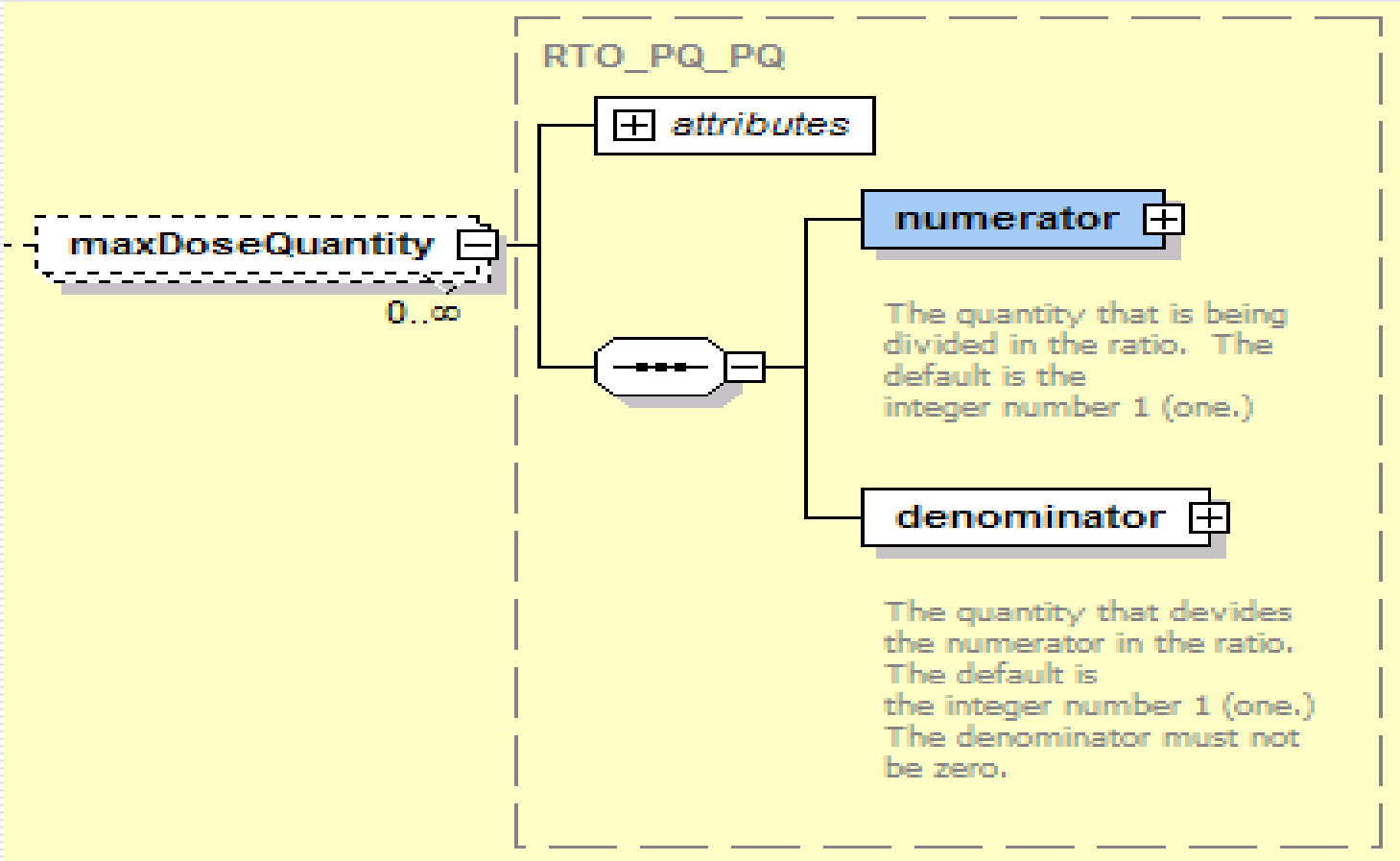
[Screening/monitoring test]

Maximum Dose



Maximum Dose

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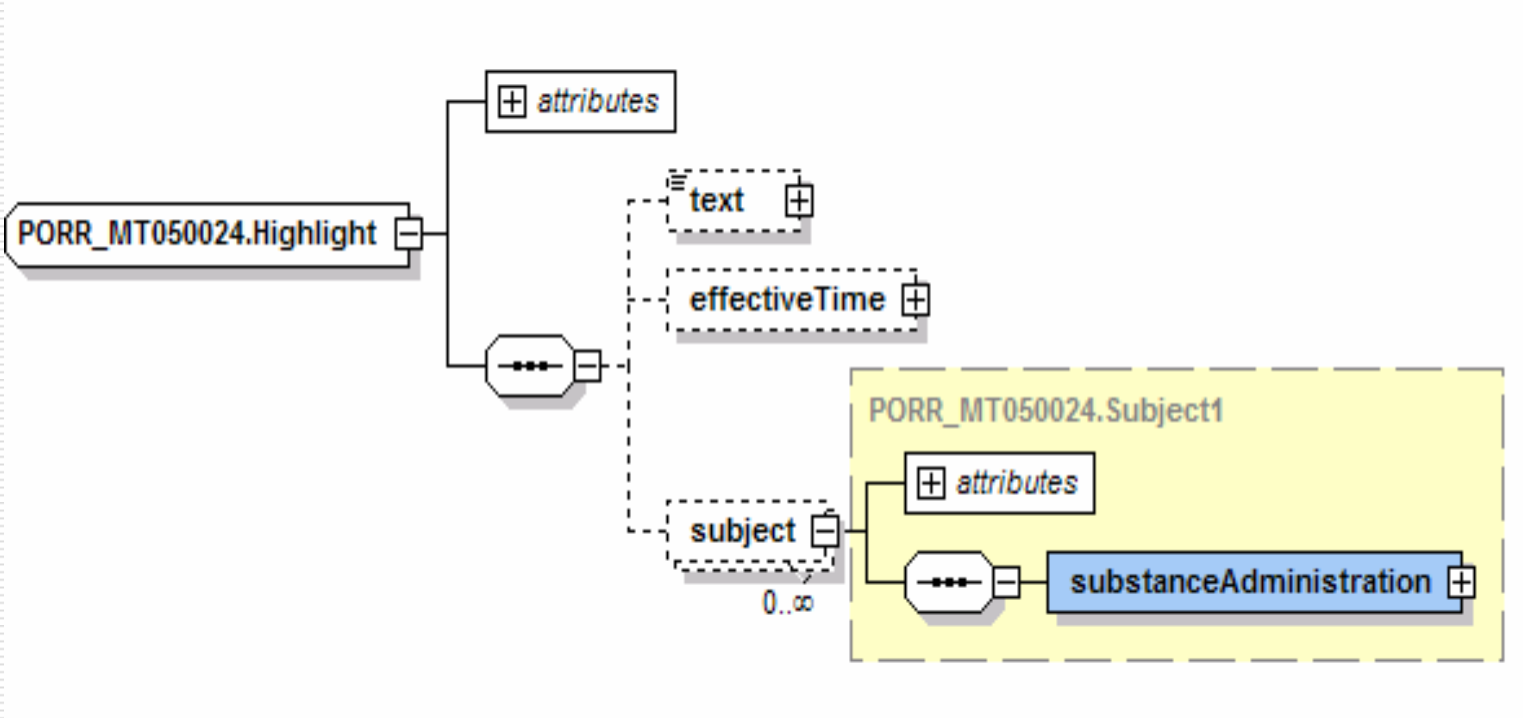
                  unit=“xxx"/>
            </maxDoseQuantity>
        </substanceAdministration>
    </subject>
</highlight>
```

Interactions and Adverse Reactions

- Interactions and Adverse Reactions
  - Highlights text
  - Contributing factor*
  - Type of consequence
  - Consequence
- Pharmacological Class

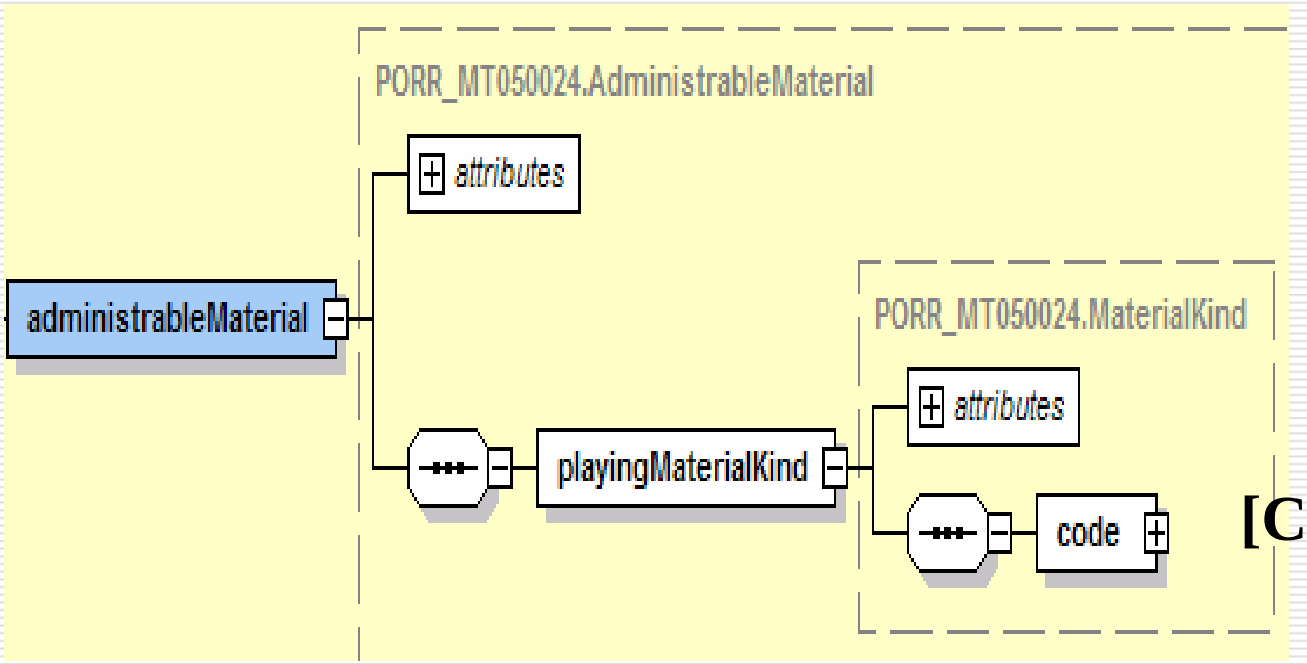
*Not applicable to Adverse Reactions

Interactions and Adverse Reactions



- **consumable**
- **subjectOf**

Contributing Factor



[Contributing factor]

Contributing Factor

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                displayName=“xxxx"/>
                </playingMaterialKind>
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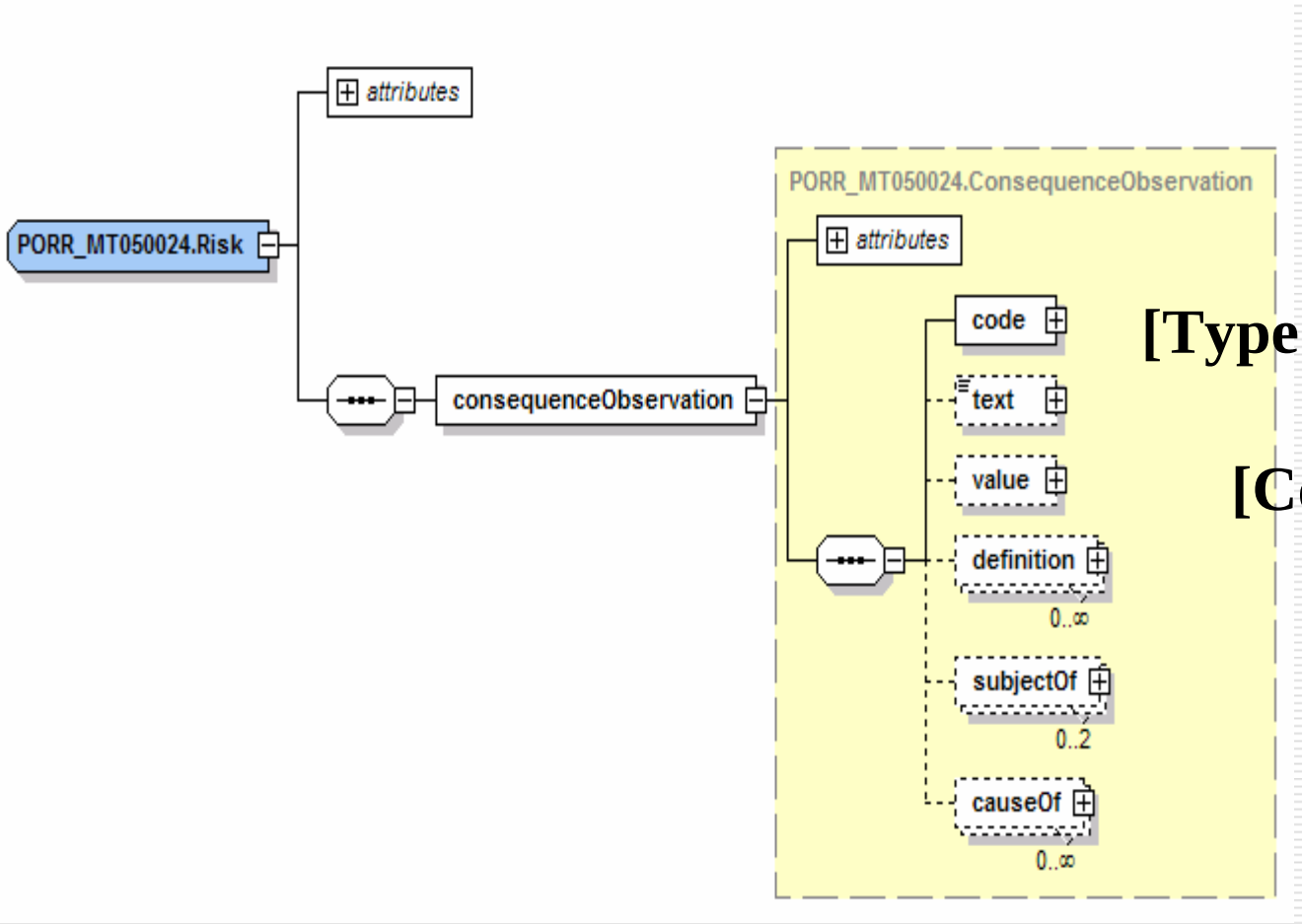
        </consumable>
    </substanceAdministrationCriterion>
  </subject>
</issue>
```

[Contributing factor]

Consequence



[Type of consequence]

[Consequence]

Consequence

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        code= “xxxx"
        codeSystem="xxx"
        displayName=“xxxx"/>
    </consequenceObservation>
</risk>
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[Type of consequence]

[Consequence]

Interaction and Adverse Reaction

```
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            <substanceAdministration>
                <subjectOf>
                    <issue>
                        <subject>
                            <substanceAdministrationCriterion></substanceAdministrationCriterion>
                        </subject>
                        <risk></risk>
                    </issue>
                </subjectOf>
            </substanceAdministration>
        </subject>
    </highlight>
</excerpt>
```

[Highlights text]

[Contributing factor]

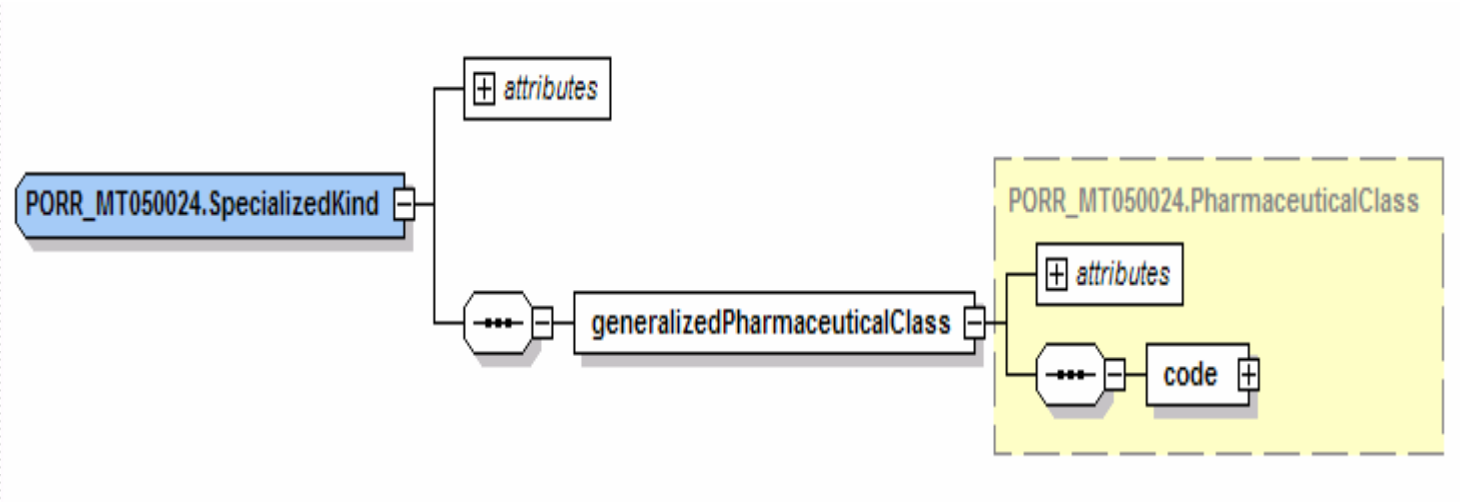
[Type of consequence]

[Consequence]

Pharmacological Class

- Important for both indications and interactions
- Pharmacological Class defined by:
  - Mechanism of action
  - Physiologic effect
  - Structural class
- Highlights data elements
  - Pharmacological class data elements under ingredient or product

Pharmacological Class



Pharmacological Class by Ingredient

```
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  <activeIngredientSubstance>
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          displayName="xxx"/>
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    </specializedKind>
  </activeIngredientSubstance>
</activeIngredient>
```

Pharmacological Class by Product

```
<manufacturedMedicine>
    <specializedKind>
        <generalizedPharmaceuticalClass>
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            codeSystem="2.16.840.1.113883.3.26.
            1.5" displayName="xxx"/>
        </generalizedPharmaceuticalClass>
    </specializedKind>
</manufacturedMedicine>
```

Terminology

- NCI Thesaurus
  - Limitation of use category
  - Sex and race
  - General contributing factors
  - Pharmacokinetic effects
  - Type of consequence
- LOINC
  - Indication category
  - Precondition category
  - Lab tests
- FDA SRS and DRLS
  - Foods and drugs
- Problem List Subset
  - Indication code
  - Medical problems
- HL7
  - Intent of use
- NDF-RT
  - Pharmacological class