HL7 Version 3 Implementation Guide: Structured Product Labeling, Release 4

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HL7 Informative Document

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Structured Product Labeling Implementation Guide for FDA Drug Establishment Registration and Drug Listing

1.   Introduction

This document provides technical conformance criteria for Structured Product Labeling (SPL) files based on the drug establishment registration and drug listing process at the United States Food and Drug Administration (FDA). Information on electronic submission may be found in guidance entitled *Providing Regulatory Submissions in Electronic Format – Establishment Registration and Drug Listing*. This document provides links to additional reference material. A link to the latest SPL schema and controlled terminology used in SPL and other technical documents and examples may be found on the FDA Data Standards Council web site at: www.fda.gov/oc/datacouncil/spl.html.

Outside the scope of this document is information on the creation of SPL for a specific product and instructions on the use of extensible mark up language (XML).

The following changes have been made from SPL Release 3 Implementation Guide:
- Clarifications
  - Character encoding
  - Proprietary and nonproprietary name
  - There may be more than one active moiety for each active ingredient
  - Clarify unit of presentation
  - Capturing content of labeling in container or carton labels
- Changes
  - Remove that element values may be changed by FDA
  - Change specifications for SPL title and Highlights "boilerplate"
  - Replace <manufacturedMedicine> with <manufacturedProduct>
  - Replace <activeIngredient> and <inactiveIngredient> with <ingredient>
  - Delete translation for units of measure for strength
  - Change unit for patch from "each" to "time"
  - Change Drug Listing data elements to Product data elements
  - Remove drug product characteristics for symbol and coating
  - Delete year of approval
  - Remove contact information for reporting adverse reactions in <author>
  - Delete telephone number and website for reporting adverse reactions
- Additions
  - Terminologies for FDA submission tracking system, Code of Federal Regulations, business registration numbers, business operations, marketing categories, marketing activity, flavors
  - Labeler and manufacturing information
  - Suffix for proprietary name
  - Manufactured product replaces <manufacturedMedicine>
  - Ingredient with class codes replaces <activeIngredient> and <inactiveIngredient>
  - Designate basis of strength
  - Business confidential attribute
  - Model number, serial number, and lot number
  - Marketing categories
  - Marketing activity
  - SPL image
  - Additional SPL characteristics

2. SPL Header

2.1. Stylesheet and schema location

Information: This information includes the location of the current stylesheet for the FDA view of the SPL and the location of the current schema.

Terminology: None

SPL location: This information is in the beginning of the SPL file.

XML details: The instructions at the start of SPL are the same for every SPL document (the encoding set is dependent on the character encoding used in the SPL) and are in the following form:

<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet href="http://www.accessdata.fda.gov/spl/stylesheet/spl.xsl" type="text/xsl"?>
<document xmlns="urn:hl7-org:v3" xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
xsi:schemaLocation="urn:hl7-org:v3 http://www.accessdata.fda.gov/spl/schema/spl.xsd">

2.2. SPL identifying information

Information: This information provides basic information for identifying the SPL document.

Terminology: The SPL document types are from LOINC. This code provides information about the subject matter of the document e.g., prescription animal drug.

SPL location: This information is in the beginning of the SPL file.

XML details: The identifying information is in the following form:

<id root="*GUID for the document*"/>
<code code="*code for the document type*" codeSystem="2.16.840.1.113883.6.1" displayName="
display name for document type"/>
<title>*title for the document*</title>
<effectiveTime value="*yyyymmdd*"/>
<setId root="*GUID for the set of documents*"/>
<versionNumber value="*version number*"/>

- The <id root> is a Globally Unique Identifier (GUID) and is unique for each version of the document. Letters used in a GUID are lower case.
- The <code> is the LOINC code which provides information on the document type.
- The <title> data element is used for the title for the document, if necessary. Images are not included in the title. Multiple lines may be used in the title with each line separated by the line break <br/> tag. (note: all titles can also be as follows: <title mediaType="text/x-hl7-title+xml">).
- The <effectiveTime> provides a date reference to the SPL version including the year, month and day as yyyymmdd.
- The <setId> is a GUID and is a unique identifier for the document that remains constant through all versions/revisions of the document.

- The <versionNumber> is an integer greater than zero that provides a sequence to the versions of the document.

2.3.   Labeler and manufacturing information

Information: The labeler and manufacturing information includes details on the businesses responsible for the product. This includes the labeler and registrant and establishments involved in manufacturing..

Terminology: The National Drug Code (NDC) and National Health Related Items Code (NHRIC) Labeler Code comes from the FDA NDC System. The Data Universal Numbering System Number (DUNS Number) comes from Dun and Bradstreet DUNS Number system. Business operations come from the National Cancer Institute Thesaurus (NCIt). HL7 confidentiality code "B" is for business confidential information. ISO 3166-1 is used for the country codes. Postal service provides the two letter state codes for US addresses. For non US addresses, no specific terminologies are defined. Telephone number structure follows the Internet Engineering Steering Group RFC 2806.

Location in SPL: This information is in the SPL header

XML details: The labeler and manufacturing information is represented in the <author> child of the <document> element. The labeler is included under <representedOrganization> which is a child of <author>. The registrant is an <assignedOrganization> of the labeler. An establishment is an <assignedOrganization> related the registrant. A US agent and importer are <assignedOrganization> of an establishment. The text for displayName is case insensitive.

The relationship between the labeler, manufacturer and establishment is as follows:

```
<author>
   <assignedEntity>
      <representedOrganization>
         …..labeler
      <assignedEntity>
         <assignedOrganization>
               …..registrant
               <assignedEntity>
                  <assignedOrganization>
                     …..establishment
                     <assignedEntity>
                        <assignedOrganization>
                           …..US agent
                     <assignedEntity>
                        <assignedOrganization>
                           …..importers
```

The following is representative coding for <author>:

```
<document>
   …..
   …..
  <author>
     <time/>
     <assignedEntity>
        <representedOrganization>
           <id extension="DUNS Number" root="1.3.6.1.4.1.519.1"/>
           <id extension="NDC Labeler Code" root="2.16.840.1.113883.6.69"/>
           <name>Labeler business name</name>
           <contactParty>
              <addr>
                 <streetAddressLine>address</streetAddressLine>
                 <city>city</city>
                 <state>state</state>
                 <postalCode>postal code</postalCode>
                 <country>country</country>
              </addr>
                 <telecom value="tel: contact telephone number"/>
                 <telecom value="mailto: email address"/>
                 <contactPerson>
                    <name>contact name for labeler</name>
                 </contactPerson>
           </contactParty>
           <assignedEntity>
              <confidentialityCode code="confidential code "B" if necessary"
              codeSystem="2.16.840.1.113883.5.25"/>
              <assignedOrganization>
                 <id extension="DUNS number" root="1.3.6.1.4.1.519.1"/>
                 <name>Registrant business name</name>
                 <contactParty>
                    <addr>
                       <streetAddressLine>address</streetAddressLine>
                       <city>city</city>
                       <state>state</state>
                       <postalCode>postal code</postalCode>
                       <country>country</country>
                    </addr>
                       <telecom value="tel: contact telephone number"/>
                       <telecom value="mailto: email address"/>
                       <contactPerson>
                          <name>contact name for registrant</name>
                       </contactPerson>
                 </contactParty>
                 <assignedEntity>
                    <confidentialityCode code="confidential code "B" if necessary"
                    codeSystem="2.16.840.1.113883.5.25"/>
```

```
<assignedOrganization>
    <id extension="DUNS number" root="1.3.6.1.4.1.519.1"/>
    <id extension="FDA establishment identifier"
    root="2.16.840.1.113883.4.82"/>
    <name>Establishment name</name>
    <addr>
        <streetAddressLine>address</streetAddressLine>
        <city>city</city>
        <state>state</state>
        <postalCode>postal code</postalCode>
        <country>country</country>
    </addr>
    <contactParty>
        <addr>
            <streetAddressLine>street address</streetAddressLine>
            <city>city </city>
            <state>state</state>
            <postalCode>postal code</postalCode>
            <country>country</country>
        </addr>
        <telecom value="tel: telephone number"/>
        <telecom value="mailto: email address"/>
        <contactPerson>
            <name>Contact person name</name>
        </contactPerson>
    </contactParty>
    <assignedEntity>
        <assignedOrganization>
            <id extension="DUNS Number" root="1.3.6.1.4.1.519.1"/>
            <name>US agent business name</name>
            <telecom value="tel: telephone number"/>
            <telecom value="mailto: email address"/>
        </assignedOrganization>
        <performance>
            <actDefinition>
                <code code="US agent business operation code"
                codeSystem="2.16.840.1.113883.3.26.1.1" displayName="display
                name"/>
            </actDefinition>
        </performance>
    </assignedEntity>
    <assignedEntity>
        <assignedOrganization>
            <id extension="DUNS number" root="1.3.6.1.4.1.519.1"/>
            <name>importer business name</name>
            <telecom value="tel: telephone number"/>
            <telecom value="mailto: email address"/>
```

```
                              </assignedOrganization>
                              <performance>
                                 <actDefinition>
                                    <code code="Importation business operation code"
                                    codeSystem="2.16.840.1.113883.3.26.1.1" displayName="display
                                    name"/>
                                 </actDefinition>
                              </performance>
                           </assignedEntity>
                        </assignedOrganization>
                        <performance>
                           <actDefinition>
                              <code code="establishment business operation code"
                              codeSystem="2.16.840.1.113883.3.26.1.1" displayName="display
                              name"/>
                           </actDefinition>
                        </performance>
                     </assignedEntity>
                  </assignedOrganization>
               </assignedEntity>
            </representedOrganization>
         </assignedEntity>
      </author>
…..
…..
</document>
```

3.   SPL Body

Information: The SPL body includes the product data elements and the content of labeling (e.g., Full Prescribing Information (FPI) and Highlights text or Drug Facts or equivalent and other information on a container or carton label).

Terminology: There is no controlled terminology for this information.

XML details: In addition to SPL header information, the <document> element contains a required <component> which contains the <structuredBody> element. The <component><structuredBody> tags enclose the body of the SPL document; the body consists of the data elements and the human readable content of labeling (text, tables and figures).

3.1.   Product data elements

Information: The listing data elements for products are provided.

Terminology: FDA terminology is used for the proprietary, non proprietary and ingredient name. FDA NDC System is used for identifiers for the NDC Labeler Code (4 or 5 digit code (e.g., 0001 or 11111)), NDC Product Code (8 or 9 characters beginning with the NDC Labeler Code separated by a hyphen from the product segment of the code (e.g., 0001-0001 or 11111-001 or 11111-0001)) and NDC Package Code (10 characters beginning with the NDC Product Code separated by a hyphen from the package segment of the code (e.g., 0001-0001-01, 11111-001-01 or 11111-0001-1)). It is also used for identifiers for the NHRIC Labeler Code (4 or 5 digit code), NHRIC Product Code (8, 9 or 10 digits beginning with the NHRIC Labeler Code separated by a hyphen from the product segment of the code and NHRIC Package Code (10 digits beginning with the NDC Product Code separated by a hyphen from the package segment of the code). ISBT-128 site and product codes are for licensed minimally manipulated cell products. FDA Substance Registration System (SRS) is used for the ingredient and active moiety Unique Ingredient Identifier (UNII). The FDA submission tracking system is used for application numbers. The Code of Federal Regulations is used for monograph citations. The National Cancer Institute Thesaurus (NCIt) is used for dosage form, product characteristics, DEA schedule, unit of presentation, route of administration and equivalent codes. The Unified Codes for Units of Measure (UCUM) is used for the unit of measure. HL7 confidentiality code "B" is for business confidential information.

SPL location: The product data elements are in the first section of the SPL Body.

XML details: The product data elements includes the product codes, proprietary and non proprietary name, dosage form, ingredient and active moiety name, ingredient identifier, ingredient strength, package quantity, type and code, marketing category, marketing status, dosage form appearance, DEA schedule, and route of administration.

The beginning of the product data elements section is as follows:

```
<component>
   <structuredBody>
      <component>
         <section>
            <id root="GUID"/>
            <code code="48780-1" codeSystem="2.16.840.1.113883.6.1" displayName="SPL
            listing data elements section"/>
            <effectiveTime value="yyyymmdd"/>
            <subject>
                  <manufacturedProduct>
```

3.1.1.   Product

The product consists of a product code, proprietary and non proprietary name, and dosage form. These are children of <manufacturedProduct>. The proprietary name is the name as it appears on the label divided between <name> and <suffix>. The <name> is the initial portion of the proprietary name describing the ingredients without any other descriptors including trademarks and dosage forms. If necessary, <suffix> is used for descriptors such as "extended release". When using the <suffix>, a space after the proprietary name is added as necessary. If there is no proprietary name,

the non proprietary name is used without any descriptors. The dosage form is described in <formCode>. The <genericMedicine><name> is the non proprietary name of the product. Device type codes and descriptions use <asSpecializedKind>.

The following is for a drug product:

```
<subject>
  <manufacturedProduct>
    <manufacturedProduct>
      <code code="NDC Product Code" codeSystem="2.16.840.1.113883.6.69"/>
      <name>proprietary name <suffix>suffix to name</suffix></name>
      <formCode code="dose form code" codeSystem="2.16.840.1.113883.3.26.1.1"
      displayName="display name"/>
      <asEntityWithGeneric>
        <genericMedicine>
          <name>non proprietary name</name>
        </genericMedicine>
      </asEntityWithGeneric>
```

The following is for referencing information already submitted for a source drug:

```
<manufacturedProduct>
        <code code="NDC Product Code" codeSystem="2.16.840.1.113883.6.69"/>
        <name>proprietary name <suffix>suffix to name</suffix></name>
        <asEquivalentEntity classCode="EQUIV">
          <code code="C64637" codeSystem="2.16.840.1.113883.3.26.1.1"
          <definingMaterialKind>
            <code code="source NDC Product Code"
            codeSystem="2.16.840.1.113883.6.69"/>
          <definingMaterialKind>
        </asEquivalentEntity>
```

The following is for a device:

```
<subject>
  <manufacturedProduct>
    <manufacturedProduct>
      <code code="NHRIC Product Code" codeSystem="2.16.840.1.113883.6.69"/>
      <name>proprietary name <suffix>suffix to name</suffix></name>
      <asSpecializedKind>
        <generalizedMaterialKind>
          <code code="device code" codeSystem="device code system OID"
      displayName="device display name"/>
        </generalizedMaterialKind>
      </asSpecializedKind>
      <asSpecializedKind>
        <generalizedMaterialKind>
```

```
            <code>
                <originalText>device description</originalText>
            </code>
        </generalizedMaterialKind>
    </asSpecializedKind>
```

When products have more than one part, each part is described under <partProduct>. The total amount of the part in the product is included as follows:

```
<part>
  <quantity>
    <numerator value="total amount of part in product" unit="UCUM code"/>
    <denominator value="1"/>
  </quantity>
  <partProduct>
```

3.1.2.   Active ingredient

The active ingredient includes the active ingredient class code, ingredient name, identifier and strength, the active moiety name(s) and identifier and a reference drug name and identifier. The element <ingredient> is a child of <manufacturedProduct>. The class code for active ingredient is dependent on the basis of the strength. If the basis of strength is the active ingredient, the class code is "ACTIB". If the basis of strength is the active moiety, the class code is "ACTIM". If the basis of strength is a reference drug, the class code is "ACTIR". The strength is represented as a numerator and denominator. The UCUM code is used for the unit of measure. The UCUM code for a unit that is an "each" is "1" Examples of "each" is in the table below.

```
<ingredient classCode="class code including basis of strength">
        <quantity>
                <numerator value="value" unit="UCUM code"/>
                <denominator value="value" unit=" UCUM code"/>
        </quantity>
        <ingredientSubstance>
                <code code="UNII " codeSystem="2.16.840.1.113883.4.9"/>
                <name>active ingredient name</name>
                    <activeMoiety>
                      <activeMoiety>
                            <code code="UNII" codeSystem="2.16.840.1.113883.4.9"/>
                            <name>active moiety name</name>
                      </activeMoiety>
                    </activeMoiety>
                        <asEquivalentSubstance>
                          <definingSubstance>
                                <code code="UNII" codeSystem="2.16.840.1.113883.4.9"/>
                                <name>reference drug  name</name>
                          </definingSubstance>
```

```
            <asEquivalentSubstance>
        </ingredientSubstance>
</ingredient>
```

In most cases, the strength used is that for a single dose following the conventions in the table 1. In the table, an example of "weight" is milligrams, an example of "volume" is milliliter, an example of "time" is hour, and an example of "each" is tablet)

Table 1: Conventions for expressing strength

Product	Numerator unit	Denominator unit
Oral solid	Weight	Each
Oral liquid	Weight	Volume
Oral powder for reconstitution with a known volume	Weight	Volume
Oral powder for reconstitution with a variable volume	Weight	Each
Suppository	Weight	Each
Injection liquid	Weight	Volume
Injection powder for reconstitution with a known volume	Weight	Volume
Injection powder for reconstitution with a variable volume	Weight	Each
Inhaler powder	Weight	Each
Inhaler liquid	Volume	Each
Inhaler blister	Weight	Each
Topical cream or ointment	Weight	Weight
Topical gel or lotion	Weight	Volume
Transdermal patch	Weight	Time
Bulk liquid	Weight	Volume
Bulk solid	Weight	Weight

3.1.3.   Inactive ingredient

The inactive ingredient includes the inactive ingredient class code, ingredient name, identifier, and strength. The element <ingredient> is a child of <manufacturedProduct>. The class code for inactive ingredient is "IACT". The strength, if needed, is represented as a numerator and denominator and is described using UCUM units of measure. If the inactive ingredient is confidential, the element <ingredient> includes <confidentialityCode code="B" codeSystem="2.16.840.1.113883.5.25"/>.

```
<ingredient classCode='"IACT">
        <confidentialityCode code="B" codeSystem="2.16.840.1.113883.5.25"/>
        <quantity>
                <numerator value="value" unit="UCUM code"/>
                <denominator value="value" unit="UCUM code"/>
        </quantity>
        <ingredientSubstance>
                <code code="UNII" codeSystem="2.16.840.1.113883.4.9"/>
                <name>inactive ingredient name</name>
        </ingredientSubstance>
</ingredient>
```

3.1.4. Device ingredient

Ingredient included in devices includes the ingredient class code, ingredient name, identifier, and strength. The element <ingredient> is a child of <manufacturedProduct>. The class code for ingredient is "INGR". The strength, if needed, is represented as a numerator and denominator and is described using UCUM units of measure.

```
<ingredient classCode='"INGR">
     <quantity>
             <numerator value="value" unit="UCUM code"/>
             <denominator value="value" unit="UCUM code"/>
     </quantity>
     <ingredientSubstance>
             <code code="UNII" codeSystem="2.16.840.1.113883.4.9"/>
             <name>ingredient name</name>
     </ingredientSubstance>
</ingredient>
```

3.1.5. Packaging

The packaging includes the quantity of product in the package and the package type and NDC Package Code. The packaging is described using a combination of <quantity> and <containerPackagedProduct> which are children of <manufacturedProduct><asContent>. If the UCUM code is "1", then it is translated using FDA units of presentation from the NCIt. Examples of Unit of presentation are the "each" is in table 1.

For example,

```
<asContent>
  <quantity>
    <numerator value="value" unit=" UCUM code">
      <translation code="value" codeSystem="2.16.840.1.113883.3.26.1.1" displayName="display
      name"/>
    </numerator>
       <denominator value="1"/>
  </quantity>
  <containerPackagedProduct>
      <code code="NDC Package Code" codeSystem="2.16.840.1.113883.6.69"/>
      <formCode code="value" codeSystem="2.16.840.1.113883.3.26.1.1" displayName="display
      name"/>
   </containerPackagedProduct>
</asContent>
```

The data element <asContent> can be nested to represent packaging from the unit of use package to the outside retail packages, if any. When package includes different drug products, the <part> and <partManufacturedProduct> is used in addition to <quantity> and <containerPackagedProduct>.

3.1.6. Device accessories and components

When device products are used together but packaged separately, the data element <asPartOfAssembly> is used to identify the other product.

```
<asPartOfAssembly>
   <wholeProduct>
      <part>
         <partProduct>
            <code code="product code for other product" codeSystem="code system OID"/>
            <name>display name for other product</name>
         </partProduct>
      </part>
   </wholeProduct>
</asPartOfAssembly>
```

When device products are packaged together in a kit, the data element <wholeProduct> is used to identify the kit.

```
<asPartOfAssembly>
   <wholeProduct>
      <code code="product code for kit" codeSystem="code system OID"/> <name>display name
         for kit</name>
   </wholeProduct>
</asPartOfAssembly>
```

3.1.7. Device model, lot and serial number

The <instanceOfKind> is used to describe a device model number and a specific lot number or serial number. The <quantity> captures number of units for the lot or serial number. Serial numbers have a <quantity value="1"/> and lot numbers have a <quantity> value that is greater than 1.

```
<instanceOfKind>
   <deviceInstance>
      <id extension="serial number or lot number"/>
      <quantity value="Number of units in a lot number or "1" if a serial number"/>
      <manufacturerModelName>model number</manufacturerModelName>
```

3.1.8. Marketing category

The marketing category provides information on the product related to marketing regulations. For example, a drug product marketed under an approved application use the <id> to provide the application number <id extension> and document tracking system under <id root> and <code> for the marketing category. In another example, drugs marketed under a monograph provide the regulatory citation for the monograph <id extension> and the Code of Federal Regulations under <id root>. If there is no application number or monograph citation, the id element is omitted.

```
<subjectOf>
   <approval>
      <id extension="application or monograph number" root="FDA document tracking system
      OID or CFR OID"/>
      <code code="code for marketing category" codeSystem="2.16.840.1.113883.3.26.1.1"
      displayName="display name"/>
      <author>
         <territorialAuthority>
            <territory>
               <code code="USA" codeSystem="2.16.840.1.113883.5.28"/>
            </territory>
         </territorialAuthority>
      </author>
   </approval>
</subjectOf>
```

3.1.9. Marketing status

The marketing status provides information on when the product is on or off the market. The <code> is marketing. The status of the product is described in the <statusCode> as either "active" for being on the market or "completed" when marketing is done the drug is no longer going to be available on the market. The date when the product is on or off the market is included in the <effectiveTime>. The date when the product is on the market is characterized by the <low value>.

```
<subjectOf>
   <marketingAct>
      <code code="C53292" codeSystem="2.16.840.1.112883.3.26.1.1"/>
      <statusCode code="active"/>
      <effectiveTime>
         <low value="date when on the market"/>
      </effectiveTime>
   </marketingAct>
</subjectOf>
```

The date off the market such as the expiration date of the last lot released to the market is characterized by the <high value>.

```
<subjectOf>
   <marketingAct>
```

```
<code code="C53292" codeSystem="2.16.840.1.112883.3.26.1.1"/>
<statusCode code="completed"/>
    <low value="date when the product is on the market"/>
    <high value="date when the product is going to be off the market"/>
</effectiveTime>
  </marketingAct>
</subjectOf>
```

3.1.10.   DEA schedule

The DEA schedule, when applicable, is described under <policy> which is a child of <subjectOf> which is a child of <manufacturedProduct> as illustrated in the following example of a drug that is schedule II.

```
<subjectOf>
      <policy classCode="DEADrugSchedule">
            <code code="DEA code" codeSystem="2.16.840.1.112883.3.26.1.1"
            displayName="display name"/>
      </policy>
</subjectOf>
```

3.1.11.   Product characteristics

Product characteristics include dosage form appearance. Dosage form characteristics are used to describe the appearance of the drug product and include the color, score, shape, size, imprint code and image. These are all under <subjectOf> which is a child of <manufacturedProduct>. Product characteristics also include product flavor and what the product contains.

```
<subjectOf>
      <characteristic classCode="OBS">
            <code code="SPLCOLOR" codeSystem="2.16.840.1.113883.1.11.19255"/>
            <value code="code for color" codeSystem="2.16.840.1.113883.3.26.1.1"
            displayName="display name for color" xsi:type="CE">
                  <originalText>optional original color description text</originalText>
            </value>
      </characteristic>
</subjectOf>
<subjectOf>
      <characteristic classCode="OBS">
            <code code="SPLSCORE" codeSystem="2.16.840.1.113883.1.11.19255"/>
            <value value="value for score" xsi:type="INT"/>
      </characteristic>
</subjectOf>
<subjectOf>
      <characteristic classCode="OBS">
            <code code="SPLSHAPE" codeSystem="2.16.840.1.113883.1.11.19255"/>
```

```
                  <value code="code for shape" codeSystem="2.16.840.1.113883.3.26.1.1"
                  displayName="display name for shape" xsi:type="CE">
                  <originalText>optional original shape description text</originalText>
                  </value>
            </characteristic>
      </subjectOf>
      <subjectOf>
            <characteristic classCode="OBS">
                  <code code="SPLSIZE" codeSystem="2.16.840.1.113883.1.11.19255"/>
                  <value unit="mm" value="value for size in mm" xsi:type="PQ"/>
            </characteristic>
      </subjectOf>
      <subjectOf>
            <characteristic classCode="OBS">
                  <code code="SPLIMPRINT" codeSystem="2.16.840.1.113883.1.11.19255"/>
                  <value xsi:type="ST">imprint separated by semicolon</value>
            </characteristic>
      </subjectOf>
      <subjectOf>
            <characteristic classCode="OBS">
                  <code code="SPLFLAVOR" codeSystem="2.16.840.1.113883.1.11.19255"/>
                  <value code="code for flavor" codeSystem="2.16.840.1.113883.3.26.1.1"
                  displayName="display name for flavor" xsi:type="CE">
                        <originalText>optional original flavor description text</originalText>
                  </value>
            </characteristic>
      </subjectOf>
      <subjectOf>
            <characteristic classCode="OBS">
                  <code code="SPLCONTAINS" codeSystem="2.16.840.1.113883.1.11.19255"/>
                  <value code="code for contains" codeSystem="2.16.840.1.113883.3.26.1.1"
                  displayName="display name for contains" xsi:type="CE">
                  <originalText>optional original description text</originalText>
                  </value>
            </characteristic>
      </subjectOf>
      <subjectOf>
            <characteristic classCode="OBS">
                  <code code="SPLIMAGE" codeSystem="2.16.840.1.113883.1.11.19255"/>
                  <value xsi:type="ED" mediaType="image/jpeg">
                     <reference value="file name.jpg"/>
                  </value>
            </characteristic>
      </subjectOf>
```

Product characteristics also include information on how a device is sterilized and whether the device is a single use or is reusable. A product that has unlimited reuses uses the <value nullFlavor="PINF" xsi:type="INT"/>.

```
<subjectOf>
   <characteristic classCode="OBS">
      <code code="SPLSTERILIZATION" codeSystem="2.16.840.1.113883.1.11.19255"/>
      <value code="code" codeSystem="2.16.840.1.113883.3.26.1.1" displayName="display name"
      xsi:type="CE"/>
   </characteristic>
</subjectOf>
<subjectOf>
   <characteristic classCode="OBS">
      <code code="SPLUSE" codeSystem="2.16.840.1.113883.1.11.19255"/>
      <value value="number of uses (1 is for single use)" xsi:type="INT"/>
   </characteristic>
</subjectOf>
```

3.1.12.   Route of administration

The routes of administration are described under <consumedIn> which is a child of <manufacturedProduct> as illustrated in the following example.

```
<consumedIn>
      <substanceAdministration>
            <routeCode code="code for route" codeSystem="2.16.840.1.113883.3.26.1.1"
            displayName="display name for route"/>
      </substanceAdministration>
</consumedIn>
```

3.2.   Content of labeling

3.2.1.   Sections and subsections

Information: Sections and subsections have titles and codes.

Terminology: LOINC codes are used for sections and subsections codes.

SPL location: The title and LOINC codes are associated with the section and subsection.

XML details: The <title>, if necessary, of the sections and subsections and order of the sections and subsections in the SPL are used to render the labeling contents. The numbering for the sections and subsections are included in the <title> text.

In the SPL schema, the <structuredBody> element contains multiple <component>s, and each <component> contains a <section>. Sections are used to aggregate paragraphs into logical groupings. The order in which sections appear in an SPL document is the order the sections will appear when displayed (rendered) using the standard stylesheet. Major sections defined by the appropriate labeling regulations (e.g., 21 CRF 201.56 and 57 for human prescription drugs and 201.66 for human over the counter drugs) such as Indications and Usage are assigned LOINC codes. Sections that have not been assigned a LOINC code are assigned the LOINC code for "SPL Unclassified Section". Major sections may also be defined by parts of a container or carton label (e.g., Principal Display panel).

Each section has a unique identifier (<id>), an <effectiveTime>, and a LOINC code (i.e., the <code> element). A section may or may not contain a <title>.

The human readable content of labeling is contained within the <text> element in the <section>. The <section> can be nested to form sub-sections. The schema for subsections in SPL requires that the nested <section> tag first be nested inside a <component> tag. Use nested sections to relate paragraphs. The section tag applies to all of the nested sections. By nesting sections, computer systems can use the section tags in SPL to display information useful for the care of patients. If information is not associated with the tag, it will not be displayed.

Using the following principles for markup of text information improves access to information in labeling:

- Capture the section heading using the <title> element rather than placing the text of the title within the <text> element. This allows computer systems to use and display this information properly.

- Capture the section heading even when the printed label does not include a heading. For example, tagging a pregnancy statement as a section in a label that does not have a heading for pregnancy is useful. Computer systems will be able to use the tag to capture the pregnancy use statement. Omitting the <title> would prevent the heading from appearing when the SPL is rendered.

- Link different parts of the labeling using the ID attribute to the <section> element. For example, <section ID="Clin_Pharm_Section"> serves as the target of a <linkHtml> element. Linking to the ID attribute of a section allows the link to 'reference' the section entirely, e.g., for retrieval of a whole section in a non-browser interface.

- For container or carton labels, when capturing text and figures outside the Drug Facts or equivalent sections, separate the text and figures for each concept using <paragraph> tags.

- The order of the placement of information is the content of the package insert, the content of the patient information and the carton and container labels with images.

3.2.2.   Labeling text

Information: This is the human readable content of labeling.

Terminology: There is no controlled terminology for this information.

SPL location: This is provided in the appropriate sections and subsections of labeling.

XML details: The human readable content of labeling (the narrative) is contained within the <text> element. The actual content is contained within a <paragraph>, <table>, and/or <list>. If a section consists only of nested sections, the <text> tag is not included. Elements that can be used within the <text> element to capture the human readable content of SPL include paragraphs (<paragraph>), lists (<list>), tables (<table>) and images (<renderMultimedia>). Elements permitted as children of the <text> element, used as children of the <paragraph> element or within <table> and <list> include superscripts (<sup>), subscripts (<sub>), links (<linkHtml>), line breaks (<br>), footnotes (<footnote>), footnote references (<footnoteRef>). Images may be included in the content of labeling using the <renderMultiMedia> tag. This tag may be used as a direct child of <text> for 'block' images or as a child of <paragraph> for inline images.

3.2.2.1.   Font effects

There are certain aspects of the rendering of SPL that must be specified in the SPL source to insure that the content of labeling is formatted correctly when rendered. For example:

    <paragraph>The next snippet <content styleCode="bold italics"> will appear as bold italics</content> in the rendering.</paragraph>

Will be rendered as:

    The next snippet ***will appear as bold italics*** in the rendering.

The <content styleCode=""> can also be nested, for example:

    <content styleCode="bold italics"> will appear as bold italics</content>"

Can also be represented as:

    <content styleCode="bold"><content styleCode="italics"> will appear as bold italics.</content></content>

The values for <styleCode> for font effect are bold, italics and underline. To assist people who are visually impaired, the <styleCode="emphasis"> is used to prompt computer screen reader programs to emphasize text such as text in a box warning. The bold, italics and underline font effects may be used together with each other and the emphasis styleCode. For example, <content styleCode="bold"><content styleCode="emphasis"> </content></content> will appear as bold and will be emphasized by the screen reader programs.

A special <styleCode> is used for recent major changes (see below).

3.2.2.2. Symbols and special characters

Special characters can be included in the text. Superscripts and subscripts are accomplished using the <sup> and <sub> tags. Unicode character references are used for special characters. Unicode characters in SPL XML are inserted as either &#dddd; where dddd is the Unicode value for decimal values or &#xdddd; where dddd is the Unicode value for hexadecimal values. The font used in the standard stylesheet is a Unicode font assuring that Unicode values in SPL content will be rendered correctly if viewed by a browser supporting this font. Because SPL XML tags begin with the less than symbol (<), use of this symbol in text content must be replaced by the XML entity &lt. For example, "<paragraph>The mean for group 1 was < 13. </paragraph>" will render as "The mean for group 1 was <13."

3.2.2.3. Footnotes

The SPL schema includes a specific footnote element <footnote>. Footnotes are rendered automatically by the standard SPL stylesheet. <footnoteRef> is used to refer to another (usually earlier) footnote. For example, "<footnote ID="testNote">This is the footnote content</footnote>" will generate the following footnote at the appropriate end of a section. "[6] This is footnote content"

The <footnoteRef> element with the appropriate IDREF attribute, e.g., <footnoteRef IDREF="testNote"/> will display the footnote reference in the text corresponding to the footnote with the same ID, e.g., in this example footnote 6.

Footnotes are rendered by the default stylesheet using Arabic numbers (e.g., 1,2 3,). Within tables, footnotes are rendered using footnote marks in the series: * † ‡ § ¶ # ♠ ♥ ♦ ♣, effectively separating numbered footnotes within general text and footnotes within tables. Footnotes within tables are rendered at the bottom of the table.

3.2.2.4. Lists

All lists are marked up using the <list> tag, and each item in a list is marked with an <item> tag. The 'listType' attribute identifies the list as ordered (numbered) or unordered (bulleted). The default numbering and bulleting are controlled by the stylesheet.

Lists featuring a standard set of specialized markers (standard specialized lists) can be created using the styleCode attribute with the <list> element. Options available for ordered lists are:

- Arabic (List is ordered using Arabic numerals: 1, 2, 3)
- LittleRoman (List is ordered using little Roman numerals: i, ii, iii)
- BigRoman (List is ordered using big Roman numerals: I, II, III)

- LittleAlpha (List is order using little alpha characters: a, b, c)
- BigAlpha (List is ordered using big alpha characters: A, B, C)

For example: <list listType="ordered" styleCode="LittleRoman">

For unordered lists the following options exist:
- Disc (List bullets are simple solid discs: ●)
- Circle (List bullets are hollow discs: ○)
- Square (List bullets are solid squares: ■)

For example: <list listType="unordered" styleCode="Disc">

In addition to the standard specialized lists, user-defined characters are also permitted as markers by nesting <caption> within the <item> tag. Note that any character, XML entity, or Unicode symbol, may be used in the <caption>, and that the <caption> for each <item> are not restricted to the same character.

For example: <item><caption>*</caption> the asterisk is used as item marker here.<item>

3.2.2.5. Tables

Tables can be created with the full structure (header (e.g., for column names), body (e.g. for the rows of the table) and footer e.g. for table footnotes)). The element <tbody> is required for an SPL table while the elements <thead> and <tfoot> are optional in the SPL schema. The structure will display a standard typographical table with rules between the caption (table title) and head, the head and body, and the body and <tfoot>. If a <tfoot> element is included and footnotes are present in a table, then footnotes are rendered after the existing content of the <tfoot> element.

It is recommended to always start with a standard table (i.e., <thead> and <tbody> elements) and test to see whether the rendering is unambiguous and interpretable. It is important that the table communicate labeling content not that it duplicates the presentation in word processed or typeset versions of the package insert. In the unusual situation where additional formatting is needed, the rule styleCode specified or certain attributes may be used to modify the table.

The rule codes are as follows (note that the control names are case sensitive).
- Rule on left side of cell is Lrule
- Rule on right side of cell is Rrule
- Rule on top of cell is Toprule
- Rule on bottom of cell is Botrule

Note: More than one rule control may be used in a cell, e.g., <td styleCode code="Botrule Lrule">Cell content </td>.

Rule control codes should be used only when necessary for the interpretability of the table. Use of these codes may result in overriding the default rules for tables. Rather than setting the rule for each

cell, table rules may also be controlled according to entire rows or columns by use of the styleCode attributes with <col>, <colgroup>, <thead>, <tfoot>, <tbody> and <tr> elements.

To make rowgroups appear with horizontal rules, use the styleCode attribute "Botrule" with the appropriate <tr> element. The Botrule value is rarely needed on the <td> element.

The preferred method for using vertical rules is to define colgroup with styleCode="Lrule" or "Rrule" (or both). Only if this does not yield the desired vertical rule should the Lrule or Rrule code value with styleCode attributes on the <td> or <th> element itself be used. Note: In general, vertical rules should not be used. Good typography for tables means using few vertical rules.

To merge cells vertically and horizontally, the rowspan and colspan attributes should be used on the <td>element.

To determine the width of a table, the width attribute may be used on the <table> element and to determine the width of a table column, the width attribute may be used on the <col> and <colgroup> elements.

For horizontal alignment, the preferred method for aligning cell content within the margins is to use <col align=".. "/> in the <colgroup> element, though this can be used in the <colgroup> element as well. Valid values for align are "left", "center", "right", "justify" (for full justification of contents within the cells), and "char" (for character alignment within the cells). Using the <col align=".. "/> markup ensures that the contents for all cells in the column share the same alignment.

For vertical alignment, the valign attribute can be used within cells. For cases in which the cell alignment must be different from other cells in the column, align is also available as an attribute on the other table elements, including <td>.

Markup for table footnote is rendered in the <tfoot> tag. This element does not need to be included in SPL; the standard stylesheet will include a <tfoot> tag if a <footnote> element is present within either the <thead> or <tbody> sections. A <tfoot> section should be included in SPL only if there is additional information other than footnotes that needs to be rendered in this section.

For table text spacing, in some instances, the use of a "tab" or text indentation is desirable in a given table cell. In an SPL document, this effect is achieved by using the nonbreaking space ( ) as if it were a "tab" space. As the following snippet of XML shows, two nonbreaking spaces were used to offset the word "Male" from the margin: <td> Male</td>. The nonbreaking space can also be used to keep text in a table from breaking inappropriately due to browser resizing.

3.2.2.6. Image

The SPL schema uses <observationMedia> elements to identify graphic files to be rendered at the locations where they are referenced by <renderMultiMedia> elements in the <section>. In other words, an image in an SPL will be rendered wherever it is referenced by the renderMultimedia markup, no matter where the observationMedia markup appears. The referencedObject attribute of

the renderMultiMedia element identifies the corresponding observationMedia instance by means of its ID identifier such as <renderMultiMedia referencedObject="MM1"/>

The <observationMedia> element does not contain the graphic file, but instead points at the file. The <reference> value is the file name. The file name should not include spaces. The observationMedia identifies the graphic media type (i.e., JPEG). In addition, the observationMedia element includes the text description of the image used by screen reader software for visually impaired users. This is included in the <text> child of <observationMedia>. Note also that observationMedia is always contained within a <component> element as illustrated.

```
 <component>
   <observationMedia ID="MM1">
     <text>descriptive text</text>
     <value xsi:type="ED" mediaType="image/jpeg">
       <reference value="drug-01.jpg"/>
     </value>
   </observationMedia>
 </component>
```

For image placement, if an image is a block image (i.e., should appear in its own space), insert the renderMultimedia tag after the closing </paragraph> tag. If an image is inline (i.e., should appear alongside text), insert the renderMultimedia tag in the text of a <paragraph> as appropriate. Inline images are expected to be uncommon and basically represent symbols that cannot be represented by Unicode characters. In addition, <caption> are not applicable for inline images since these are not offset from the surrounding text.

The SPL schema does not allow for resizing graphics or changing the resolution of graphics files. Thus, all images are rendered in the browser as-is, with all characteristics of the actual graphic file itself. To ensure that a graphic will appear as desired, it is very important that the graphic file is edited to a dimension appropriate for its presentation within the browser. If this is not done, the appearance of the graphic may not be consistent with the narrative content reducing the readability of the file. JPEG image file type using appropriate pixels per inch for images for viewing in a browser using the standard stylesheet.

3.2.2.7. Hypertext links

SPL offers hypertext linking capabilities generally similar to those found in the HTML specification. Links are specified by the <linkHtml> construct, where the value for the href attribute of <linkHtml> (the target of the link) is the ID attribute value of a <section>, <paragraph>, <table>, <list>, <content>,<renderMultimedia> element. The stylesheet does not support the styleCode attribute of the <linkHtml> element; if a styleCode is needed for a link, this should be coded via the <content> element within the link as with other text.

3.2.2.8. Recent major changes in labeling text

SPL offers a notation to identify recent major changes in the labeling text including table elements <table> and table data <td>. The recent major text is tagged using the <content styleCode="xmChange">. For example,

> <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>

3.2.3. Highlights text

Information: The actual Highlights of a rendered SPL are constructed from four sources: "boilerplate" text rendered directly from the stylesheet, information from data elements inserted into the boilerplate text, <title> in the header which includes the drug names, dosage form, route of administration, controlled substance symbol and year of initial US approval, and text blocks corresponding to each major highlights part (Highlights text). Highlights section titles are derived from the FPI section LOINC codes. The Highlights text is captured for the following sections: Microbiology, Boxed Warning, Recent Major Changes, Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions and Use in Specific Populations.

Terminology: There is no controlled terminology for this information.

SPL location: The text blocks for Highlights are coded with the <excerpt> <highlight> elements of the major section of labeling in which they are contained. For example, the Highlights for Indications and Usage are located with the Indications and Usage section of the labeling. The Highlights text is placed under the main section and not under subsections.

XML details: The text blocks of Highlight are coded with the <excerpt> <highlight> elements of the section in which they are contained. The following is sample coding:

```
<component>
    <section>
        <id root="47ef84cd-8314-48c3-8ee2-bdff3087f83f"/>
        <code code="43685-7" codeSystem="2.16.840.1.113883.6.1" displayName="warnings and
        precautions section"/>
        <title>5 WARNINGS AND PRECAUTIONS </title>
         <excerpt>
            <highlight>
                <text>
                    <list listType="unordered">
                        <item>
                            Aplastic anemia has been observed in 8% of recipients and is irreversible in the
                            majority of patients who experience this. (<linkHtml
                            href="#Section_5.1">5.1</linkHtml>)
                        </item>
                        <item>
                            Monitor for hematological adverse reactions every 2 weeks through the second
                            month of treatment (<linkHtml href="#Section_5.2">5.2</linkHtml>)
```

```
            </item>
          </list>
        </text>
      </highlight>
    </excerpt>
    <component>
        <section ID="Section_5.1">
            <id root="a857689e-9563-43c0-a244-8a6d5a25966a"/>
            <title>5.1 Aplastic anemia</title>
            <text>
                <paragraph>
                    Aplastic anemia has been observed in…..
                </paragraph>
            </text>
        </section>
    </component>
  </section>
</component>
```

The following principles are illustrated by this example:

a. The <text> block for the Highlights is included as the <excerpt> <highlight> <text> children of the respective section. In the example above, the text block rendered in the highlights section is the child of the "Warnings and Precautions" section.
b. The coding of the highlights text block is not in a subsection.
c. The text block is rendered similar to any other text block, although in a location separate from its actual position in the rendered SPL document.
d. Links to the section or subsection where the primary content exists are explicitly entered in the Highlights text block.
e. Section numbering is included in the title of sections and subsections (e.g., '5' and '5.1', above).

Highlights and labeling boilerplate items include:

- Statement -"Highlights of Prescribing Information"
- Highlights section titles
- Patient counseling statement with information taken from FPI section LOINC codes for patient information sections, specifically information for patient section (34076-0), SPL Medguide section (42231-1), SPL patient package insert section (42230-3) and SPL supplemental patient material (38056-8)
- Revision date is taken from the effective time
- Full Prescribing Information: Contents
- Statement – "Full Prescribing Information"