SPL Implementation Guide for FDA Content of Labeling Submissions[1]

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[1] Note: This document is not an HL7 informative document. It is an interim implementation guide for the "SPL Release 2a" schema used by FDA for validating SPL submissions. The SPL Release 2a schema is posted on the FDA website at http://www.fda.gov/oc/datacouncil/spl.html).

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Record of Changes

History of changes:		
Version / Revision #	**Date of Change**	**Description of Changes**
2A	March, 2005	Modify to baseline IG with schema 2a.
2A, Rev. 1	10/07/2005	Update and consolidate IG with multiple examples and documents.
2A, Rev. 2	10/26/2005	Update IG to correct examples and fix formatting problem (to support PDF).
2A, Rev. 2	January, 2006	Incorporate comments from SPL WG.

1.

Introduction

Structured Product Labeling (SPL) Release 2 is a Health Level Seven (HL7) standard for the exchange of product labeling. The Food and Drug Administration (FDA) has adopted this standard for submission of the content of labeling in electronic format for human pharmaceuticals associated with New Drug Applications (NDA), Abbreviated New Drug Applications (ANDA) and Biological Licensing Applications (BLA). SPL submitted to FDA uses only a subset of the information described in the SPL Release 2 schema. This subset is called "SPL Release 2a". The "SPL Release 2a" schema is posted on the FDA website at http://www.fda.gov/oc/datacouncil/spl.html. This schema is used by FDA for validating SPL submissions. The full SPL release schema is planned for use with future changes in the labeling regulations.

This document is an interim implementation guide for use only with the "SPL Release 2a" schema. It is not an HL7 informative document. In the future, this document will be updated as the implementation guide for SPL Release 2 and will be balloted as a HL7 Informative Document.

Further information on the submission of SPL to the FDA is provided in section 0 of this document and in the Guidance to Industry: *Providing Regulatory Submissions in Electronic Format – Content of Labeling*. This document is available on the FDA website noted above along with other useful resources for submitting SPL to FDA. There is also a companion document *SPL Implementation Guide for FDA Content of Labeling Submissions – Companion Document* that contains general information to help in the understanding and use of the implementation guide. Information on validation rules used in the Electronic Labeling Information Processing System (ELIPS)[3] is found in the document *Electronic Labeling Information Processing System Structured Product Labeling Validation Rules*.

2. Creating an SPL Document

An SPL document consists of an eXtensible Markup Language (XML) file that contains the content of labeling (all text, tables and figures) for a product along with additional information for machine processing of label content (header information and data elements). The SPL XML file may be displayed (rendered) in a human-readable format by the use of a set of files collectively referred to as a stylesheet. Using a web browser, the stylesheet displays the information in the XML file in a consistent format for viewing. The stylesheet for displaying SPL is posted on the FDA website.

An SPL document may be created using a variety of editing environments ranging from a general purpose word processor to an XML editor to an SPL-specific editing tool. For submission purposes, as long as the file is valid against the SPL schema, the method of creating the file is not important.

SPL has been developed as a document format to exchange the content of labeling rather than as a mechanism for reproducing the exact format of a printed package insert. The standard stylesheet specifies the default font, indentation, orientation, formatting, word wrapping, line spacing, and other properties that will be used for the 'standard' display. Formatting (cascading stylesheet [css]) classes standardize the formatting of specific sections within the SPL document (instance). For example, text within a section coded as a 'Box Warning' is displayed within a black box using a standard cascading

[3] ELIPS is an FDA developed system to allow FDA to process, review and archive the electronic content of labeling. The system requires the content of labeling to be in SPL format.

stylesheet . Formatting codes for standard text such as italicizing or bolding are included in SPL as the styleCode attribute for most narrative block elements.

An SPL document consists conceptually of two sections, a header and a body. The body comprises the content of labeling and includes the human readable text and the data elements (intended for machine processing). The human readable text includes the text, tables and figures found in the package insert. For example, patient information required to be reprinted at the end of the package insert is included in SPL. The SPL structure is illustrated in Figure 1 below.

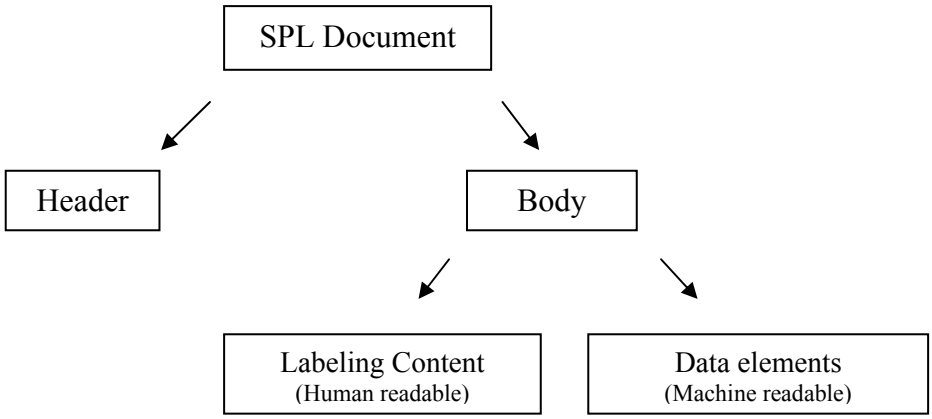

Figure 1: Conceptual SPL Structure

Construction of the header and body are discussed in sections 3 and 0, respectively. The two parts of the body, the labeling content and the data elements are discussed in Sections 0 and 0, respectively.

3. Creating the SPL Header

3.1 Processing Instructions and the Root Element

All XML documents, including SPL, must include processing instructions and the root <document> element to be considered valid XML document.[4] The processing instructions at the start of SPL and the root element must be identical for every SPL document submitted to FDA and have the following form[5]:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="spl-2a.1.xsl "?>
<document xmlns="urn:hl7-org:v3" xmlns:voc="urn:hl7-org:v3/voc"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance">
```

Figure 2: Example of SPL Processing Instruction

[4] The following general conventions are followed in this document (with occasional exceptions). Element names in examples are in brown, and the left and right angle brackets for an element are in blue e.g., <car>. Attribute names are in red, e.g., <person age="20">, and attribute values in black. This general convention may be expanded on or altered in certain complex examples. All elements in SPL begin in lower case and follow a camelCase convention (e.g., <activeIngredient>).

[5] This specific code may change, particularly as the xsl file is updated to later versions. The most current recommendations for the processing instruction/root element syntax is available at www.fda.gov/oc/datacouncil/spl.html

Although this information appears at the start of each SPL document, it is conceptually separate from the SPL header described below.

3.2 SPL Header Elements

The header contains information about the document (SPL metadata). It is similar to the type of information that would be contained in the 'properties' box of a word processing document or in the information that a document management system would use for identifying a document. The elements are summarized in Table 1: SPL Header Elements. [6] These elements follow the root <document> element shown above.[7] Note that some elements that are not required in the schema are necessary with SPL submitted to the FDA. Elements that are not used as noted in the table below are not processed by FDA systems and should not be included with the SPL submitted to the FDA.

Table 1: SPL Header Elements

Element	Schema Req.	FDA Req. [a]	Comment	Examples
id	**Yes**	**Yes**	<id> is a globally unique identifier (GUID)[8] for the specific document (SPL instance) and will differ for every regulatory submission.	<id root="F975E42A-06CD-E7E9-6825-9A40F8C7534D"/>
code	**Yes**	**Yes**	<code> contains via its code attribute the LOINC[9] code for the type of content of labeling (see example). At this time, human prescription drug label is the only type so this line should be identical in all SPL submitted to FDA. As implementation of SPL is expanded to other type of product labeling (e.g., OTC labeling), other codes will be available. The codeSystemName attribute is optional because it is determined by the codeSystem attribute. The codeSystemVersion attribute is not used at this time	<code code="34391-3" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC" displayName="HUMAN PRESCRIPTION DRUG LABELING"/>

[6] Please refer to the SPL normative standard at http://www.hl7.org/Special/committees/rcrim/docs.cfm for a complete description of all SPL header elements and attributes.
[7] The <document> element is the root element of an SPL document.
[8] Globally Unique Identifier (GUID), also known as a Universally Unique Identifier (or UUID) are128 bit integer values, or in hexadecimal, 32 hexadecimal digits that are statistically likely to be different from any other GUID and are automatically generated using freely available software programs.
[9] LOINC is one of the coding systems that have been adopted by HL7 for use in SPL and other HL7 standards. For a complete description of the LOINC database, see http://www.regenstrief.org/loinc/.

Element	Schema Req.	FDA Req. [a]	Comment	Examples
title	**No**	**Yes**	<title> corresponds to the title string of the package insert. If special characters or symbols are used, (e.g., ™) these are inserted as Unicode characters. Images such as company or product logos are not included in the title (See **Table 5: Symbols and Special Characters**). The <title> element is rendered by the standard stylesheet. Multiple lines may be used in the title with each line separated by the line break tag.	<title>SPLDemoDrug ® SPL Demo </title>
effectiveTime	**Yes**	**Yes**	This element is required by the SPL schema and therefore must be present. However, the value attribute should not be included. The value for this element is populated by FDA to correspond to the receipt date for annual report and changes being effected labeling changes and the date of sign off for new labeling or prior approval labeling changes.	<effectiveTime />
setId	**No**	**Yes**	<setId> is the unique identifier for the document that remains constant through all versions/revisions of the document. The value for the <setId> root attribute is the GUID used to identify the <id> of the first document of a set submitted to FDA. Therefore, <setId root> would equal the <id> for the first regulatory SPL submission for a specific product. FDA uses this information to identify and process changes to a particular product label.	<setId root="F975E42A-06CD-E7E9-6825-9A40F8C7534D"/>

Element	Schema Req.	FDA Req. [a]	Comment	Examples
versionNumber	**No**	**Yes**	<versionNumber> identifies a version of the document. The combination of <setId> and <versionNumber> is unique for each version of a product label. The value attribute should not be included. The value for this element is populated by FDA to correspond to the receipt date for annual report and changes being effected labeling changes and the date of sign off for new labeling or prior approval labeling changes.	<versionNumber/>
availabilityTime	**No**	**No**	This should not be used at this time[10]	
confidentialityCode	**No**	**No**	This should not be used at this time	
languageCode	**No**	**No**	This should not be used at this time	
author	**No**	**No**	This should not be used at this time	
legalAuthenticator	**No**	**No**	This should not be used at this time	
verifier	**No**	**No**	This should not be used at this time	
relatedDocument	**No**	**No**	This should not be used at this time	

[a] Schema req. and FDA req. refers to whether the element is required by the schema and/or FDA. Elements that are required by the schema must be present although the information may not be used by FDA.

The following is an example of the SPL header (with the root element) as it would appear in a FDA submission.

```
<document xsi:schemaLocation="urn:hl7-org:v3 PORR_MT050020.xsd" xmlns="urn:hl7-org:v3"
xmlns:voc="urn:hl7-org:v3/voc" xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance">
<id root="4c18c125-6a14-48d9-a5d0-65374e7f100e "/>
<code code="34391-3" codeSystem="2.16.840.1.113883.6.1" displayName="Human Prescription Drug
Labeling"/>
<title>SPLDemoDrug<sup>&#174;</sup><br/>For SPL Demo</title>
<effectiveTime/>
<setId root="4c18c125-6a14-48d9-a5d0-65374e7f100e"/>
```

Figure 3: Example of SPL Header with Root Element

Creating the SPL Body

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 human readable content of labeling (text, tables and figures) plus structured data elements intended for machine processing.

[10] Even if used by the applicant, the information should not be included with the submission. This is for all of the elements marked as "This should not be used at this time".

The primary "building blocks" for the body of the document are sections. 'Sections' of the label content (or 'sections' of the narrative) represent related information; for example, sections required in FDA labeling regulations (e.g., Description, Indications and usage, Warnings) are marked as a section in SPL. A section may contain other sections, i.e., there may be sub-sections (also known as nested sections). In every case, a section contains paragraphs of information that are related and belong together. For example, several paragraphs discussing a specific precaution would be a sub-section within the larger 'Precautions' section: this is referred to as a 'semantic unit', i.e., a set of related information. This is discussed further below.

Sections

In the SPL schema, the <structuredBody> element contains multiple <component>s, and each <component> contains a <section>. This is illustrated below. The example is not valid SPL code and is used only to illustrate the structure of SPL[11]:

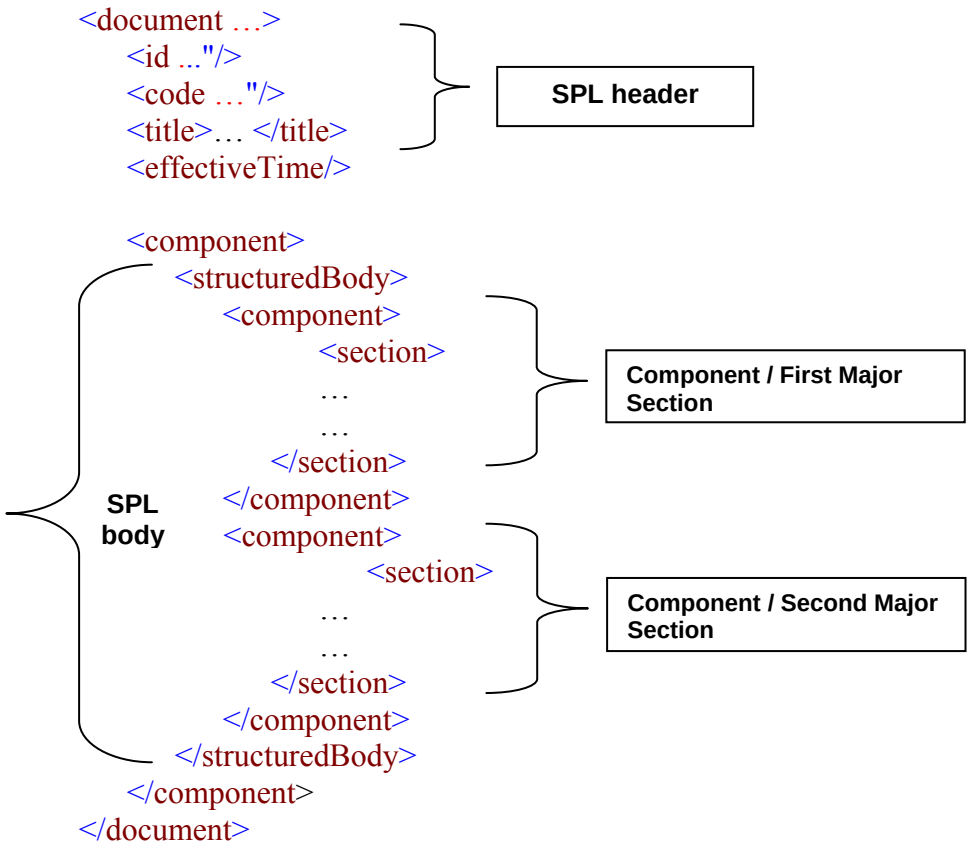

Figure 4. Example of SPL structure for structuredBody and sections within a structuredBody.

[11] Although the option exists for a nonXMLBody in the SPL schema (i.e., <nonXMLBody> instead of <structuredBody>), all SPL submissions to FDA use the <structuredBody> structure/element after the header elements. The <nonXMLBody> element is not used at this time.

Sections are used to aggregate paragraphs into logical groupings. For the FDA implementation of SPL, <section>s defined by the labeling regulations in 21 CFR 201.56 and 57 (e.g., Indications and Usage) are assigned LOINC codes (see Table 18: LOINC Codes). These sections are expected to be coded with the appropriate LOINC code in SPL. Sections that have not been assigned a LOINC code have the option of not being assigned a code (i.e., does not contain the <code>) or may be assigned the LOINC code for an unclassified section. Either option is acceptable for submission of SPL. The following is an example of a section assigned a LOINC code with a sub-section not assigned a LOINC code:

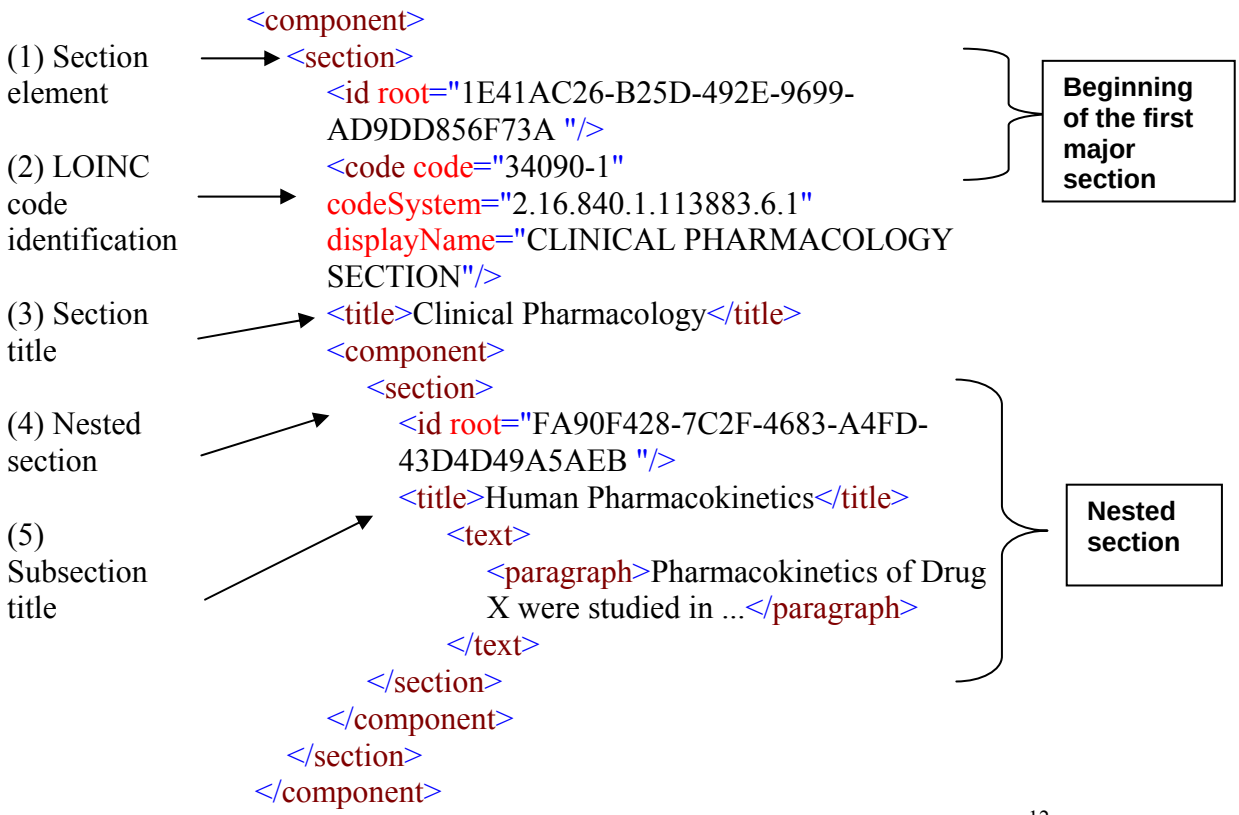

Figure 5. SPL markup for sections, nested sections, and titles.[12]

The SPL standard does not dictate the order of the sections. The order in which sections appear in an SPL document is the order the sections will appear when displayed (rendered) using the standard stylesheet and are defined by the labeling regulations in 21CRF 201.56 and 57.

A <section> may also contain sub-elements or metadata that uniquely identify and classify the section, similar to what is used to identify the document in the SPL header. As shown in Figure 5, each section

[12] This structure may be counterintuitive, i.e., why a <component><section> tag is always needed for non-nested sections rather than <section> alone. The model-based derivation of the SPL schema from the overall HL7 Reference Information Model mandates this element. The author only need note that for non-nested sections, <component><section> should be used. (Similarly, <component> preceding <structuredBody> is mandated at the start of the body section although the <component> tag may appear unnecessary.)

has a unique identifier (<id>), may be identified semantically by a LOINC code (i.e., the <code> element), and may contain a <title>. These are also described further below.[13]

The human readable content of labeling is contained within the <text> element in <section>s.[14] It should be noted that in all cases the structured narrative contained in SPL is the content of labeling as required in the regulations.

Nesting of Sections and Subsections

<section>s can nest to form sub-sections. The schema for subsections in SPL requires that the nested <section> tag first be nested inside a <component> tag, as illustrated in Figure 4 above.

The <component> element is used for nesting a section within another section. The following illustrates the method for creating nested sections (using non-valid code for illustrative purposes):[15]

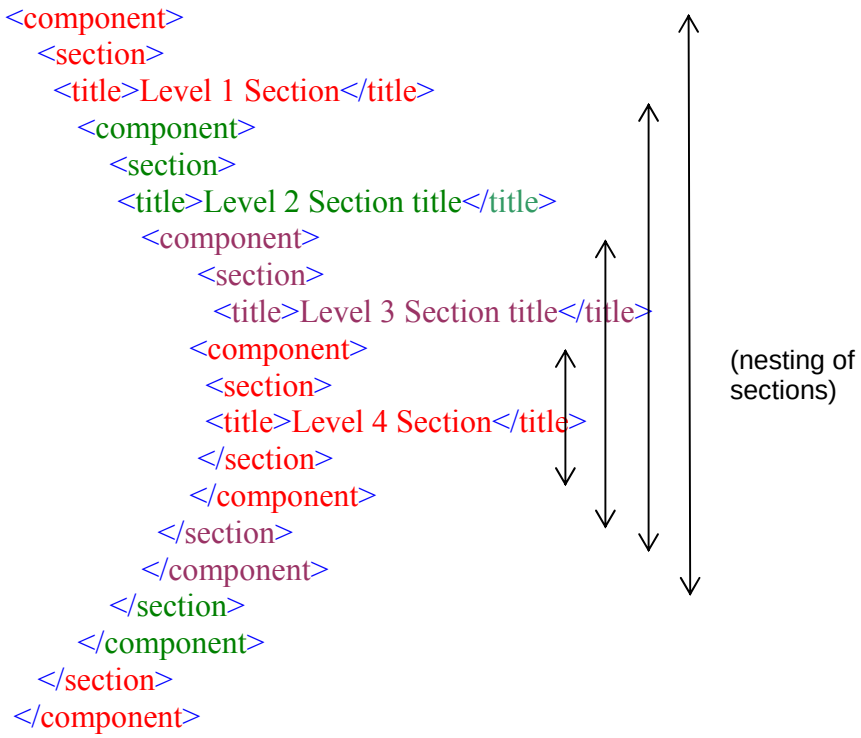

Figure 6. Use of <component> and <section> markup to nest sections in SPL.

Best Practices for Creating Sections

Using the following principles for markup of text information provides improved access to the information in labeling.

[13] A section may also have an ID attribute used for reference purpose, e.g., <section ID="renal_effects_section">. This is discussed further below.

[14] A separate Narrative Block schema referenced by the main SPL schema describes the content model for <text>. This is described further below.

[15] Similar to first-level sections, the nesting of sections by <component><section> tagging may seem unnecessary, but is mandated by HL7 methodology.

- Use nested sections to relate paragraphs. The section tag applies to all of the nested sections. By nesting sections, computer system 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.[16]

- Use the <title> element to capture the section heading that appears in the label instead of placing the text of the title within the <text> element. This allows computer systems to use and display this information properly.

- Use assigned section tags 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.

- Use the ID attribute to the <section> element, e.g., <section ID="Clin_Pharm_Section"> if the section is to serve 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.

The following examples demonstrate two methods of creating a section. The first example demonstrates best practices for utilizing nested sections. The second example does not utilize nested sections. While the content is the same and both examples are valid against the SPL schema, the markup used in the second example, Figure 8 does not clearly delineate the relationships between the sections, subsections, and paragraphs of the labeling content resulting in a loss of important computer accessible information.

CLINICAL PHARMACOLOGY
Human Pharmacokinetics—Pharmacokinetics of Drug X were studied in…

Absorption: The absorption of drug x in volunteers was…

The following shows the markup format using nested sections and the <title> element:

```
<component>
  <section>
    <id root="2EFE2C58-A9EB-4689-BD05-443C534D7D93"/>
    <code code="34090-1" codeSystem="2.16.840.1.113883.6.1" displayName="CLINICAL
    PHAMACOLOGY SECTION"/>
    <title>CLINICAL PHARMACOLOGY</title>
    <component>
      <section>
        <id root="5708BCA0-8189-4331-83BA-08C7BDBD5C03"/>
```

[16] For example, in an adverse events section without a subheading, 3 paragraphs may describe the renal toxicity of the drug. These paragraphs should be captured in a single, separate section reflecting that this information forms a separate 'semantic' unit. This would be even more apparent if a subheading were present in the original text identifying the information as a separate and related.

```
            <title>Human Pharmacokinetics</title>
              <text>
                <paragraph>Pharmacokinetics of Drug X were studied in ...</paragraph>
              </text>
              <component>
                <section>
                  <id root=" CAC6A763-D3FB-42B2-9187-570BFA1CBE39"/>
                  <title>Absorption</title>
                  <text>
                    <paragraph>The absorption of drug x in volunteers was  ...</paragraph>
                  </text>
                </section>
              </component>
          </section>
        </component>
    </section>
</component>
```

Figure 7: Example markup for a nested section

The following does not use nested sections or subsection titles.

```
<component>
    <section>
        <id root="51A61815-06CE-47CA-A2D2-ECB2F24EFA44"/>
        <code code="34090-1" codeSystem="2.16.840.1.113883.6.1" displayName="CLINICAL
       PHAMACOLOGY SECTION"/>
        <title>CLINICAL PHARMACOLOGY</title>
        <text>
            <paragraph><content styleCode=”italics”>Human Pharmacokinetics</content> of
              Drug X were studied in ...</paragraph>
            <paragraph><content styleCode=”italics”>Absorption</content> The absorption of
              drug x in volunteers was  .....</paragraph>
        </text>
    </section>
</component>
```

Figure 8: Example markup not using nested sections

These principles may be used for any part of the label where specific information exists within a section with an assigned LOINC code (e.g., PRECAUTIONS or WARNING sections). In those sections without an assigned LOINC code, the optional LOINC code for unclassified section may be used. The following example demonstrates the use of nested sections using the unclassified section LOINC code.

```
        <component>
            <section>
                <id root="67B8BC10-8189-4331-83BA-08C7BDBD5C03"/>
                <code code="42229-5" codeSystem="2.16.840.1.113883.6.1" displayName="SPL
                UNCLASSIFIED SECTION "/>
```

```
<title>Human Pharmacokinetics</title>
  <text>
    <paragraph>Pharmacokinetics of Drug X were studied in ...</paragraph>
  </text>
  <component>
    <section ID=”absorption_section”>
      <id root="CAC6A763-D3FB-42B2-9187-570BFA1CBE39"/>
      <code code="42229-5" codeSystem="2.16.840.1.113883.6.1"
      displayName="SPL UNCLASSIFIED SECTION "/>
      <title>Absorption</title>
      <text>
        <paragraph>The absorption of drug x in volunteers was  ...</paragraph>
      </text>
    </section>
  </component>
</section>
</component>
```

Figure 9: Example markup for a nested section using an unclassified section

<section> Elements

The <section> elements are handled as described for the header elements and are summarized in Table 2. Elements that are noted as not used in the table below are not processed by FDA systems and should not be included with the SPL submitted to the FDA.

Table 2. SPL Elements within the <section> Element

Element	Schema req	FDA req.[a]	Comment	Examples
id	**Yes**	**Yes**	<id> is a GUID for the specific section instance. Note that the <id> element is separate from the ID attribute that may exist on a <section> element, e.g., <section ID="Human_PK_Section">. The ID attribute does not need to be a GUID. It must begin with a letter or underscore, and cannot contain spaces.	<id root="2 F33776B3-2DC8-435B-856B-444DD69F6CD7"/>

Element	Schema req	FDA req.[a]	Comment	Examples
code	**No**	**Yes**[b]	<code> contains the LOINC code for certain sections described in the regulations (e.g., Indications and Usage). The LOINC codes are available at http://www.regenstrief.org/loinc and in **Table 18**. When a section has not been assigned a LOINC code, the element may be absent or the 'UNCLASSIFIED' LOINC code may be used. The displayName in the <code> element is for information purposes only. It is not used to generate a title for a section in the rendered document but should be included. The codeSystemName attribute is optional because it is added by the FDA, if needed. The value is based on the codeSystem attribute. The codeSystemVersion attribute is not applicable at this time.	<code code="34067-9" codeSystem="2.16.840.1.113883.6.1" displayName=" INDICATIONS & USAGE SECTION"/> <code code="42229-5" codeSystem="2.16.840.1.113883.6.1" displayName="SPL UNCLASSIFIED SECTION "/>

Element	Schema req	FDA req.[a]	Comment	Examples
title	**No**	**No**	The <title> element is used to capture the section heading that appears in the label. The title of a section is rendered from the content of the <title> tag by the standard stylesheet: if the <title> tag is not populated, then no title will be displayed. The title is NOT rendered from the value of displayName attribute if a <code> element is present. Not every section will have a title; however even in the absence of a title, paragraphs can be grouped into separate sections based on the relationships between the content. Sections and their titles may be nested, resulting in an implied hierarchy that is rendered appropriately in the standard stylesheet.	<title>INDICATIONS AND USAGE</title>

Element	Schema req	FDA req.[a]	Comment	Examples
text	**No**	**No**	The human readable content of labeling (the narrative) is contained within the <text> element. The actual content is contained within a <paragraph>, <table>, or <list>. If a section consists only of nested sections, the <text> tag is not included. Below are some of the elements that can be used within the <text> element to capture the human readable content of SPL: • paragraphs (<paragraph>) • lists (<list>) • tables (<tables>) • images <renderMultimedia>) The following elements are also permitted as children of the <text> element, used as children of the <paragraph> element or within <table>s and <list>s. • superscripts (<sup>) • subscripts (<sub>) • links (<linkHtml>) • line breaks ( ) • 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. Images are discussed in 0 further below. See below for additional discussion of the <text> content model.	<text><paragraph> This drug exhibits analgesic and… </paragraph></text>
effectiveTime	**No**	**No**	This element should not be used at this time. Similar to <effectiveTime> in the SPL header, this element will be populated by FDA.	
confidentiality Code	**No**	**No**	This should not be used at this time.	
languageCode	**No**	**No**	This should not be used at this time.	

Element	Schema req	FDA req.[a]	Comment	Examples
author	**No**	**No**	This should not be used at this time.	
component	**No**	**Yes**	<component> is used to link sections to sections nested within them (see Figure 5 for levels of nesting available in SPL). Rendering of the titles for nested sections is defined by the SPL stylesheet and depends on the level of nesting.	<section> <id root="192D3B70-0457-4F92-AA4A-8B30928A32A9"/> <code code="34090-1" codeSystem="2.16.840.1.113883.6.1" displayName="CLINICAL PHARMACOLOGY SECTION"/> <title>CLINICAL PHARMACOLOGY</title> <component> <section> <id root="192D3B70-0457-4F92-AA4A-8B30928A32A9"/> <title>Human Pharmacokinetics</title> <text> <paragraph>Pharmacokinetics of Drug X were…</paragraph> </text> </section> </component> </section>
replacementOf	**No**	No	This should not be used at this time.	
subjectOf	**No**	No	<subjectOf><comment> is designed to annotate narrative text.	
subject	**No**	**Yes**	<subject> is used to contain the data elements for describing the drug listing data elements in SPL. See Section 0 for a full description of this element.	
excerpt	**No**	No	This element should not be used at present but is planned to have a role with future changes in the labeling regulations.	

[a] FDA and Schema required refers to whether the element is required by the schema and/or FDA. Elements that are required by the schema must be present although the information may not be used by FDA.

[b] <code> is required only for 21CFR201.56/57 sections

The following shows the markup format for section without the use of subsection concept:

```
<!-- - - - - - - - - - -  Sample Contraindications section  - - - - - - - - - - - - - - - - - - - - - -->
  <component>
     <section>
        <id root="02128CFE-34DB-428A-B92F-A155103C354D"/>
        <code code="34070-3" codeSystem="2.16.840.1.113883.6.1"
       displayName="CONTRAINDICATIONS SECTION "/>
        <title>CONTRAINDICATIONS</title>
        <text>
           <paragraph>DrugX is contraindicated in those patients with a known hypersensitivity
           to the drug.
           </paragraph>
        </text>
     </section>
  </component>
```

Figure 10: Example markup for section without subsection

The following shows the markup format using the subsection concept:

```
<!-- - - - - - - - - - -  Sample Clinical Pharmacology section- - - - - - - - - - - - - - - - - - - -->
  <component>
     <section>
        <id root="5031A439-E76A-4FEB-827D-9AC5A758076A "/>
        <code code="34090-1" codeSystem="2.16.840.1.113883.6.1"
       displayName="CLINICAL PHARMACOLOGY SECTION"/>
        <title>CLINICAL PHARMACOLOGY</title>
        <component>
           <section>
              <id root="51A61815-06CE-47CA-A2D2-EFB2F24EFA44"/>
              <title>Human Pharmacokinetics</title>
                 <text>
                    <paragraph>Pharmacokinetics of Drug X were studied in….</paragraph>
                 </text>
           </section>
        </component>
     </section>
   </component>
```

Figure 11: Example markup for section with subsection

Formatting SPL

This section discusses several aspects broadly defined as 'Formatting SPL, including (a) use of the <styleCode> element for certain formatting options, (b) font effects (e.g., bold, underline, and italics), (c) symbols and special characters (Unicode), (d) footnotes, and (e) default and specialized lists. Tables are discussed separately in Section 0.below.

<styleCode> attribute

A major design goal of XML (and SPL) documents is to separate formatting from content; accordingly, the SPL schema contains minimal formatting features. However, the SPL standard also specifies that an SPL document should be human readable, and further specifies that a standard stylesheet be available for rendering SPL labeling in modern Web browsers.

Despite use of a stylesheet with an SPL document, 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. An example of this is the use of rules separating rows in a table into sections. Certain other aspects of the printed labeling, e.g., surrounding box printed box that defines a box warning, are defined in the stylesheet are automatically rendered when a <section> is codeed as a BOXED WARNING SECTION.

For example:

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

The above will be rendered as:

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

<content styleCode=””> can also be nested, i.e., “<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>”.

Font Effects

As discussed earlier, the <content styleCode=”” > element is the primary mechanism for including font effects in text. Currently bold, italics, and underline are supported. These are shown in Table 3 below.

Table 3: Font Effects

Attribute value for ‘styleCode’	**Recognized by FDA**	**Example Rendering**	**Examples**
bold	Yes	**contraindicated**	<content styleCode=”bold”>contraindicated</content>
italics	Yes	*in vitro*	<content styleCode=”italics”>in vitro</content>
underline	Yes	fever	<content styleCode=”underline”>fever</content>

Note that combined font effects for bold, italics, and underline are permitted in SPL as shown in the following table:

Table 4: Multiple Font Effects

Desired Font Effect	Rendering	Examples
bold-italics	***contraindicated***	<content styleCode="bold italics">contraindicated</content>
italics-underline	*in vitro*	<content styleCode="italics underline">in vitro</content>
bold-underline	**fever**	<content styleCode="bold underline">fever</content>
bold-italics-underline	***pharmacology***	<content styleCode="bold italics underline"> pharmacology</content>

Symbols and Special Characters

Special characters can be included in narrative (i.e., the text content) or the header <title> and may be created in different ways. Simple superscripts and subscripts are accomplished with tagging included in the SPL schema, i.e., <sup> and <sub> tags. Unicode[17] character references are used for special characters.[18]. The Unicode value for common symbols (e.g., &#8482 for ™) are in Table 5: Symbols and Special Characters.

Table 5: Symbols and Special Characters

[17] Complete information regarding Unicode is available at http://www.unicode.org and http://www.alanwood.net/unicode/index.html#links. A well indexed table of Greek and other special characters can be found at http://www.alanwood.net/demos/symbol.html#s0080.

[18] Unicode character set UTF-8 is the default character set in W3C XML Schemas

Symbol or Character	Solution	Sample Markup
mg/m^2 (superscript)	Tagging	mg/m²
• (e.g., $C_9H_{11}F_2N_3O_4$•HCl)	Tagging + Unicode	C₉H₁₁F₂N₃O₄•HCl)
© (copyright)	Unicode	&#169;
º (degree)	Unicode	&#176;
<	Entity	&lt;
≤	Unicode	&#8804;
— (m-dash)	Unicode	&#8212;
β (e.g., β-isomer)	Unicode	β-isomer
® (e.g., Registered 1996)	Unicode	Registered® 1996.
™ (e.g., Trademark™ 1998)	Unicode	Trademark™ 1998
± (plus-minus sign)	Unicode	&#177;
& (ampersand)	Entity	&amp;
†	Unicode	&#8224;
‡	Unicode	&#8225;
§	Unicode	&#167;
' (apostrophe)	Entity	&apos;

Unicode characters in SPL (and XML) are inserted as either &#dddd; where dddd is the Unicode value (for decimal values) or &#xdddd; when hexadecimal values are used.

Native XML authoring tools automatically insert the proper Unicode value for special characters or symbols during the authoring process. However, because of differences in coding systems and software, some symbols or special characters may not carry over properly when copied and pasted from a word processing document into an XML document. If text is copied or otherwise converted from a word processing document into SPL-compliant XML, verify that special symbols and characters are properly encoded in the XML document.

The font used in the standard stylesheet is a Unicode font (Arial Unicode MS), assuring that Unicode values in SPL content will be rendered correctly if viewed by a browser supporting this font. Also note that because XML (SPL) tags begin with the less than symbol (<), use of this symbol in text content must be replaced by the XML entity &lt: e.g., "<paragraph>The mean for group 1 was < 13. </paragraph>" will render as "The mean for group 1 was <13."

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, "This is text <footnote ID="testNote">This is the footnote content</footnote>now more content…" will generate a footnote "[6] This is footnote content" at the appropriate end of a section. 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 mode, at present using Arabic numbers (i.e., 1,2 3, etc.).[19] 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.

Table 6: Footnotes

SPL Footnote Markup	Sample Footnote
<paragraph>This is a test of a footnote<footnote>28-day schedule – SPL drug1 plus SPL drug2: SPL drug1 1000 mg/m² on Days 1, 8, and 15 and SPL drug2 100 mg/m² on Day 1 every 28 days; Single-agent SPL drug2: SPL drug2 100 mg/m² on Day 1 every 28 days.</footnote> to see if it works. More text…..</paragraph>	This is a test of a footnote[3] to see if it works. More text…. …….. [3]28-day schedule – SPL drug1 plus SPL drug2: SPL drug1 1000 mg/m^2 on Days 1, 8, and 15 and SPL drug2 100 mg/m^2 on Day 1 every 28 days; Single-agent SPL drug2: SPL drug2 100 mg/m^2 on Day 1 every 28 days.
<td align="left" valign="top"><content styleCode="bold">Vaccine serotypes<footnote>All vaccine serotypes were used.</footnote></content></td>	Vaccine Serotypes* A B * All vaccine serotypes were used.

Lists (Default and Specialized)

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 style or bullet type is not specified in the SPL schema; default numbering and bulleting are controlled by the stylesheet.

Table 7: Default Lists

Markup	Presentation via Standard Stylesheet

[19] The styleCode attribute in <footnote> is not supported in the standard stylesheet.

Markup	Presentation via Standard Stylesheet
<list listType="ordered"> <item> Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Printing Office, Washington, DC 20402. </item> <item> Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590. </item> </list>	1. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. 2. Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.
<list listType="unordered"> <item> Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Printing Office, Washington, DC 20402. </item> <item> Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590. </item> </list>	• Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. • Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.

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”>

Table 8 shows examples of the styleCode values available for ordered and unordered lists:

Table 8: Specialized Lists

Ordered Lists:

Specialized Type	styleCode Value	Sample Rendering
Arabic (same as default ordered list)	Arabic	1.Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. 2.Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.
Lowercase Roman Numeral	LittleRoman	i. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. ii. Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.
Uppercase Roman Numeral	BigRoman	I. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. II. Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.
Lowercase Western Alphabetical	LittleAlpha	a. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. b. Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.
Uppercase Western Alphabetical	BigAlpha	A. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. B. Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.

Unordered Lists:

Specialized Type	styleCode Value	Sample Rendering
Disc (same as default unordered list)	Disc	• Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. • Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.
Circle, hollow disc	Circle	o Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. o Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.
Filled square	Square	▪ Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. ▪ Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.

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

Table 9: User-defined Characters

SPL Markup	Sample Rendering
<list> <item><caption>@</caption>Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621.US Government Printing Office, Washington, DC 20402.</item> <item><caption>@</caption>Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.</item> </list>	@ Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Print Office, Washington, DC. 20402. @ Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.

Tables

Attributes for the <table> element (e.g., rules, cell spacing, etc.) are currently not supported by the standard stylesheet.

Table markup in SPL is similar to the XHTML table model for structural tagging (i.e., <tr>, <td>, etc.) but lacks much of the XHTML formatting and style markup.[20]

Tables can be created with the full structure as shown below when needed. <thead> and <tfoot> are optional elements in the SPL schema but <tbody> is required for an SPL table. 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.

Table 10: Sample Table

SPL Table Markup	Sample Table
<table> <caption>…</caption> <thead> <tr .../> </thead> <tbody> <tr .../> </tbody> </table>	**Table 1: This is a Table Title** % Patients SPLDemoDrug® (N= 2) / Placebo (N= 3) **Category** 1* 1 (50%) 1 (33%) 2 1 (50%) 1 (33%) 3 1 (50%) 1 (33%) * This is a table footnote

[20] A complete description of the XHTML document model is available at http://www.w3.org/TR/xhtml-modularization/Overview.html. Specific defaults regarding the XHTML table model can be found at http://www.w3.org/TR/xhtml-modularization/abstract_modules.html#s_tablemodule.

The SPL schema enforces the positioning of <tfoot> before <tbody>. <thead> and <tfoot> are optional elements in the SPL schema but <tbody> is required for an SPL table. Footnotes within an SPL table are automatically rendered in an <tfoot> element; this element does not need to be included for footnotes within a table to be rendered correctly.

It is recommended to always start with a standard table (e.g., <thead> and <tbody> elements and test to see whether the rendering is unambiguous and interpretable. Use the rule styleCodes specified below to modify the table only when absolutely necessary. SPL is used to communicate labeling content rather than the exact representation of drug information present in a typeset document. The table presentation in SPL is unlikely to exactly duplicate the presentation in word processed or typeset versions of the package insert.

Table Rules (Gridlines)

The SPL schema allows users to control rules for each cell by setting the styleCode attribute code on <td>, e.g., <td styleCode="Lrule">.

The rule codes are shown in the following table. Note that the control names are case sensitive.

Table 11. Optional Table Rules

Rule Placement	styleCode attribute	Appearance
Rule on left side of cell	Lrule	
Rule on right side of cell	Rrule	
Rule on top of cell	Toprule	
Rule on bottom of cell	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.

Horizontal rules

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.

Vertical rules

The preferred method for using vertical rules is to define colgroups with styleCode="Lrule" or "Rrule" (or both). Only if this does not yield the desired vertical rule should you use the Lrule or Rrule code value with styleCode attributes on the <td> or <th> element itself.

Note: Vertical rules should be used sparingly! Good typography for tables means using few vertical rules.

Cell text alignment

Horizontal alignment: Similar to XHTML tables, 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.

Vertical alignment: Analogous to XHTML, 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>. The following example demonstrates the XML markup and the result of using the align attribute on <td>.

```
<tr>
        <td>Number of patients</td>
        <td align="right">260</td>
        <td align="left">262</td>
        <td/>
        <td>69</td>
        <td>66</td>
        <td/>
</tr>
 <tr>
        <td>&amp;#160;&amp;#160;Male</td>
        <td align="left">182</td>
        <td align="right">186</td>
```

```
        <td/>
        <td>64</td>
        <td>61</td>
        <td/>
</tr>

<tr>
        <td>&amp;#160;&amp;#160;Female</td>
        <td>78</td>
        <td>76</td>
        <td/>
        <td>5</td>
        <td>5</td>
        <td/>
</tr>
```

Number of patients	260	262	69	66
Male	182	186	64	61
Female	78	76	5	5

Figure 12: Sample table markup

Footnotes

Markup for table footnote is rendered in the <tfoot> tag, as is common practice. 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.

Table text spacing

In some instances, the use of a “tab” or text indentation is desirable in a given table cell, as in the “Trial” column of the following example:

Trial	28-day Schedule		21-day Schedule	
Treatment Arm	Drugapil/ Goodrug	Goodrug	Drugapil/ Goodrug	Goodrug/ Asistix
Number of patients	260	262	69	66
Male	182	186	64	61
Female	78	76	5	5
Median age, years	62	63	58	60
Range	36 to 88	35 to 79	33 to 76	35 to 75

Figure 13: Table text spacing

Note that "Male," "Female," and "Range" appear offset from the cell margin. 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>&amp;#160;&amp;#160;Male</td>
```

The nonbreaking space can also be used to keep text in a table from breaking inappropriately due to browser resizing. To build upon the above example, if the user did not want "Number of patients" to wrap, he or she can use the nonbreaking space to ensure this. The following XML encoding

```
<td>Number&amp;#160;of&amp;#160;patients</td>
```

ensures that the text will not break when the browser window is resized.

Trial	28-day Schedule		21-day Schedule	
Treatment Arm	Drugapil/ Goodrug	Goodrug	Drugapil/ Goodrug	Goodrug/ Asistix
Number of patients	260	262	69	66
Male	182	186	64	61
Female	78	76	5	5

Images

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.

```
<renderMultiMedia referencedObject="MM1"/>
```

Per XML convention, the <observationMedia> element does not contain the graphic file, but instead points at the file. Additionally, observationMedia identifies the graphic media type (e.g., JPEG or GIF). Note also that observationMedia is always contained within a <component> element.

```
<component>
    <observationMedia ID="MM1">
        <value xsi:type="ED" mediaType="image/jpeg">
            <reference value="SPLDemoDrug_structure.jpg"/>
        </value>
    </observationMedia>
</component>
```

For example:

```
…
<paragraph>
   QOL was a secondary endpoint in both randomized studies….
</paragraph>
<renderMultiMedia referencedObject="MM1"/>
…
…
```

would display image MM1 defined by <observationMedia ID="MM1"> in the document as a block image.

The actual image file is enclosed by an <observationMedia> element, contained in any <component> in any section, e.g.,

```
<section>
……..
<text>…… </text>
<component>
   <observationMedia ID="MM2">
      <value xsi:type="ED" mediaType="image/jpeg">
         <reference value="SPDemoDrug_2.jpg"/>
      </value>
   </observationMedia>
</component>
</section>
```

Size and resolution

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, the graphic file should be edited to a dimension appropriate for its presentation within the browser.

File type

The file type for images should be appropriate for the intended use of the SPL document. For SPL graphic files to be viewed in a browser according to the standard stylesheet only JPEG and GIF files should be used.

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>s are not applicable for inline images since these are not offset from the surrounding text.

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 <id>, <paragraph>, <table>, <list>, <content>, <renderMultimedia>, etc., element. For example:

<linkHtml href="#test_table_3">Table 1</linkHtml> shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.
…
…

```
<table ID="test_table_3”>
<caption>test table</caption>
    <thead>
        <tr .../>
    </thead>
    <tfoot>
        <tr .../>
    </tfoot>
    <tbody>
        <tr .../>
    </tbody>
</table>
```

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

Creating the Drug Listing Data Elements Section

The drug listing data elements section of SPL contains information included in both drug listing and drug labeling.[21] Future releases of SPL may include data elements covering other areas of the content of labeling.

At present, only the following information should be included in the data elements section of SPL:

Active ingredient(s) - name, strength
Active moiety - name
Inactive ingredient(s) - name and strength (if required in labeling)
Drug product: Proprietary name and product code
Drug product: Nonproprietary name
Package type(s)
Quantity per package
National Drug Code(s) (NDC)
Drug Enforcement Administration (DEA) schedule
Dosage Form
Labeled route(s) of administration
Imprinting characteristics

- Color
- Shape
- Size
- Coating
- Scoring
- Symbol
- Imprint Code

The specific coding for each item is discussed in Table 16 .

The following discussion addresses how to author the data elements section of the SPL. Information on the drug listing data elements is in 21 CRF 207 and associated guidance documents. See http://www.fda.gov/cder/drls/default.htm for detailed information on the drug listing process. Information on imprinting is in 21 CFR 206.

Conceptual View of the Model

The following is a conceptual view of the SPL drug model. The standard diagrammatic view used by HL7 is available in the SPL specification. The conceptual model is presented as a guide to thinking about organizing the information for encoding in XML and as a way of rendering it for easy reading.

An SPL document may include information about one or more approved drug products. A drug product represented by SPL is described by the data elements in the following table:

[21] Drug listing is a process used by the FDA to maintain an inventory of drug products marketed in the United States. The regulations for the drug listing process are in Title 21 of the Code of Federal Regulations (CFR) part 207. The drug listing data elements in SPL are described in the regulation.

Table 12: Conceptual view of the model for a drug product in the data elements section (Single drug product with one or more package configurations)

Proprietary Name	Nonproprietary Name	Active Ingredients & Strength	Inactive Ingredients & Strength	Dosage Form & Route	Imprinting for solid oral dosage forms only	Package Type & Quantity	NDC
Name goes here	Name goes here	List of Active ingredients	List of inactive ingredients	Dose form and route of admin. Here	List of characteristics	Package/Qty 1	NDC 1
						Package/Qty 2	NDC 2
						Package/Qty ...	NDC ...

This table represents the simplest possible case of a drug product modeled in SPL where there is a single drug product distributed in one or more package configurations.

A single drug product with a single strength and a single dosage form (e.g., a 75 mg tablet) would have one proprietary name and one nonproprietary name. If there is only one packaging option (e.g., bottles of 100), then there would be only one NDC. If there are several packaging configurations, each configuration would have a separate NDC (e.g., bottles of 10, bottles of 100). This would result in multiple minor rows in the final 2 columns. A specific drug product/package type/quantity triad is associated with a single NDC.[22]

In some cases a product may consist of multiple identical packages/containers contained in an outer package. If the outer package unit has its own NDC, it must also be included in the Drug Listing Data Elements. Example: a product supplied in a pre-filled syringe packaged in cartons of five syringes, with an NDC assigned to the carton. Both packaging units – the syringe and the carton – need to be listed. This "package nesting" is represented in the SPL markup by means of nested <asContent> elements, and may be represented in the *conceptual view* by listing the inner package followed by the outer package (with its NDC) prefixed by some symbol (say " →") to indicate that the second is associated with (encloses) the first, as follows:
Conceptual view:

Package Type & Qty	**NDC**
syringe, 50mL	9999-0000-01
→ carton, 5	9999-0000-02

The above applies to multi-component drug products as well. Refer to the "SPL Examples" document for specific examples.

A slightly more complex model is where there are multiple drug products in one SPL document as illustrated in the following table.

Table 13: Conceptual view of the model for multiple drug products in one SPL Document

[22]There should be a minor row in the table for every packaging configuration that is associated with an NDC number. This should only include packaging options that are in the How Supplied section of labeling.

Proprietary Name[a]	Nonproprietary Name	Active Ingredients & Strength	Inactive Ingredients & Strength	Dosage Form & route	Imprinting	Package Type & Quantity[b]	NDC[c]
Name 1	Name 1	List of active ingredients	List of inactive ingredients	Dose form and route of admin. Here	List of characteristics	Package/Qty 1	NDC 1a
						Package/Qty 2	NDC 1b
						Package/Qty etc.	NDC …
Name 2	Name 2	List of active ingredients	List of inactive ingredients	Dose form and route of admin. here	List of characteristics	Package/Qty 1	NDC 2a
						Package/Qty 2	NDC 2b
						Package/Qty etc.…	NDC …
Name 3	Name 3	List of active ingredients	List of inactive ingredients	Dose form and route of admin. here	List of characteristics	Package/Qty 1	NDC 1c
						Package/Qty 2	NDC 2c
						Package/Qty etc.	NDC …

[a] Proprietary name is likely to be identical for all rows of the table, e.g., when the difference between row1 and row2 is a different dose form, but different proprietary names may exist and are accommodated in the model. Similar considerations exist for the nonproprietary name in that it is expected that the nonproprietary name will be identical for all rows in the table.
[b] There may be only one package/quantity/NDC triad for each major row in this table. The additional Package/Qty minor rows are for illustrative purposes. [c] Every NDC is unique in this model.

The following is an example of a two drug products differing only by the strengths of the active ingredient:

Table 14: Example of Two Drug Products

Proprietary name	Nonproprietary name	Active Ingredients	Inactive Ingredients	Dosage Form & Route	Impr.[a]	Package Type & Quantity	NDC
SPL demo drug	drug HCl	• ingredient hydrochloride[b]; 200 mg	• inactive1; 200 mg • inactive2; 12.5 mg	Injection, Powder, Lyophilized, For Solution; Intravenous		Vial, Single Dose; 10 ml	0001-7501-01
SPL demo drug	drug HCl	• ingredient hydrochloride; 1 g	• inactive1; 200 mg • inactive2; 12.5 mg	Injection, Powder, Lyophilized, For Solution; Intravenous		Vial, Single Dose; 10 ml	0001-7502-01

[a] Imprinting characteristics of an oral solid dose form are not applicable to a non-solid dose form.
[b] Unless used as an abbreviation in the name in narrative text or in titles, all names/salts should be spelled out, e.g., hydrochloride rather than HCL.

More complex examples are multi-component products. These can take several forms, the simplest being where there are two drugs provided as components of a single drug product (even if names do not exist for the individual components, e.g., oral contraceptives). Kits, consisting of separate products packaged together are another form of a multi-component product. This would be approached conceptually as follows:

Table 15: Conceptual view of the Model for Data Elements (listing elements) for a 'Multiple Component' Product

Overall Proprietary name	Overall nonproprietary Name	Proprietary Name[a]	Nonproprietary Name	Active Ingred. & strength	Inactive Ingred. & strength	Dose Form	Imprinting	Comp. Pack. Type & Quan. [b]	NDC	Overall Pack. Type & Quan.	NDC[c]
Name here	Name here	Comp 1	Name here	List of active ingredients	List of inactive ingredients	Dose form here	List of characterist ics	Pack type and quantity	NDC here	Pack type and quantity	NDC here
		Comp 2	Name here	List of active ingredients	List of inactive ingredients	Dose form form	List of characterist ics	Pack type and quantity	NDC here		
		Comp 3.	Name here	List of active ingredients	List of inactive ingredients	Dose form form	List of characterist ics	Pack type and quantity	NDC here		

[a] Proprietary names may not exist for one or more of the components. Although there may be more than one package/quantity (and associated NDC number) for a component, it is unlikely in this setting.
[b] Package type is also unlikely for a component; the overall product should have this property.
[c] This is the NDC for the overall product; individual components may or may not have an NDC.

In this example, there is an overall brand proprietary name and an overall nonproprietary name. For the example of an oral contraceptive product, the package type could be a 'wheel' with a quantity of 1. However, there could be separate entries for each of the components as the minor rows of the table. For each component there may not be all the entries as there would be for a stand-alone product. For example, there may not be a proprietary name for a component, but the established name could be substituted for this value.[23]

Shown below is the structure of the SPL elements for each of the conceptual elements described above.

[23] An example of coding the data elements for this situation, i.e., multiple drug products forming one drug product with a separate NDC is not included in this version of the implementation guide.

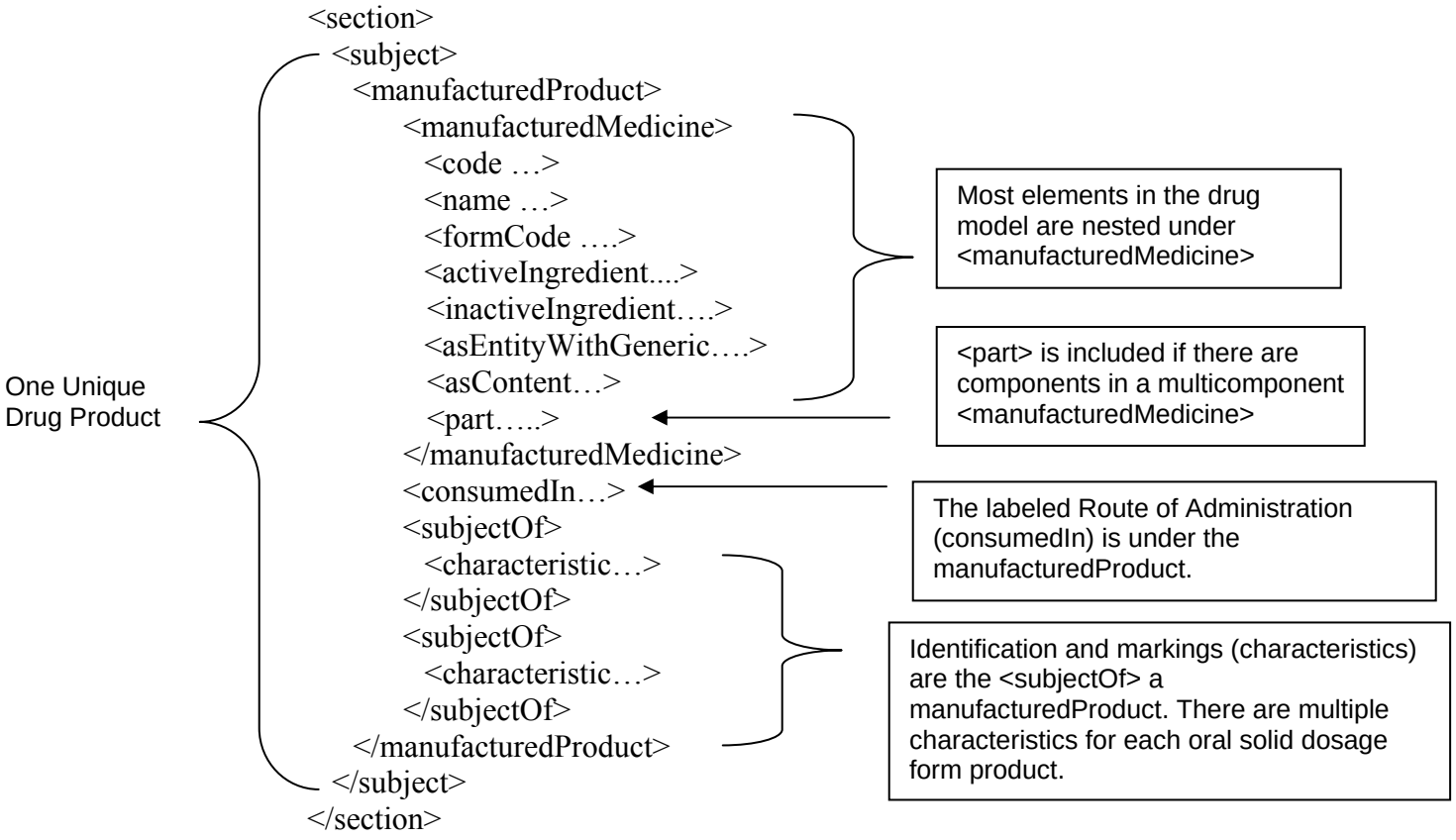

Figure 14: 'Schema' Model of SPL Data Elements section.

Multiple products are represented by multiple <subject> elements within the same enclosing <section>. Multiple different products contained within one package should each be described by <part> within the same <manufacturedMedicine>. Each <part> should describe the individual drug contained within the product. Refer to the "SPL Examples" document for specific examples.

Coding the Data Elements

The table below describes the actual coding of elements in an SPL document for the elements described in the earlier conceptual view.

Table 16: Mapping and Coding of Data Elements

Element	Schema/ FDA req	Comment	Examples
Proprietary name	No/Yes	The proprietary name is the actual text string for the proprietary name from the label. The code for the drug product is the combination of the labeler code and product code from the NDC separated by a dash. Trademark or registered trademark symbols are not included. The code system is the NDC code system. In the SPL document proprietary name is in the <name> element, a child of <manufacturedMedicine>	<manufacturedProduct> <manufacturedMedicine> <code code="0002-7501" codeSystem=”2.16.840.1.113883.6.69”> <name>SPLDemoDrug</name> .... </manufacturedMedicine> </manufacturedProduct>
Nonproprietary Name	No/Yes	The nonproprietary name is the actual text string for the nonproprietary name from the label. All names/salts should be spelled out in the <name> element, e.g., 'gemcitabine hydrochloride' rather than 'gemcitabine HCl', although the shortened name can be used in narrative text or titles. The nonproprietary name is included in SPL as the content of <name> under <genericMedicine>. It is a child of <asEntityWithGeneric>.[24]	<manufacturedProduct> <manufacturedMedicine> … <!-- name, form code, etc. --> <asEntityWithGeneric> <genericMedicine> <name>gemcitabine hydrochloride</name> </genericMedicine> </asEntityWithGeneric> … </manufacturedMedicine> </manufacturedProduct>

[24] Earlier versions of this document implied there would be a coding system for <genericMedicine>. No code system will be used with this element.

Active Ingredients and Active Moiety	No/Yes	Active ingredient name is part of a complex structure and includes name, code, strength and active moiety. The <activeIngredient> is a child of <manufacturedMedicine>. It has several children. Strength (or potency) is indicated by the <quantity> tag, with the <numerator> and <denominator> children. The <numerator> and <denominator> each have the <translation> child. The submitted SPL uses the <translation> child to indicate the quantity values and the code for units. The unit codes are from the NCI Thesaurus. The display name should be included using the FDA preferred term listed in the NCI Thesaurus. This is checked by FDA. The <activeIngredientSubstance> child contains the name of the activeIngredient and the Unique Ingredient Identifier (UNII) from the FDA Substance Registration system (SRS). The <activeIngredientSubstance> child also contains the <activeMoiety><activeMoiety> children, the latter of which has its own code and name. (Note that <activeMoiety> is repeated in the schema [and therefore in SPL].) Submitted SPL includes the name(s) of the active moiety (if applicable) and the ingredient(s) as they appear in the label. The code system for this element is the FDA SRS. For the first SPL submitted for a product, the element for the UNII is omitted because, FDA populates the UNII. All subsequent versions of a specific SPL document are expected to contain the coded UNII values for each ingredient as assigned by FDA. The process is repeated with any new ingredients or	<manufacturedProduct> <manufacturedMedicine> <!-- name, form code, etc. --> … <activeIngredient> <quantity> <numerator><translation code="unit code from NCI thesaurus" codeSystem=" 2.16.840.1.113883.3.26.1.1" value="250" displayName="MILLIGRAM"/> </numerator> <denominator><translation value="1" /></denominator> </quantity> <activeIngredientSubstance> <name>demoingredient</name> <activeMoiety> <activeMoiety> <name>demoingredient active moiety</name> </activeMoiety> </activeMoiety> </activeIngredientSubstance> </activeIngredient> </manufacturedMedicine> </manufacturedProduct>

Inactive ingredients	No/Yes	The inactiveIngredient element description parallels the Active Ingredient element although an 'active moiety' child is not applicable for an inactiveIngredient. The code system for this element and all nested elements in inactive ingredients will be the FDA SRS; At present, listing of inactive ingredients should parallel what is required for printed labeling and SPL should include the inactive ingredients and quantity currently required in the regulations. Similar to active ingredients, for the first SPL submitted for a product, the element for the UNII should be omitted because FDA populates the UNII. All subsequent versions of a specific SPL document are expected to contain the coded UNII values for each ingredient if assigned by FDA.	<manufacturedProduct> <manufacturedMedicine> <!-- name, form code, etc. --> <activeIngredient ….> </activeIngredient> <inactiveIngredient> <quantity> <numerator><translation code="unit code from NCI thesaurus" codeSystem="2.16.840.1.113883.3.26.1.1" value="250" displayName="MILLIGRAM"/></numerator> <denominator> <translation value="1"/> </denominator> </quantity> <inactiveIngredientSubstance> <name>demo inactive ingredient</name> </inactiveIngredientSubstance> </inactiveIngredient> ……
Dosage Form	No/Yes	Dosage form is coded in the 'formCode' element, a direct child of the manufacturedMedicine element. Submitted SPL includes the formCode from the NCI Thesaurus. The displayName may be included using the FDA preferred term from the NCI Thesaurus. The display name is checked by the FDA. The codeSystem value for this element is in Table 19.	<manufacturedProduct> <manufacturedMedicine> <!-- name, form code, etc. --> <formCode code="C42950" codeSystem="2.16.840.1.113883.3.26.1.1" displayName="Injection, Lipid Complex" /> <activeIngredient....> <inactiveIngredient….> <asEntityWithGeneric….> <asContent….> </manufacturedMedicine> </manufacturedProduct>

Labeled Route of Administration	No/Yes	Labeled route of administration is coded in the routeCode element, a child of the <manufacturedProduct>, <consumedIn>, and <substanceAdministration> elements. Submitted SPL includes the routeCode from the NCI Thesaurus. The displayName may be included using the FDA preferred term from the NCI Thesaurus. The display name is checked by the FDA. The codeSystem value for this element is in Table 19. If more than one route of administration is approved, <consumedIn> blocks are repeated.	<manufacturedProduct> …….. <consumedIn> <substanceAdministration> <routeCode code="C38209" codeSystem="2.16.840.1.113883.3.26.1.1" displayName="Enteral"/> </substanceAdministration> </consumedIn> </manufacturedProduct> Repeated blocks used if more than one route of administration <manufacturedProduct> …….. <consumedIn> <!--- first route or administration --> …… </consumedIn> <consumedIn> <!--- second route of administration--> </consumedIn> </manufacturedProduct>

Package Type/ Quantity and NDC	No/Yes	The package type is contained in the <manufacturedMedicine> as the child of <asContent><containerPackagedMedicine>. Quantity is the direct child of <asContent> and has the same structure as <quantity> when used with other elements (e.g., active ingredients). For products packaged in a nested fashion, with an inner container contained within another container with its own NDC code, see *SPL Examples* document. Package Type is the value of <formCode> under <containerPackagedMedicine>. Submitted SPL includes the formCode from the NCI Thesaurus. The displayName may be included using the FDA preferred term from the NCI Thesaurus. The display name is checked by the FDA. The codeSystem value for this element is in Table 19. The NDC is the code child of the <containerPackagedMedicine> element; as such it is directly associated with a containerA <container> has a <quantity> and a package/container) and associated NDC number. The code system for the NDC is in Table 19	<manufacturedProduct> <manufacturedMedicine> …… <asContent> <quantity> <numerator><translation code="C28254" codeSystem="2.16.840.1.113883.3.26.1.1" value="50" displayName="MILLILITER"/></numerator> <denominator><translation value="1"/></denominator> </quantity> <containerPackagedMedicine> <code code="0001-7502-01" codeSystem="2.16.840.1.113883.6.69" codeSystemName="NDC"/> <formCode code="C43226" displayName="Vial" /> </containerPackagedMedicine > </asContent> </manufacturedMedicine> </manufacturedProduct>

DEA schedule	No/Yes	The DEA schedule in which the product is controlled is included in the SPL model as the <code> for <policy>, a <subjectOf> a <manufacturedProduct>. Submitted SPL includes the code from the NCI Thesaurus. The displayName may be included using the FDA preferred term from the NCI Thesaurus. The display name is checked by the FDA. The code value for this element is in Table 19.	<manufacturedProduct> <manufacturedMedicine> …… </manufacturedMedicine> <subjectOf> <policy classCode=”DEADrugSchedule”> <code code="C48675" codeSystem="2.16.840.1.113883.3.26.1.1" > displayName="CII" /> </policy> </subjectOf> </manufacturedProduct>
Approval information	No/No	<approval> is included in the SPL schema in anticipation of changes in labeling regulations and should not be used at this time.	This should not be used at this time.
Imprinting	No/Yes	Imprinting are the characteristics of oral solid dosage form drug product that are included as <characteristic> of the <manufacturedProduct> in the data elements section of SPL. The following characteristics are provided for all oral solid dosage forms – color, scoring, shape, size, coating, symbols, imprint codes. The coding of the characteristics within SPL are described in the following rows.	See below

Color	No/Yes	See http://www.fda.gov/oc/datacouncil/spl.html for information on determining the color value. Submitted SPL includes the code from the NCI Thesaurus. The displayName may be included using the FDA preferred term from the NCI Thesaurus. The display name is checked by the FDA. The codeSystem value for this element is in Table 19. For multiple colors on a dosage form, the <subjectOf> block would be repeated.	The form is as follows: <manufacturedProduct> <manufacturedMedicine> … </manufacturedMedicine> … <subjectOf> <characteristic classCode="OBS"> <code code="SPLCOLOR" codeSystem="2.16.840.1.113883.1.11.19255"/> <value xsi:type="CE" code="C48333" codeSystem=" 2.16.840.1.113883.3.26.1.1" displayName="BLUE"> originalText>blue</originalText> </value> </characteristic> </subjectOf> </manufacturedProduct>

Score	No/Yes	See http://www.fda.gov/oc/datacouncil/spl.html for information on determining the scoring value. Submitted SPL includes the code for scoring. The codeSystem value for this element is in Table 19.	The form is as follows: <subjectOf> <characteristic classCode="OBS"> <code code="SPLSCORE" codeSystem="2.16.840.1.113883 .1.11.19255"/> <value xsi:type="INT" value="4"/> </characteristic> </subjectOf> Solid dosage forms that can only be divided into unequal pieces are given a value of nullFlavor=”OTH”: <subjectOf> <characteristic classCode="OBS"> <code code="SPLSCORE" codeSystem="2.16.840.1.113883 .1.11.19255"/> <value xsi:type="INT" nullFlavor="OTH"/> </characteristic> </subjectOf>
Shape	No/Yes	See http://www.fda.gov/oc/datacouncil/spl.html for information on determining the shape value. Submitted SPL includes the code from the NCI Thesaurus. The displayName may be included using the FDA preferred term from the NCI Thesaurus. This is checked by the FDA. The codeSystem value for this element is in Table 19.	The form is as follows: <subjectOf> <characteristic classCode="OBS"> <code code="SPLSHAPE" codeSystem="2.16.840.1.113 883.1.11.19255”/> <value xsi:type="CE" code="C48338" codeSystem="2.16.840.1.113 883.3.26.1.1"/> displayName="DIAMOND"> <originalText>diamond- shaped</originalText> </value> </characteristic> </subjectOf>

Size	No/Yes	See http://www.fda.gov/oc/datacouncil/spl.html for information on determining the size value. Submitted SPL includes the code for scoring. The codeSystem value for this element is in Table 19.	The form is as follows: <subjectOf> <characteristic classCode="OBS"> <code code="SPLSIZE" codeSystem="2.16.840.1.113883.1.11.19255"/> <value xsi:type="PQ" value="5" unit="mm"/> </characteristic> </subjectOf>
Coating	No/Yes	See http://www.fda.gov/oc/datacouncil/spl.html for information on determining the coating value. Submitted SPL includes the code for scoring. The codeSystem value for this element is in Table 19.	The form is as follows: Example: <subjectOf> <characteristic classCode="OBS"> <code code="SPLCOATING" codeSystem="2.16.840.1.113883.1.11.19255"/> <value xsi:type="BL" value="true"/> </characteristic> </subjectOf>
Symbol	No/Yes	See http://www.fda.gov/oc/datacouncil/spl.html for information on determining the scoring value. Submitted SPL includes the code for scoring. The codeSystem value for this element is in Table 19.	The form is as follows: Example: <subjectOf> <characteristic classCode="OBS"> <code code="SPLSYMBOL" codeSystem="2.16.840.1.113883.1.11.19255"/> <value xsi:type="BL" value="true"/> </characteristic> </subjectOf>

Imprint	No/Yes	See http://www.fda.gov/oc/datacouncil/spl.html for information on determining the imprint code value. Submitted SPL includes the code for scoring. The codeSystem value for this element is in Table 19.	The form is as follows: <subjectOf> <characteristic classCode="OBS"> <code code="SPLIMPRINT" codeSystem="2.16.840.1.113883.1.11.19255"/> <value xsi:type="ST">MDL1230;X23</value> </characteristic> </subjectOf>

All data elements for one unique product (corresponding to a major row in the conceptual view table) are contained within a single <component><section> in the SPL body; each unique product (<manufacturedProduct>) will have its own section. This means that information about a drug product intended for machine processing will be aggregated in one section, even though the textual (human readable) information may tend to be scattered in different sections in the narrative text (e.g., in the Description and How Supplied sections). Sections that contain these structured data elements that are built around <manufacturedProduct> will only contain structured data and not text.

An conceptual example of the XML markup of structured data elements that describe a drug product (one section per product) intended for machine processing is shown below. By convention it is requested that the <manufacturedProduct> sections be present as the initial sections in the body following the header elements.

```
<Header Section….>
……
<Body Section …..>
<component>
    <structuredBody>
        <component><!-- this component/section contains all the data elements -->
            <section>
                <id root="81E32825-5BC8-46EB-8043-AE607B3819FA " />
                <!-- Each proprietary drug product as a separate subject -->
                <subject>
                    <manufacturedProduct>
                        <manufacturedMedicine>
                            ….
                        </manufacturedMedicine>
                        <consumedIn>
                            ….
                        </consumedIn>
                            <subjectOf>
```

GUID for section

Drug information (see above) for drug product 1

Labeled Route of Administration for drug product 1

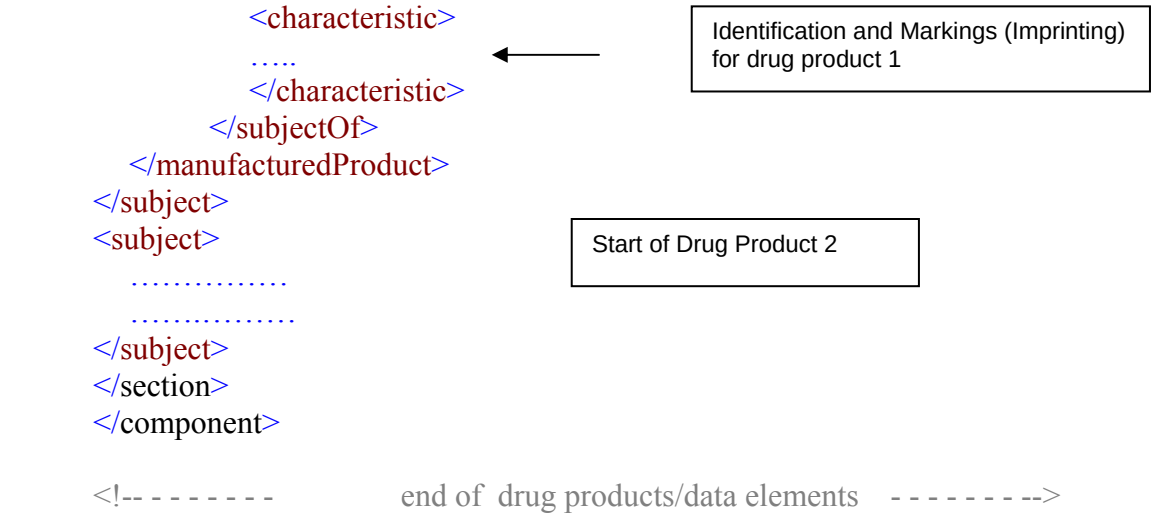

Figure 15: A Conceptual Example of SPL 'Drug Elements' section.

The following example shows a drug product section for an SPL document with insertion of more detailed data elements. Note that this identical format would be repeated for each row in the conceptual view table above.

```
<component>
  <section>
    <id root="675D3B70-0457-4F92-AA4A-8B30928A32A9"/>
    <subject>
      <manufacturedProduct>
        <manufacturedMedicine>
          <code code="0004-2601"
          codesystem=”2.16.840.1.113883.6.69” />
          <name>Example Drug</name>
          <formCode code="C25158"
          codeSystem="2.16.840.1.113883.3.26.1.1"
          displayName="Capsule" />
          <activeIngredient>
            <quantity>
```

```
            <numerator><translation code="C28253"
            codeSystem=" 2.16.840.1.113883.3.26.1.1
            value="87.5" displayName="MILLIGRAM"/>
            </numerator>
            <denominator>
            <translation value="1"/>
        </denominator>
        </quantity>
        <activeIngredientSubstance>
            <name>MyDrugSalt</name>
            <activeMoiety>
                <activeMoiety>
                    <name>MyDrug</name>
                </activeMoiety>
        </activeMoiety>
        </activeIngredientSubstance>
    </activeIngredient>
    <inactiveIngredient>
        <inactiveIngredientSubstance>
            <name>inactive ingredient 1</name>
        </inactiveIngredientSubstance>
    </inactiveIngredient>
    <inactiveIngredient>
        <inactiveIngredientSubstance>
            <name>inactive ingredient 2</name>
        </inactiveIngredientSubstance>
    </inactiveIngredient>
    <asEntityWithGeneric>
        <genericMedicine>
            <name>My Drug generic Name</name>
        </genericMedicine>
    </asEntityWithGeneric>
    <asContent>
     <quantity>
            <numerator><translation code="
    C28254" codeSystem="2.16.840.1.113883.3.26.1.1"
    value="50" displayName="MILLILITER"/></numerator>
     <denominator><translation value="1"/>
     </denominator>
     </quantity>
     <containerPackagedMedcine>
        <code code="12345-678-90"
        codeSystem="2.16.840.1.113883.6.69"
        codeSystemName="NDC"/>
            <formCode code="C43182"
            displayName="Carton"/>
      </containerPackagedMedcine>
```

```
                    </asContent>
                </manufacturedMedicine>
                <subjectOf>
                    <characteristic classCode="OBS">
                     <code code="SPLSHAPE"
                     codeSystem="2.16.840.1.113883.1.11.19255”/>
                        <value xsi:type="CE" code="C48338"
                        codeSystem="2.16.840.1.113883.3.26.1.1.6"
                        displayName="DIAMOND">
                            <originalText>diamond-shaped</originalText>
                        </value>
                    </characteristic>
                </subjectOf>
                <subjectOf>
                    <characteristic classCode="OBS">
                        <code code="SPLCOLOR"
                        codeSystem="2.16.840.1.113883.1.11.19255"/>
                        <value xsi:type="CE" code="C48326" codeSystem="
                        2.16.840.1.113883.3.26.1.1”
                        displayName="RED">
                            <originalText>Reddish-tinted</originalText>
                        </value>
                    </characteristic>
                </subjectOf>
                <consumedIn>
                    <substanceAdministration>
                        <routeCode code="C38209"
                        codeSystem="2.16.840.1.113883.3.26.1.1"
                        displayName="Enteral"/>
                    </substanceAdministration>
                </consumedIn>
            </manufacturedProduct>
        </subject>
    <component> <!-- This component contains all the content of labeling -->
            <section>
                <id root="887C4DF62-7F0B-4267-A1A7-50F22BA35446"/>
                    <code code="34089-3"
                codeSystem="2.16.840.1.113883.6.1"
                displayName="DESCRIPTION SECTION"/>
                <title>DESCRIPTION</title>


                .....
                .....
            </section>
        </component>
    </section>
```

```
        </component>

        ........
```

Figure 16: Annotated Example of SPL 'Drug Product' section.

For examples of multi-component drug products, refer to the “SPL Examples” document.

Submitting SPL to FDA

See FDA guidance to industry: *Regulatory Submissions in Electronic Format – Content of Labeling* for information on submitting SPL to FDA. This guidance may be found on the FDA web site at http://www.fda.gov/cder/guidance/guidance.htm.

Organization and naming of files for submission to FDA

SPL submitted to FDA should have all files organized at one level, i.e., there should not be relative or nested subdirectories. All files should be included in a folder named ‘spl’. The following principles should be followed:

- The name of the xml file containing the spl file has the *.xml extension and the file name reflects the name of the product or a variation, e.g., "SPLdemoDrug.xml".
- Only one SPL (.xml) file should be provided with a submission
- It is helpful for the *.xml file name to be identical in all submissions/revisions of the document sent to FDA.
- Each submission to FDA should include the *.xml file and all associated image files, even if these have not changed.
- Multi-word file names are built using dashes, e.g., "First-Drug.xml"
- Absolute URLs or URLs containing scheme identifiers (file: or http :) or any path names (e.g., "..", or ”graphics/") should not be used in SPL.
- No spaces are permitted in the file names
- Image file names use the same prefix as the main SPL file followed by a dash and a short suffix to distinguish it e.g.,SPLdemoDrug-figure-01.jpg, SPLdemoDrug-figure-02.jpg,SPLdemoDrug-structure.jpg, or SPLdemoDrug-figure-01.jpg
- Image file extensions are restricted to 3 characters, e.g., jpg and not jpeg for JPEG files
- JPEG (*.jpg) is the preferred file format for images. GIF (*.gif) file formats may be used if a JPEG alternative does not exist. It is expected this will be extremely uncommon.
- The recommended resolution is 300 dpi. Images greater than 300 dpi should not be submitted to keep the file size manageable.
- It is required that all image file names cited in the SPL document match exactly the actual file names. For example:

```
<observationMedia ID="MM1">
    <value xsi:type="ED" mediaType="image/jpeg">
        <reference value="SPLdemoDrug-figure-01.jpg"/>
    </value>
```

</observationMedia>

An example set of files submitted to FDA might consist of the following:

SPLdemoDrug.xml
SPLdemoDrug-figure-01.jpg
SPLdemoDrug-figure-02.jpg
SPLdemoDrug-figure-03.jpg

For information where to send SPL for products regulated by CDER, see http://www.fda.gov/cder/regulatory/ersr/default.htm. When SPL is accompanying a paper submission, SPL should also be included on electronic media (e.g., CD). On the electronic media, SPL and all associated image files should be located in an electronic folder also named spl. See the Guidance for Industry : *Providing Regulatory Submissions in Electronic Format - Content of Labeling* for additional information.

eCTD and SPL

Within an eCTD, all files should be referenced in the XML backbone (i.e., the SPL document, and associated graphics). SPL should be included in a subfolder named *spl* in the appropriate labeling folder under the *m1* folder. Leaf elements in the eCTD currently support SPL files.

Appendices

Table 17: Glossary

Term or Abbreviation	Definition
21CFR201.56	Code of Federal Regulations, Title 21, Federal Food, Drug and Cosmetic Act, Part 201.56, "General Requirements on content and format of labeling for human prescription drugs." Access via: http://www.gpoaccess.gov/cfr/index.html
21CFR201.57	Code of Federal Regulations, Title 21, Federal Food, Drug and Cosmetic Act, Part 201.57, "Specific Requirements on content and format of labeling for human prescription drugs." Access via: http://www.gpoaccess.gov/cfr/index.html
ANSI	American National Standards Institute
ASCII	American Standard Code for Information Interchange, a common 8-bit character encoding of printed (and some non-printed characters) for electronic communication.
Attribute	A name-value pair included inside an XML element tag, e.g., <id root="2 F33776B3-2DC8-435B-856B-444DD69F6CD7"/> where 'id' is the element name and 'root' the attribute.
Content of labeling	All text, tables and figures in labeling as described in regulations for a specific product (e.g., 21 CFR 201.56 and 201.57 for human prescription drugs, 201.66 for human over-the-counter drugs). For SPL, content of labeling includes sections such as the Patient Package Insert (PPI) or MedGuide if these are included as part of the printed package insert.

Term or Abbreviation	Definition
Electronic Labeling Rule	"Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format",Published in the Federal Register: December 11, 2003, Volume 68, Number 238. (http://frwebgate1.access.gpo.gov/cgi-bin/waisgate.cgi?WAISdocID=154453135555+1+0+0&WAISaction=retrieve) Guidance for Industry regarding the Electronic Labeling Rule is available at: http://www.fda.gov/ohrms/dockets/98fr/2004d-0041-gdl0001.doc
Element	A section of text in an XML document delimited by start and end tags; or in the case of empty elements (elements with no content, only attributes), indicated by an empty tag.
Entity	A representation of a special character that cannot be used in XML coding of text, e.g., "<" must be coded as "<" if used within a paragraph to avoid confusion with element tags. Entities are described in Table 5.
ELIPS	FDA's Electronic Labeling Information Processing System.
Granularity	The relative size of a defined 'semantic' or informational unit; in the context of this specification, granularity refers to the size of an information unit where <section> would be coarse grained and a data point would be fine grained. The degree of granularity in SPL is defined by the ability of the author to define related information into <sections> of the SPL. Increased granularity is recommended by dividing <section>s into smaller sub<section>s where each subsection contains related information. See section 0 for a discussion of this in the context of SPL.
GUID	A Globally Unique Identifier (GUID) used to identify an element, that is, a unique value that does not exist in any other SPL (or in any other context where GUID are used).
Health Level Seven (HL7)	An ANSI-accredited Standards Development Organization (SDO) operating in the healthcare arena. (See http://www.hl7.org)
LOINC	LOINC® (Logical Observations, Identifiers, Names, and Codes, http://www.regenstrief.org/loinc.htm). LOINC® is a coding system maintained by the Regenstrief Institute for Health Care primarily for coding and electronic transmission of laboratory and other medical information.
Markup	Annotations within an XML document intended for machine processing and not meant to be displayed but needed to structure the document, e.g., element names such as <section>.
Schema	A formal definition of the structure and content of a type of XML document.
Section	The <section> element identifies units of information within SPL and can include nested subsections. See Section 0.
SPL body	The SPL Body is a section containing the data elements and content of labeling.
SPL header	The SPL Header identifies and classifies the document and may provide information on the owner of the marketing authority for the product, the author, legal authenticator, and reviewers
SPL Instance	An SPL instance is a specific SPL document, e.g., a SPL for singulair.
SPL specification	The SPL specification is a document markup standard that specifies the structure and semantics for the regulatory requirements and content of product labeling.
SRS	The FDA Substance Registration System, the source for UNII codes used in SPL (see UNII below)
Stylesheet	A file that describes how to display an XML document of a given type.
UNII	Unique identifier codes for active and inactive ingredients. FDA provides these coded

Term or Abbreviation	Definition
	values.
UUID	Universally Globally Unique Identifier, an alternative name for GUID's (see above).
Valid document	A document that meets all of the validity constraints in the XML Specification. In SPL this is a document that is well formed (follows the rules of XML) and is valid, i.e., follows the rules of the SPL schema.
W3C	The World Wide Web Consortium, an international industry consortium (http://www.w3.org)
W3C Schema	The three-part schema specification issued by the W3C XML Schema Part 0: Primer, W3C Recommendation 2-May-2001, http://www.w3.org/TR/xmlschema-0/ XML Schema Part 1: Structures, W3C Recommendation, 2-May-2001, http://www.w3.org/TR/xmlschema-1/ XML Schema Part 2: Datatypes, W3C Recommendation, 2-May-2001, http://www.w3.org/TR/xmlschema-2/
XML	Extensible Markup Language, specification of the W3C, a formal subset of SGML (http://www.w3.org/TR/REC-xml).
XML document	SPL is an XML document. An XML consists of a prolog (processing instructions), a root document element, and other objects.
XML schema	See W3C Schema
XSL	Extensible Style Language, a specification of the W3C (www.w3.org/Style/XSL/). An XSL stylesheet in SPL collectively consists of several files, a transformation file (e.g., spl.xsl) and a cascading style sheet (e.g., spl.css). These files 'transform' SPL into an HTML files that can be viewed by a standard Web browser.
XSLT	XSL transformation language, a specification of the W3C (http://www.w3.org/TR/xslt). XSLT is one part of what is collectively considered the XSL stylesheet (see XSL above).

Table 18: LOINC Codes

LOINC code	SPL displayName
	Document type
34391-3	HUMAN PRESCRIPTION DRUG LABELING
	Section type
34066-1	BOXED WARNING SECTION
34089-3	DESCRIPTION SECTION
34090-1	CLINICAL PHARMACOLOGY SECTION
34067-9	INDICATIONS & USAGE SECTION
34070-3	CONTRAINDICATIONS SECTION
34071-1	WARNINGS SECTION
42232-9	PRECAUTIONS SECTION
34072-9	GENERAL PRECAUTIONS SECTION
34076-0	INFORMATION FOR PATIENTS SECTION
34075-2	LABORATORY TESTS SECTION
34073-7	DRUG INTERACTIONS SECTION
34074-5	DRUG &OR LABORATORY TEST INTERACTIONS SECTION
34083-6	CARCINOGENESIS & MUTAGENESIS & IMPAIRMENT OF FERTILITY SECTION
42228-7	PREGNANCY
34077-8	TERATOGENIC EFFECTS SECTION
34078-6	NONTERATOGENIC EFFECTS SECTION
34079-4	LABOR & DELIVERY SECTION
34080-2	NURSING MOTHERS SECTION
34081-0	PEDIATRIC USE SECTION
34082-8	GERIATRIC USE SECTION
34084-4	ADVERSE REACTIONS SECTION
42227-9	DRUG ABUSE AND DEPENDENCE SECTION
34085-1	CONTROLLED SUBSTANCE SECTION
34086-9	ABUSE SECTION
34087-7	DEPENDENCE SECTION
34088-5	OVERDOSAGE SECTION
34068-7	DOSAGE & ADMINISTRATION SECTION
34069-5	HOW SUPPLIED SECTION
34091-9	ANIMAL PHARMACOLOGY &OR TOXICOLOGY SECTION

34092-7	CLINICAL STUDIES SECTION
34093-5	REFERENCES SECTION
38056-8	SUPPLEMENTAL PATIENT MATERIAL SECTION
42231-1	SPL MEDGUIDE SECTION
42230-3	SPL PATIENT PACKAGE INSERT SECTION
42229-5	SPL UNCLASSIFIED SECTION

Table 19: Code Systems Used in SPL

Usage	Code System Object Identifier (OID)	System
Document and Section Type	2.16.840.1.113883.6.1	LOINC
Route of Administration	2.16.840.1.113883.3.26.1.1	NCI Thesaurus Drug_Route_of_Administration
Dosage Form	2.16.840.1.113883.3.26.1.1	NCI Thesaurus Pharmaceutical_Dosage_Form
Package Type	2.16.840.1.113883.3.26.1.1	NCI Thesaurus Drug_Packaging_Device
Potency Unit	2.16.840.1.113883.3.26.1.1	NCI Thesaurus Unit_of_Potency
DEA Schedule	2.16.840.1.112883.3.26.1.1	NCI Thesaurus
NDC and product code	2.16.840.1.113883.6.69	FDA
UNII	2.16.840.1.113883.4.9	FDA Substance Registration System
SPL Color value	2.16.840.1.113883.3.26.1.1	NCI Thesaurus Structured_Product_Labeling_Color
SPL Shape value	2.16.840.1.113883.3.26.1.1	NCI Thesaurus Structured_Product_Labeling_Shape
SPL characteristic	2.16.840.1.113883.1.11.19255	HL7

Table 20: Source of Information on the Data Elements

Header	**Header data elements**	**Information provided by applicant**	**Information provided by FDA**
	id	GUID	GUID
	code	LOINC code for type	-
	title	Title text	-

	effectiveTime	Leave empty (<effectiveTime/>)	Receipt date for annual report and changes being effected labeling changes and the date of sign off for new labeling or prior approval labeling changes.
	setId	setId	-
	VersionNumber	-	incremented for each new version of labeling
Section	**Section data elements**	**Information provided by applicant**	**Information provided by FDA**
	id	GUID	GUID
	code	LOINC code for section if needed	-
	title	Title text if needed	-
	text	Content of labeling (text, tables and figures)	-
	effectiveTime	-	Receipt date for annual report and changes being effected labeling changes and the date of sign off for new labeling or prior approval labeling changes.
Drug Listing	**Drug listing data elements**	**Information provided by applicant**	**Information provided by FDA**
Proprietary name	name	Text of name as in the label	-
	code	Labeler and product code from NDC	-
	codeSystem	NDC codeSystem OID	-
Nonproprietary name	name	Text of name as in the label	-
Active and inactive ingredient and active moiety	name	Text of name as in the label (active ingredient with counterion, active moiety without counterion)	-
	code	-	UNII value
	codeSystem	-	FDA SRS codeSystem OID
	codeSystemName	-	"FDA SRS"
Active and	value	-	FDA enters value from translator

inactive ingredient quantity numerator and denominator	unit	-	FDA enters UCUM equivalent of NCI Thesaurus unit "code" from translator.
Active and inactive ingredient quantity translator numerator and denominator	code	Unit code from the NCI Thesaurus	-
	codeSystem	NCI Thesaurus units OID	-
	codeSystemName	-	"NCI Thesaurus"
	displayName	FDA preferred term from NCI Thesaurus	Check or add FDA preferred term from NCI Thesaurus
	value	Quantity numerator value	-
Dosage form	formCode	NCI Thesaurus code	-
	codeSystem	NCI Thesaurus OID	-
	codeSystemName	-	"NCI Thesaurus"
	displayName	FDA preferred term from NCI Thesaurus	Check or add FDA preferred term from NCI Thesaurus
Labeled route of administration	routeCode	NCI Thesaurus code	-
	codeSystem	NCI Thesaurus OID	-
	codeSystemName	-	"NCI Thesaurus"
	displayName	FDA preferred term from NCI Thesaurus	Check or add FDA preferred term from NCI Thesaurus
Package type	formCode	NCI Thesaurus code	-
	codeSystem	NCI Thesaurus OID	-
	codeSystemName	-	"NCI Thesaurus"
	displayName	FDA preferred term from NCI Thesaurus	Check or add FDA preferred term from NCI Thesaurus
Package quantity	The same as active ingredient		
DEA schedule	code	NCI Thesaurus code	-
	codeSystem	NCI Thesaurus OID	-
	codeSystemName	-	"NCI Thesaurus"
	displayName	DEA Schedule number (CI, CII, CIII, CIV, CV)	Check or add DEA schedule
NDC number	code	NDC number	-
	codeSystem	NDC code system OID	-
SPL color	Value code	NCI Thesaurus code	-
	Value codeSystem	NCI Thesaurus OID	-
	codeSystemName	-	"NCI Thesaurus"

	displayName	FDA preferred term from NCI Thesaurus	Check or add FDA preferred term from NCI Thesaurus
	originalText	Text as it appears in the labeling	-
	code	HL7 characteristic code	
	codeSystem	HL7 characteristic OID	
SPL shape	Value code	NCI Thesaurus code	-
	Value codeSystem	NCI Thesaurus OID	-
	codeSystemName	-	"NCI Thesaurus"
	displayName	FDA preferred term from NCI Thesaurus	Check or add FDA preferred term from NCI Thesaurus
	originalText	Text as it appears in labeling	
	code	HL7 characteristic code	
	codeSystem	HL7 characteristic OID	
SPL score	code	HL7 characteristic code	-
	codeSystem	HL7 characteristic OID	-
	value	Scoring number	-
SPL size	code	HL7 characteristic code	-
	codeSystem	HL7 characteristic OID	-
	value	size	-
SPL coating	code	HL7 characteristic code	-
	codeSystem	HL7 characteristic OID	-
	value	True or false	-
SPL symbol	code	HL7 characteristic code	-
	codeSystem	HL7 characteristic OID	-
	value	True or false	-
SPL imprint	code	HL7 characteristic code	-
	codeSystem	HL7 characteristic OID	-
	value	Imprint codes	-