

## **SPL Implementation Guide for FDA Content of Labeling Submissions**

**Ver. 0.6c**

*8/19/04: Note: this is a draft document currently under development. This version is being released to aid SPL authors as they develop SPL. This document does not represent the final version of this document and contents may be altered when the final version is released.*

Changes from Version 0.6b:

This section will contain significant changes to this document as changes are incorporated until the time of formal acceptance as version 1.0.

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**I. Introduction**

The Structured Product Labeling Implementation Guide for FDA Content of Labeling Submissions (SPL Implementation Guide) is a companion to the Health Level Seven (HL7) Structured Product Labeling (SPL) normative standard. HL7 is one of several American National Standards Institute (ANSI) accredited Standards Developing Organizations (SDO) for health care. The latest version of SPL Schema, which is the strict technical definition of an SPL document, is available from HL7 at [www.hl7.org](http://www.hl7.org).<sup>1</sup>

This SPL Implementation Guide was created by the HL7 SPL working group specifically to provide additional information for creating Content of Labeling submissions to the FDA described in the guidance to industry: *Providing Regulatory Submissions in Electronic Format – Content of Labeling*<sup>2</sup>. An extensive Technical Section is being developed by the HL7 SPL working group to be added to this document and addresses specific technical issues in authoring an SPL document in greater detail. When this is completed it will be integrated into this document.

<sup>1</sup>A brief overview of XML that includes a definition of XML schemas is included in Appendix VII.G, XML Primer.

<sup>2</sup> See *Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Content of Labeling* (February, 2004) at <http://www.fda.gov/cder/guidance/6028dft.doc>.

## II. Creating an SPL Document

### A. Introduction

Structured Product Labeling (SPL) is the HL7 standard for describing the content of prescription drug labeling in an XML document. An SPL document consists of an XML (extensible markup language) document that contains the text and images in an approved prescription package insert (i.e., the content of labeling) along with additional information for machine processing of label content (i.e., header information and data elements, described below). The SPL XML file is converted to a human-readable format by the use of a set of files collectively referred to as a stylesheet. The stylesheet displays the information in the XML file in a consistent format for viewing. Currently, the standard stylesheet supports display in web browsers only.

An SPL document may be created using a variety of possible editing environments, ranging from a general purpose word processor to an XML editor to a SPL-specific editing tool. Although considerable differences in the approach to creating an SPL document are determined by the choice of environment, the final document will be independent of the tool used for creation; all will be expected to be valid against the SPL schema as defined by the SPL standard.<sup>3</sup> It is also anticipated that where options exist in creating the actual SPL document, 'Best Practices' and regulatory requirements will be followed.

This section specifically addresses creating an SPL document outside of a dedicated SPL-specific environment, i.e., using a text-processing environment or a general XML-oriented editing environment. Ideally, use of a dedicated 'SPL creation' tool will 'blind' the SPL author to many of the details addressed in this section. This section may also be of interest to developers or individuals engaged in the quality control of SPL documents.

The HL7 SPL stylesheet is the method adopted by HL7 to produce a standard display<sup>4</sup> of SPL, i.e., a common 'appearance' of all SPL documents when displayed. At present, the stylesheet is specific for viewing SPL in a web browser.<sup>5</sup> SPL also provides a mechanism whereby additional display 'styles' can be added when SPL is used in different regulatory environments. For US regulatory purposes, FDA will maintain (as necessary) a separate stylesheet which 'adds' to the HL7 standard stylesheet for the display of the content of labeling for documents submitted to FDA. Specific details regarding the FDA-developed stylesheet are described in Appendix VII.B: SPL Standard Stylesheet and FDA Implementation. For conceptual purposes, the display of SPL in a web browser can be considered simply as drawing from 'styles' that are available in both the HL7 and FDA stylesheets; whenever reference is made to display by the 'standard stylesheet', in effect this refers to the HL7 standard stylesheet.

This SPL rendition (i.e., display by the 'standard stylesheet') presents only the content of labeling contained in SPL for viewing by the user. Additional information in SPL, e.g., header information (see Sec. III.B) or data elements, are not part of this display. Other stylesheets are likely to be available which will highlight these features based on individual needs.

SPL has been developed as a document format to transmit the content of labeling rather than a mechanism for reproducing the exact format of printed package inserts. 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 are available that allow the formatting of specific sections within the SPL instance. For example, css allows a paragraph to appear as a 'Black box' when displayed even though a specific 'black box' element or attribute value is not defined in the SPL schema.

<sup>3</sup> Validity of an XML document is discussed in the XML Primer in Appendix VII.G

<sup>4</sup> Rendition, display, and presentation are all used synonymously in this section to refer to the display of SPL on an output device, e.g., a web browser.

<sup>5</sup> Technical details regarding the HL7 standard stylesheet are provided in Section VII.B SPL Standard Stylesheet and FDA Implementation of Stylesheets, although how the stylesheet is used to display SPL is discussed in Section IV.A.4: IFormatting SPL.

An SPL document is used in this guide as a general term to refer to any SPL document; SPL instance is used to refer a specific SPL document, e.g., the gemcitabine example in Appendix VII.C is a specific instance of an SPL document. For the purposes of the implementation guide, these terms are used synonymously.

## B. The SPL Document

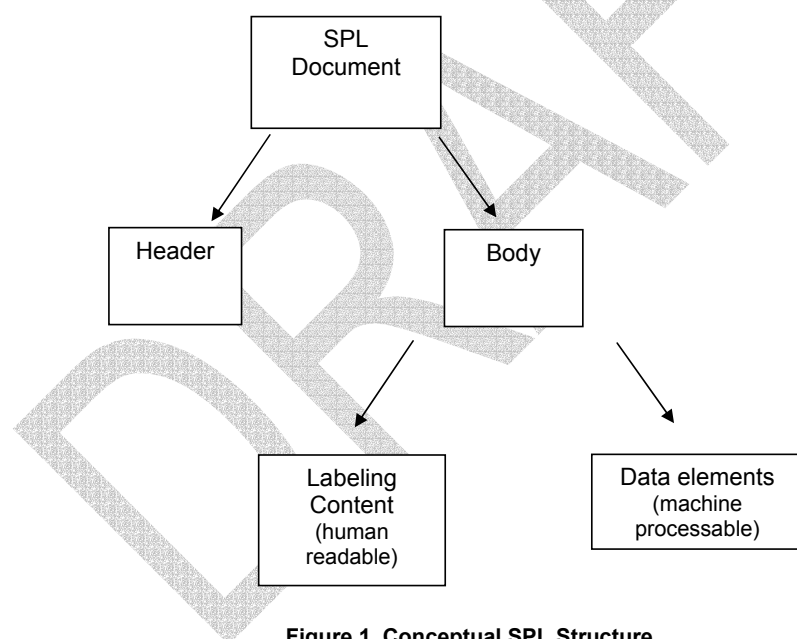
An SPL document consists conceptually of two sections:

- Header
- Body

The body comprises the content of labeling, with two representations of the content:

- Labeling content (human readable text)<sup>6</sup>
- Data elements (machine processable content)

This is illustrated below:



**Figure 1. Conceptual SPL Structure**

The following sections address construction of the header and body. The two parts of the body, the labeling content and the data elements, are considered separately in Sections IV.A and V, respectively.

An SPL document (as does all XML documents) must include a special section at the start of the document with processing instructions and the root element. Although these are XML structures and are not unique to

<sup>6</sup> The label content in SPL is also referred to as the narrative, or narrative text, reflecting its origin from the narrative text of the printed package insert.

the SPL header, for convenience they are discussed in the Creating the SPL Header section below since they will always be the initial part of an SPL document.

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### III. Creating the SPL Header

#### A. Processing Instructions and the Root Element

All XML documents, including SPL (which is a specific type of XML document), must include processing instructions and the root element<sup>7</sup>. The processing instructions at the start of SPL and the root element must be identical for every document submitted to FDA and have the following form:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="spl-1.1.xsl"?>
<Document xmlns="urn:hl7-org:v3" xmlns:voc="urn:hl7-org:v3/voc"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xmlns:splx="urn:hl7-org:splx">8
```

**Comment:** Footnote added.

Although this information appears at the start of each SPL document, it is conceptually separate from the SPL header as discussed previously and explained further below. It may be best considered as a mandatory part of an XML document and as such is not included in descriptions of the SPL header.<sup>9</sup>

#### B. 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 header section contains the following elements following of the <Document> element.<sup>10,11</sup> With the exception of the <title> element in the header, none of the elements in the header that are optional in the SPL schema are necessary in SPL documents submitted to FDA. These fields may be used by the author but the information will not be processed by FDA.

<sup>7</sup> Processing instructions and the root element are discussed in VII.G, XML Primer. These are mandatory parts of an XML document; as such, they are not directly relevant to the discussion of the conceptual outline of an SPL document that follows. It should simply be noted that these lines must appear at the start of any SPL document submitted to FDA to be a valid SPL document (see VII.G, XML Primer for a discussion in of XML/SPL validity). Note that the start of an SPL document may not begin exactly as in the text since comments may be interspersed.

<sup>8</sup> The following general conventions are followed in this document (with occasional exceptions). Element names are in brown and usually in italics in the text, e.g., <car> in an example and *car* when discussed in the text. The left and right angle brackets for an element are in blue as in <car>. Attribute names are in red, e.g., <person age="20">. Attribute values are in black. This general convention may be expanded on in certain complex examples. For more information regarding elements and attributes, see Appendix VII.G - XML Primer.

<sup>9</sup> These specific lines may change, particularly in 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/](http://www.fda.gov/oc/datacouncil/spl/)

<sup>10</sup> Please refer to the SPL normative standard at <http://www.hl7.org> for a complete description of all SPL header elements and attributes.

<sup>11</sup> The <Document> element is the root element of the SPL document.



Table 1. SPL Header Elements<sup>a</sup>

Element	SPL Schema Req.	FDA Req.	Comment	Examples
id	Yes	Yes	<id> is a globally unique identifier for the specific document instance and will differ for every regulatory submission. Information regarding the creation of an id for a specific SPL instance (and for other parts of SPL) is discussed in Section IV.A.3(a).	<id root="35F683E0-94C2-47FE-8925-43D170787B5D"/>
Code	Yes	Yes	<p>&lt;code&gt; represents the LOINC code for human prescription drug labeling<sup>12</sup>. This line should be identical in all SPL submitted to FDA at this time. As implementation of SPL is expanded to other type of product labeling (e.g., OTC labeling), other codes will be available.</p> <p>It is important to note that for the &lt;code&gt; element and in all subsequent elements where codeSystemName is used, this attribute is optional since the codeSystem is determined by the value for the codeSystem. Similarly, the displayName is unnecessary since the value for the displayName is contained in the code value. These attributes are only for human readability and are otherwise unnecessary.</p>	<pre>&lt;code code="34391-3" codeSystem="2.16.840.1.1138 83.6.1" codeSystemName="LOINC" displayName="Human prescription drug label"/&gt;</pre>
Title	No	Yes	<p>&lt;title&gt; should correspond exactly to the title string on the package insert with the exception that trademark and registered trademarks should not be included in the character string.</p> <p>The &lt;title&gt; element is the only header element rendered by the standard stylesheet. In the current version of the stylesheet, a line feed in the title is rendered as a line feed in the title of the SPL document, i.e., use a line feed in the title element when a line feed is necessary for a multi-line title. (Future versions of the SPL schema will permit a &lt;BR&gt; tag in the title element to address multi-line titles.)</p>	<p>Example 1:  &lt;title&gt;GEMZAR&amp;#174;  (GEMCITABINE HCL)  FOR INJECTION&lt;/title&gt;</p>
effectiveTime	Yes	Yes	Although required by the SPL schema, this element is not used by FDA at present. This value must use the HL7 TS data type; although different formats can be used, yyyyymmdd is recommended.	<effectiveTime value="20050106"/>
availabilityTime	No	No	Not used at present. If included, it will be ignored by the FDA receiving system. If this element is used, it should have an HL7 time stamp format.	
confidentialityCode	No	No	All FDA submissions are considered confidential by definition. If used, this code is taken from the HL7 value set.	
languageCode	No	No	All submissions to FDA are required to be in English rendering this field unnecessary. If used for internal systems, this code is taken from the HL7 value set for this element.	

<sup>12</sup> LOINC is one of the coding systems that has been adopted by HL7 for use in SPL and other HL7 standards. LOINC code to be used with SPL are listed in section VII.H LOINC codes for SPL. For a complete description of LOINC codes, see <http://www.LOINC.org>

setId	No	No <sup>a</sup>	<set ID> will be a unique identifier for the document that will remain constant through all versions/revisions of the document. The information in this field will not be processed by FDA until further specifications are published at the time ELIPS is implemented. The value for the <setID> root attribute, when used, must be a GUID (described below)	<setID root="372CB899-A37A-4898-8E91-B96B849C3673"/>
versionNumber	No	No <sup>b</sup>	<versionNumber> will identify a version of the document; the combination of <setID> and <versionID> will be unique for each regulatory submission. The information in this field will not be processed by FDA until further specifications are published at the time ELIPS is implemented.	
author	No	No	<author> is a complex element not used by FDA at present; contents of this element will be ignored by FDA. The complete description of the complexType author element is available in the SPL normative standard.  The representedOrganizaton is not required at present as the mechanism for submission of SPL will identify the represented organization to FDA.	
legalAuthenticator	No	No	<legalAuthenticator> is a complex element not used by FDA at present; contents of this element will be ignored by FDA. The complete description of the complexType <legalAuthenticator> element is available in the SPL ballot.	
verifier	No	No	<verifier> is a complex element not used by FDA at present; contents of this element will be ignored by FDA. The complete description of the complexType <verifier> element is available in the SPL ballot.	
relatedDocument	No	No	<relatedDocument> is a complex element permitting reference to other SPL documents through setId and versionNumber child elements. relatedDocument is not used by FDA at present; contents of this element will be ignored by FDA. The complete description of the complexType <relatedDocument> element is available in the SPL ballot.	

<sup>a</sup> If additional requirements are identified in future, this document will be updated to include them

<sup>b</sup> These elements are not required by FDA at this time, and if included the information will not be processed. The specifications for these fields will be published when the Electronic Labeling Information Processing System (ELIPS) is implemented at FDA.

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

```
<Document xmlns="urn:hl7-org:v3" xmlns:voc="urn:hl7-org:v3/voc"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xmlns:splx="urn:hl7-org:splx" >
  <id root="81E32825-5BC8-46EB-8043-AE607B3819FA"/>
  <code code="34391-3" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
  displayName="Human prescription drug label"/>
  <title>GEMZAR
    (GEMCITABINE HCL)
    FOR INJECTION
  <effectiveTime value="20050106"/>
```

Note: For the <code> element and in all subsequent elements where codeSystemName is used, the codeSystemName attribute is optional since the codeSystem is determined by the value for the codeSystem, not by the value of codeSystemName. Similarly, the displayName is unnecessary since the value for the displayName is contained in the actual code value. These attributes are only for human readability and are otherwise unnecessary

The following is a visual representation of the header elements in the SPL header:

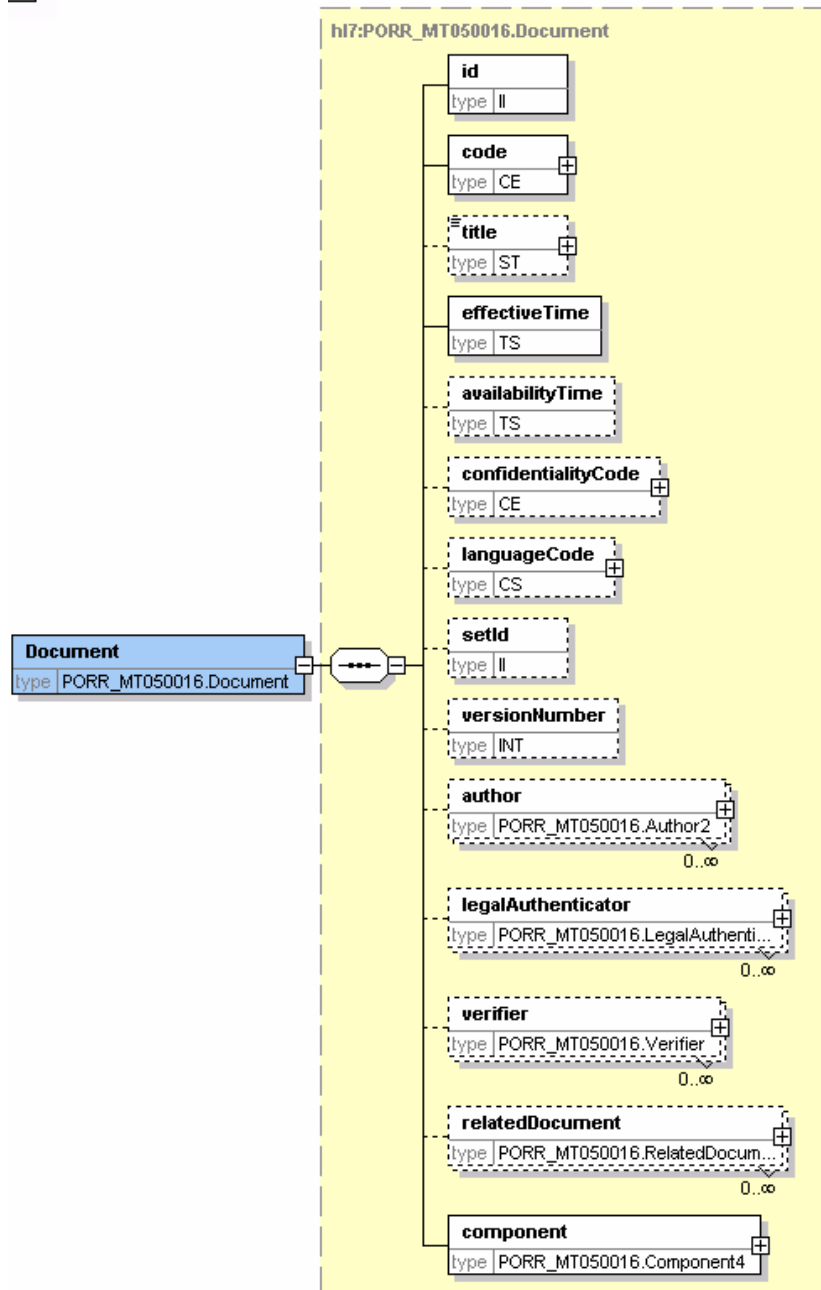


Figure 2: SPL Header Schema

## IV. 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><sup>13</sup> tags enclose the body of the SPL document; the body consists of the human readable content of labeling (i.e., the narrative text) plus structured data elements intended for machine processing (currently limited to specific drug listing information regarding the drug product, e.g., the active ingredients).<sup>14</sup>

The primary “building blocks” for the body of the document is the section. ‘Sections’ of the label content (or ‘sections’ of the narrative) represent related information; for example, each major ‘section’ of the printed labeling (e.g., Description, Indications and usage, Warnings) should be marked as a section in SPL. A section may contain sections, i.e., there may be sub-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 discussed further below.

### A. Sections

In the SPL schema, the <documentBodyChoice><StructuredBody> sequence contains <component>s, and <component>s each contain a <section>. This is illustrated below. The example is not valid SPL code and is used only to illustrate the structure of SPL<sup>15</sup>:

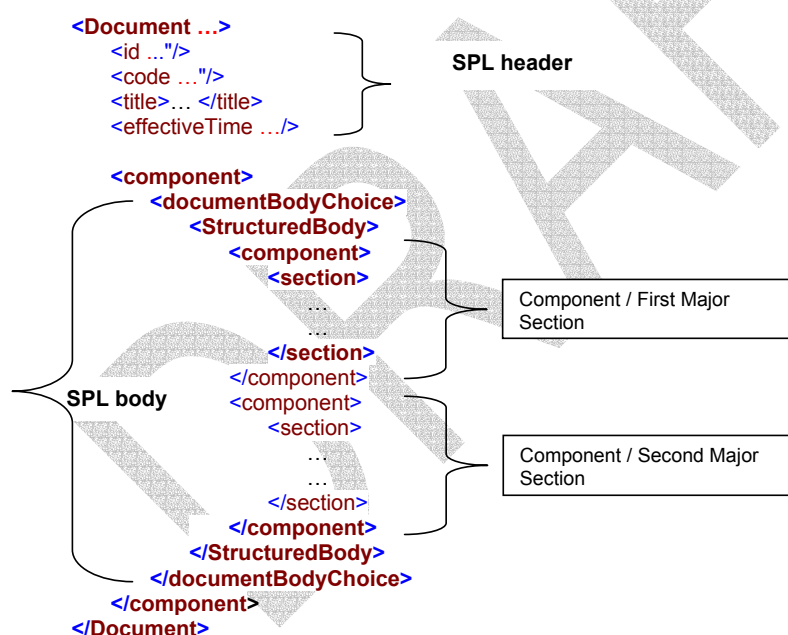


Figure 3. Example of SPL structure for StructuredBody and sections in StructuredBody.

<sup>13</sup> Up-to-date information regarding the <StructuredBody> tag and the most current version of the SPL schema (as adopted by FDA) are available at <http://www.hl7.org>

<sup>14</sup> Please refer to the SPL standard at <http://www.hl7.org> for a complete description of all SPL body elements and attributes.

<sup>15</sup> Although the option exists for a nonXMLBody in the SPL schema (i.e., <nonXMLBody> instead of <StructuredBody>), all SPL submissions to FDA must use the <StructuredBody> structure after the header elements.

Sections are used to aggregate paragraphs into logical groupings. For the FDA implementation of SPL, some sections are major sections of labeling as defined by the labeling regulations in 21 CFR 201.56 and 57 (e.g., Indications and Usage) and are defined by LOINC codes; others are sub-sections that may or may not be identified with a title.

An example of a section identified by a LOINC code with a sub-section not identified by a LOINC code:

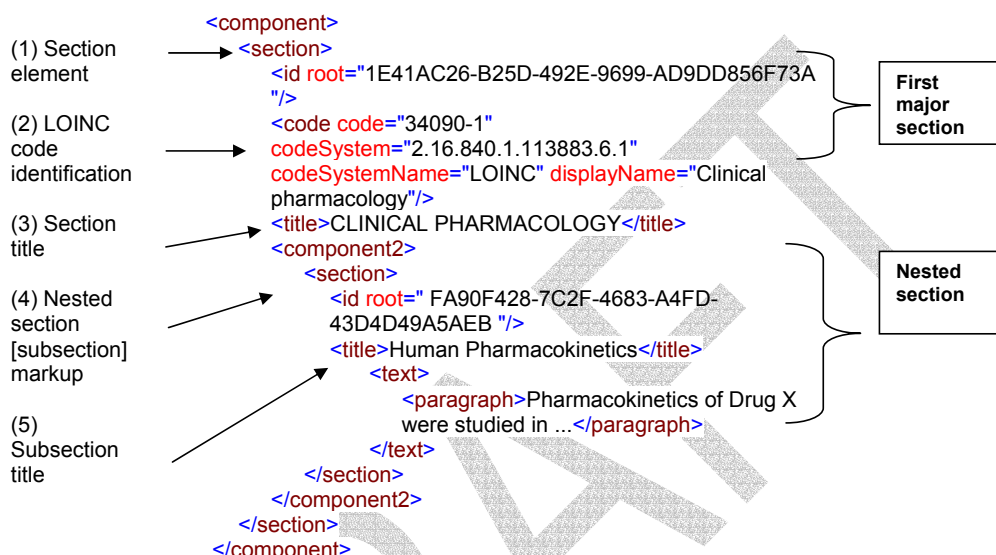


Figure 4. SPL markup for sections, nested sections, and titles.

The SPL standard does not dictate the order of the sections; it merely provides a mechanism for identifying them. Therefore, it is important to note that the order in which sections are added to an SPL document is the order the sections will appear when displayed (rendered) using the standard stylesheet. Standard rendering of the content of SPL (see Formatting and Stylesheets below) results in display of sections in the order in which they appear in the source XML document. The required section order and section nomenclature are specified in FDA regulations.<sup>16</sup>

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 4, SPL markup for sections, nested sections, and titles, each section has a unique identifier (<id>), and may be identified semantically by a LOINC code (i.e., the <code> element), and may contain a <title>. These are also described further below.

The human readable content of labeling is contained within the <text> element in <section>s.<sup>17</sup> It should be noted that in all cases the structured narrative contained in SPL must match the narrative text (i.e., the content of labeling) as exists in the printed final product labeling.

<sup>16</sup> This structure may be counterintuitive, i.e., why a <component><section> tag 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 <documentBodyChoice><StructuredBody> is mandated at the start of the body section although the <component> tag may appear unnecessary.) In addition, the numerical ordering of different component tags, e.g., <component>, <component1>, etc., has no semantic meaning in SPL; the values are used only to separate the different component tags.

<sup>17</sup> A separate NarrativeBlock schema referenced by the main SPL schema describes the content model for <text>. This is described in this document but further details are available in the SPL ballot.

## 1. Nesting of Sections and Subsections

<section>s can nest to form sub<section>s. The schema for subsections in SPL requires that the nested <section> tag first be nested inside a <component2> tag, as illustrated in the Figure 4 above.

The <component2> element is used for nesting any section within any other section. The following illustrates the method for creating nested sections (using non-valid code for illustrative purposes):<sup>18</sup>

```
<component>
  <section>
    <title>Level 1 Section</title>
    <component2>
      <section>
        <title>Level 2 Section</title>
        <component2>
          <section>
            <title>Level 3 Section</title>
            <component2>
              <section>
                <title>Level 4 Section</title>
              </section>
            </component2>
          </section>
        </component2>
      </section>
    </component2>
  </section>
</component>
```

Figure 5. Use of <component>, <component2>, and <section> markup to nest sections in SPL.

## 2. Best Practices for Creating Sections

Best practices for markup of the label content (i.e., narrative) involve tagging for content rather than appearance.

- **Multiple paragraphs are related by the use of nested sections.** If information that belongs together is captured within sections, viewers can identify the information as related and present this to users in customized applications that use SPL. Future use of SPL may make extensive use of sections as identifying related information.
- Use of the <title> element is the preferred method for capturing string text that appears as a heading in current labeling documents.
- Use of either a caption on a paragraph or special formatting on a string of text (e.g., italics) to obtain the appearance of a heading is not acceptable.

It is possible to represent the following example using acceptable markup or unacceptable markup:

CLINICAL PHARMACOLOGY  
*Human Pharmacokinetics*—Pharmacokinetics of Drug X were studied in . .

<sup>18</sup> Similar to first-level sections, the nesting of sections by <component2><section> tagging may seem unnecessary, but is mandated by HL7 methodology.

In patients with renal function impairment . .

*Animal studies*—In monkey studies over a two-year period . .

The following example is *acceptable* markup format when there are subsections (i.e., sub-headings) within a major section:

```
<component>
  <section>
    <id root="2EFE2C58-A9EB-4689-BD05-443C534D7D93"/>
    <code code="34090-1" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
    displayName="Clinical pharmacology"/>
    <title>CLINICAL PHARMACOLOGY</title>
    <component2>
      <section>
        <id root="5708BCA0-8189-4331-83BA-08C7BDBD5C03"/>
        <title>Human Pharmacokinetics</title>
        <text>
          <paragraph>Pharmacokinetics of Drug X were studied in ...</paragraph>
          <paragraph>In patients with renal function impairment ...</paragraph>
        </text>
      </section>
    </component2>
    <component2>
      <section>
        <id root="CAC6A763-D3FB-42B2-9187-570BFA1CBE39"/>
        <title>Animal studies</title>
        <text>
          <paragraph>In monkeys studied over a two-year period...</paragraph>
        </text>
      </section>
    </component2>
  </section>
</component>
```

The following is the same content as in the above example, but the markup is *not* acceptable. The markup format does not clearly delineate the relationships between the section, subsections, and paragraphs of the labeling content. The major sections have been lost. This markup format is not an acceptable SPL FDA submission.

```
<component>
  <section>
    <id root="51A61815-06CE-47CA-A2D2-ECB2F24EFA44"/>
    <code code="34090-1" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
    displayName="Clinical pharmacology"/>
    <title>CLINICAL PHARMACOLOGY</title>
    <text>
      <paragraph><content emphasis="italics">Human Pharmacokinetics</content>Pharmacokinetics
      of Drug X were studied in ...</paragraph>
      <paragraph>In patients with renal function impairment ...</paragraph>
      <paragraph><content emphasis="italics">Animal studies</content>In monkeys studied over a
      two-year period ...</paragraph>
    </text>
  </section>
```



</component>

Both examples are valid against the SPL schema; however, the latter would not be acceptable for SPL FDA submissions.

### 3. <section> Elements

The <section> element can contain the elements described in Table 2. SPL Elements within <section> Element<sup>19</sup> below. Each element is optional under the schema except for the <id> element. All fields may be used by the author but only the <id>, <code>, <title>, and <text> elements will be processed by FDA at this time. Values for elements in each <section> that are similarly named to elements in the SPL header inherit the values of the header if they were specified in the section but were included in the header. (This is not true for the id, code, and title elements in the header.) For example, if an optional element were included in the header (e.g., <author>), by default the value for <author> in each section would be the same if that value is not explicitly included in a specific section.

#### (a) <id> elements

The <id> element is present in each section and in the header of the SPL document. The <id> tag takes the form <id root="...."> where the value for root must be a Globally Unique Identifier (GUID), also known as a Universally Unique Identifier, GUID, or UUID<sup>19</sup>. Each <id> root value must have a unique GUID different from every other GUID that exists *anywhere*. This mandates that GUIDs cannot be generated manually, since this could not insure that a specific GUID would be different from all other GUID that exist.

Multiple shareware/freeware computer programs exist that generate GUIDs automatically<sup>20</sup>. GUIDs are 128 bit integer values, or in hexadecimal, 32 hexadecimal digits. Examples are: 1C35F85F-9DE8-41CB-92EA-AC343157A935 and E470F428-7C2F-4683-A4FD-43D4D49A5AEB.

#### (b) <code> elements

Sections that represent regulatorily mandated labeling sections (e.g, Indications and Usage, WARNINGS, etc.) must have the appropriate <code> element following the <section> element. <code> contains the attribute values for the LOINC code that matches the specified section. <code> tags take the form <code code="...." codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC" displayName="....."/>, e.g., <code code="34067-9" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC" displayName="Indications and Usage"/>. The codeSystem and codeSystemName attributes are always codeSystem="2.16.840.1.113883.6.1" and codeSystemName="LOINC". (The LOINC code system is the only FDA-acceptable code system for this attribute.) The code will be the LOINC code for the section as in this example. The complete list of LOINC codes for use with SPL is listed in section VII.H LOINC codes for SPL .

If a LOINC code is not available (i.e., for subsections not mandated by FDA regulations), the <code> element does not need to be included in the section; e.g., <section><id><text>..... is permitted.

The available LOINC code set for Human Prescription Drug Product sections has been determined by the label (package insert) sections defined in the FDA regulations. The LOINC code for Human Prescription Drug label is 34391-3. Other LOINC codes for the <section><code> available as of June 2004 are shown below. When submitting SPL documents to FDA, use of these codes is required for sections mandated by regulation.

<sup>19</sup> These terms are used synonymously in this document.

<sup>20</sup> Numerous freeware computer programs exist that generate GUID values, e.g., GuidGen at <http://www.csc.calpoly.edu/~bfriesen/software/console.shtml> or GUIDgen at <http://www.microsoft.com>.

## (c) &lt;text&gt; elements

The <text> element in a <section> can contain PCDATA<sup>21</sup>, <paragraph>s, <list>s, or <table>s, and <renderMultimedia> (which designates where externally stored images are located). Captions can be applied to any of these text structures. The <text> element contains labeling content, i.e., the human readable text content of SPL that is rendered. Text strings in paragraphs may be enclosed by <sup>...</sup> (superscripts) and <sub>...</sub> (subscripts); the <content> and associated *emphasis* attribute can be used to designate a limited set of styles (bold, italic, underline, etc.). Inline images may be included via the <renderMultiMedia> tag. Although the <content> tag potentially could be used for multiple purposes, it should only be used to add emphasis to certain text (see Sec. IV.A.4(b)) and should not be used to enclose non-emphasized text content. <renderMultimedia> is described under Images below (see Sec. IV.A.6).

---

<sup>21</sup> PCDATA is normal character data, i.e., the normal content of labeling. Certain characters cannot be used (e.g., <), but essentially this will be information as you might normally enter in a word processor.

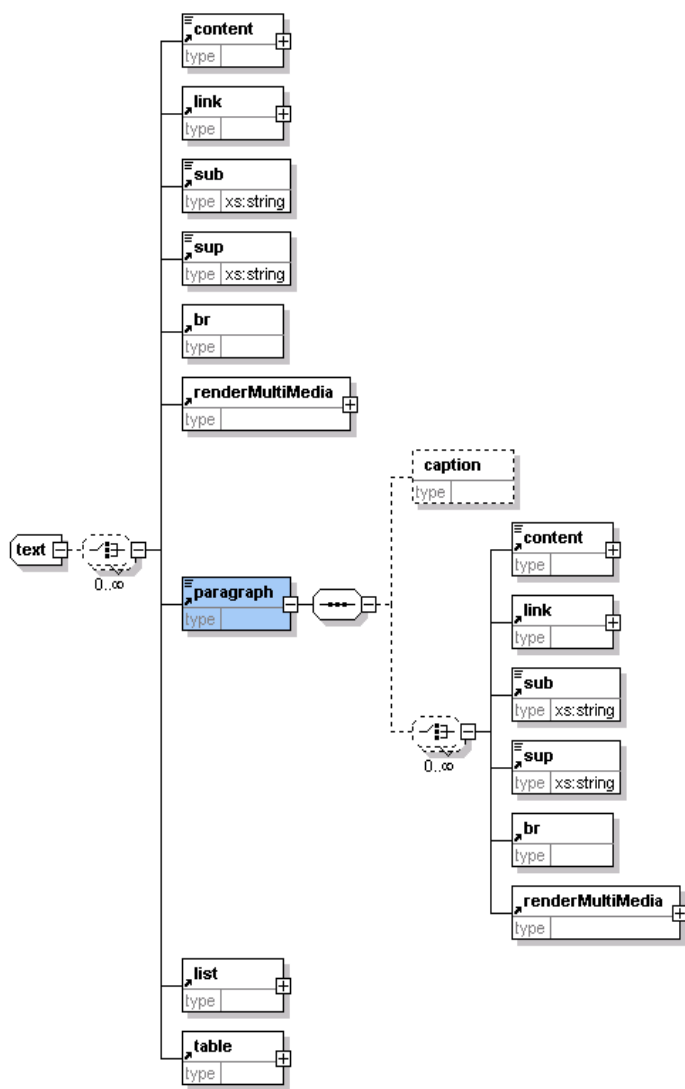


Figure 6: Schema for &lt;text&gt; and &lt;paragraph&gt; elements.

## (d) Listing of all &lt;section&gt; elements

**Table 2. SPL Elements within <section> Element<sup>a</sup>**

Element	Schema Req.	FDA Req.	Comment	Examples
id	Yes	Yes	<id> is a globally unique identifier for the specific section instance. See Section IV.A.3(a) for more information regarding creation of an id for an SPL section.	<code>&lt;id root="2 F33776B3-2DC8-435B-856B-444DD69F6CD7"/&gt;</code>
code	No	Yes <sup>b</sup>	<p>&lt;code&gt; represents the LOINC code for the section (e.g., Indications). The list of currently available US-labeling document section codes that have been assigned by LOINC is included in the SPL specification or is searchable in the LOINC database (<a href="http://www.loinc.org">http://www.loinc.org</a>). When no code is available, a local code may be used but will be ignored by FDA.</p> <p>The displayName in the code is for information purposes only – it is not used to generate a title for a section in the rendered document.</p> <p>At present there is no LOINC code for additional material after the How Supplied Section, e.g., if a Patient Package Insert or MediGuide is included as the final part of a package insert. A LOINC code has been requested for patient information such as a MedGuide or PPI; this section is labeled as 'Supplemental Patient Information. (It is possible that specific LOINC codes will be requested for the PPI and MediGuide; if so, these will be included in a future revision of this guide.) Until LOINC codes are assigned, this material should be included in a non-coded &lt;section&gt;.</p>	<pre> &lt;code code="34067-9" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC" displayName="Indications and Usage"/&gt; </pre>
title	No	Yes <sup>c</sup>	<p>The major sections in the labeling document must have titles (the appropriate titles are defined by regulations).</p> <p>The title of a section is rendered from the content of the &lt;title&gt; tag by the standard stylesheet. If the &lt;title&gt; tag is not populated, then no title will be displayed.</p> <p>Not every section will have a title; in some cases there may be a desire to group paragraphs into a section without a title.</p> <p>Titles should be included whenever they are present in a printed document from which label content has been converted to SPL.</p> <p>Sections and their titles may be nested, resulting in an implied hierarchy that is rendered appropriately in the standard stylesheet. For more information, see the "component2" entry, below, and also Section IV.A.</p>	<code>&lt;title&gt;INDICATIONS AND USAGE&lt;/title&gt;</code>

Element	Schema Req.	FDA Req.	Comment	Examples
text	No	Yes <sup>d</sup>	The human readable content of labeling (the narrative) is contained within the <text> element. See below for additional discussion of the <text> content model.	<pre> &lt;text&gt;   &lt;paragraph&gt;     inflammatory drug (NSAID) that     exhibits anti-inflammatory, analgesic,     and antipyretic activities in animal     models.   &lt;/paragraph&gt; &lt;/text&gt; </pre>
effectiveTime	No	No	<effectiveTime> contains a timestamp for when the section was written. Format is timestamp format, yyyyymmdd (4 digit year/2 digit month/2digit day). This element is not used by FDA at this time.	
confidentialityCode	No	No	This code is used to override the document confidentiality code in the SPL header if the confidentiality level for the section is different. If used, this code is taken from the HL7 value set. There are no plans to use this element at this time.	
languageCode	No	No	This code is used to override the document language code in the SPL header if the language for the section is different. If used, this code is taken from the HL7 value set. There are no plans to use this element at this time.	
author	No	No	<p>This element is used to override the author of the document (identified in the SPL header) if the author for the section is different.</p> <p>&lt;author&gt; is a complex element not used by FDA at present. The complete description of the complexType author element is available in the SPL specification.</p>	
component2	No	No	<p>This element is used to link sections to sections nested within them (see Figure 3 for levels of nesting available in SPL).</p> <p>Rendering of the titles for nested sections is set in the stylesheet and depends on the level of nesting. See Section IV.A. for more information.</p>	<pre> &lt;section&gt;   &lt;id root="192D3B70-0457-4F92-     AA4A-8B30928A32A9"/&gt;   &lt;code code="34090-1"     codeSystem="2.16.840.1.113883.     6.1" codeSystemName="LOINC"     displayName="Clinical     pharmacology"/&gt;   &lt;title&gt;CLINICAL     PHARMACOLOGY&lt;/title&gt;   &lt;component2&gt;     &lt;section&gt;       &lt;id root="192D3B70-         0457-4F92-AA4A-         8B30928A32A9"/&gt;       &lt;title&gt;Human         Pharmacokinetics&lt;/title&gt;       &lt;text&gt;         &lt;paragraph&gt;Pharmac           okinetics of Drug X           were studied in ...         &lt;/paragraph&gt;       &lt;/text&gt;     &lt;/section&gt;   &lt;/component2&gt; &lt;/section&gt; </pre>

Element	Schema Req.	FDA Req.	Comment	Examples
sectionReplaced	No	No	<sectionReplaced> is a complex element permitting reference to previous versions of a section through the <id> child element. <sectionReplaced> is not used by FDA at present; contents of this element will be ignored by FDA during the SPL test phase. The complete description of the complexType <sectionReplaced> element is available in the SPL specification.	

<sup>a</sup> If additional requirements are identified in future, this document will be updated to include them

<sup>b</sup> For sections mandated by regulation. The code is not required for other sections

<sup>c</sup> Titles are required only for sections mandated in FDA regulations, but may be used for other sections as appropriate.

<sup>d</sup> If a section consists only of nested sections, this tag is not required; however, it is required if any text in that section is to be rendered.

## Sample Section Markup

### (e) Isolated Major Section

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

### (f) Major Section (with LOINC code) and subsection (without LOINC code)

```
<!-- ----- Clinical Pharmacology section----- -->
<component>
  <section>
    <id root="5031A439-E76A-4FEB-827D-9AC5A758076A"/>
    <code code="34090-1" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
    displayName="Clinical pharmacology"/>
    <title>CLINICAL PHARMACOLOGY</title>
    <component2>
      <section>
        <id root="51A61815-06CE-47CA-A2D2-EFB2F24EFA44"/>
        <title>Human Pharmacokinetics</title>
        <text>
          <paragraph>Pharmacokinetics of Drug X were studied in . </paragraph>
        </text>
      </section>
    </component2>
  </section>
</component>
```

</section>  
</component>

#### 4. Formatting SPL

This section discusses several aspects broadly defined as 'Formatting SPL', including (a) use of the `splx:styleCode` attribute for certain formatting options, (b) font effects (bold, underline, italics), (c) symbols and special characters (Unicode), (d) footnotes, and (e) default and specialized lists. Tables are discussed separately in Section IV.A.5.below.

##### (a) Splx Namespace

A major design goal of XML (and SPL) documents is to separate formatting from content; accordingly, the SPL schema contains minimal formatting features. (Essentially, the only tag available for formatting SPL documents is the `<content emphasis="...">` tag for bold/italics/underline [described in Sec. IV.A.4(b)]). 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. Examples of this are rules separating rows in a table into a section or the printed box that defines a black box.

To accomplish this, the SPL schema permits reference to an external schema (`splx.xsd`) which is not strictly part of the SPL schema but can be used to add a formatting attribute to certain elements. The `splx.xsd` schema and two stylesheet files (currently `spl-1.1.xsl` and `spl-1.1.css`) permit extending several elements by adding the attribute `splx:styleCode` to the element, e.g., `<paragraph splx:styleCode="Footnote">` or `<colgroup splx:styleCode="Lrule">`.<sup>22</sup>

There are multiple examples of the use of the `splx:styleCode` attribute in the Gemcitabine example in Sec. VII.C, where the `splx:styleCode` attribute is used to insure that tables have appropriate rules and that footnotes are formatted correctly. The use of the SPL stylesheet is discussed extensively in Appendix VII.B

##### (b) Font Effects (content emphasis)

The content model for `<paragraph>` contains limited features that allow the addition of certain markup for the purposes of formatting. Text that requires special font-effect formatting is wrapped in the `<content>` element, which has an 'emphasis' attribute with allowed values of bold, italics, underline. The attribute value of 'yes' is for use when there is a desire to indicate a generic emphasis.

**Table 3. Font Effects**

<u>Attribute value for 'emphasis'</u>	<u>Recognized by FDA</u>	<u>Example Rendering</u>	<u>Examples</u>
bold	Yes	<b>contraindicated</b>	<code>&lt;content emphasis="bold"&gt;contraindicated&lt;/content&gt;</code>
italics	Yes	<i>in vitro</i>	<code>&lt;content emphasis="italics"&gt;in vitro&lt;/content&gt;</code>
underline	Yes	<u>fever</u>	<code>&lt;content emphasis="underline"&gt;fever&lt;/content&gt;</code>

<sup>22</sup> The set of CSS classes supported by the stylecode attribute are described in Appendix VII.B. An xsl file, referred to above, is an XML file used by SPL to 'transform' SPL to a format that can be viewed in standard web browsers. It is discussed in more detail in Appendix VII.B.

Note that combined font effects for bold, italics, and underline are permitted in SPL. In order for the effect to render properly through the standard stylesheet, the emphasis markup *must be separated by a single space* as shown in the following table:

**Table 4. Multiple Font Effects**

Desired Font Effect	Rendering	Examples
bold-italics	<b><i>contraindicated</i></b>	<content emphasis="bold italic">contraindicated</content> </content>
italics-underline	<i><u>in vitro</u></i>	<content emphasis="italics underline">in vitro</content>
bold-underline	<b><u>fever</u></b>	<content emphasis="bold underline">fever</content>
bold-italics-underline	<b><i><u>pharmacology</u></i></b>	<content emphasis="bold italics underline"> pharmacology</content> emphasis="underline">pharmacology</content> </content></content>

### (c) Symbols and Special Characters

Special characters can be included in narrative (i.e., the text content) 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<sup>23</sup> character references are used for special characters.<sup>24</sup> The Unicode value for common symbols (e.g., &#8482 for ™) are in Table 5. Symbols and Special Characters. Complete lists are available in the references cited in footnote 23.

**Table 5. Symbols and Special Characters**

Symbol or Character	Solution	Sample Markup
mg/m <sup>2</sup>	Tagging	mg/m<sup>2</sup>
C <sub>9</sub> H <sub>11</sub> F <sub>2</sub> N <sub>3</sub> O <sub>4</sub> •HCl	Tagging + Unicode	C<sub>9</sub>H<sub>11</sub>F<sub>2</sub>N<sub>3</sub>O<sub>4</sub>&#8226;HCl
Copyright © 1996	Unicode	Copyright &#169; 1996
°	Unicode	&#176;
<	Entity	&lt;
≤	Unicode	&#8804;
— (m-dash)	Unicode	&#8212;
β-isomer	Unicode	&#946;-isomer
Registered® 1996	Unicode	Registered&#174; 1996.
Trademark™ 1998	Unicode	Trademark&#8482; 1998
Plus-minus sign ±	Unicode	Plus-minus sign &#177;
ampersand	Entity	&amp;

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

<sup>23</sup> 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>.

<sup>24</sup> Unicode character set UTF-8 is the default character set in W3C XML Schemas



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.

As noted in Appendix VII.B, 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;. For example, <paragraph>The mean for group 1 was &lt; the mean for group 2.</paragraph>

#### (d) Footnotes

The SPL schema lacks a specific footnote element. Footnote markup is implemented by a styleCode extension of the <paragraph> tag (see Sec. IV.A.4(a)). There are two styleCode footnote attributes: (1) *Footnote*, which creates a hanging indent paragraph in smaller pointsize font than normal paragraph text; and (2) *Footnotesize*, which creates a normal-margined paragraph in a smaller pointsize. For the Footnote attribute, the <caption> tag is used to denote footnote markers, which can be any typed character or Unicode value.

**Table 6. Footnotes**

SPL Footnote Markup	Sample Footnote
<pre>&lt;paragraph   splx:styleCode="Footnotesize"&gt;   The p-value for clinical benefit   response was calculated using   the two-sided test for difference in   binomial proportions. All other p-   values were calculated using the   Logrank test for difference in   overall time to an   event.&lt;/paragraph&gt;</pre>	<p>The p-value for clinical benefit response was calculated using the two-sided test for difference in binomial proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.</p>
<pre>&lt;paragraph   splx:styleCode="Footnote"&gt;   &lt;caption&gt;a&lt;/caption&gt; 28-day   schedule – Gemzar plus cisplatin:   Gemzar 1000 mg/m&lt;sup&gt;2&lt;/sup&gt;   on Days 1, 8, and 15 and cisplatin   100 mg/m&lt;sup&gt;2&lt;/sup&gt; on Day 1   every 28 days; Single-agent   cisplatin: cisplatin 100   mg/m&lt;sup&gt;2&lt;/sup&gt; on Day 1   every 28 days.&lt;/paragraph&gt;</pre>	<p><sup>a</sup> 28-day schedule – Gemzar plus cisplatin: Gemzar 1000 mg/m<sup>2</sup> on Days 1, 8, and 15 and cisplatin 100 mg/m<sup>2</sup> on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m<sup>2</sup> on Day 1 every 28 days.</p>

#### (e) 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
<pre>&lt;list listType="ordered"&gt;   &lt;item&gt; Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Printing Office, Washington, DC 20402.   &lt;/item&gt;   &lt;item&gt; Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.   &lt;/item&gt; &lt;/list&gt;</pre>	<ol style="list-style-type: none"> <li>1. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Printing Office, Washington, DC 20402.</li> <li>2. Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.</li> </ol>
<pre>&lt;list listType="unordered"&gt;   &lt;item&gt; Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Printing Office, Washington, DC 20402.   &lt;/item&gt;   &lt;item&gt; Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.   &lt;/item&gt; &lt;/list&gt;</pre>	<ul style="list-style-type: none"> <li>• Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Printing Office, Washington, DC 20402.</li> <li>• Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. JAMA 1985;253:1590.</li> </ul>

Lists featuring a standard set of specialized markers (standard specialized lists) can be created using the extended attribute *splx:styleCode* in the `<list>` tag. Specialized ordered and unordered lists are available by referencing the appropriate styleCode in the `<list>` opening tag:

```
<list listType="ordered" splx:styleCode="LittleRoman">
```

The following table describes the standard specialized list styleCodes 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. Recommendation publication No. 8: 2. Council on Science JAMA 1985;253:
Lowercase Roman Numeral	LittleRoman	i. Recommendation publication No. 8: ii. Council on Science JAMA 1985;253:
Uppercase Roman Numeral	BigRoman	I. Recommendation publication No. 8: II. Council on Science JAMA 1985;253:
Lowercase Western Alphabetical	LittleAlpha	a. Recommendation publication No. 8: b. Council on Science JAMA 1985;253:
Uppercase Western Alphabetical	BigAlpha	A. Recommendation publication No. 8: B. Council on Science JAMA 1985;253:

**Unordered Lists:**

Specialized Type	styleCode Value	Sample Rendering
Disc (same as default unordered list)	Disc	• Recommendation publication No. 8: • Council on Science JAMA 1985;253:
Circle, hollow disc	Circle	○ Recommendation publication No. 8: ○ Council on Science JAMA 1985;253:
Filled square	Square	■ Recommendation publication No. 8: ■ Council on Science JAMA 1985;253:

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 <captions> for each <item> are not restricted to the same character.

**Table 9. User-defined Characters**

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

## 5. Tables

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.<sup>25</sup>

Tables should always be created with the full structure as shown below. 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 footnote:

**Table 10. Sample Table**

SPL Table Markup	Sample Table																														
<pre>&lt;table&gt;   &lt;caption&gt;...&lt;/caption&gt;   &lt;thead&gt;     &lt;tr .../&gt;   &lt;/thead&gt;   &lt;tfoot&gt;     &lt;tr .../&gt;   &lt;/tfoot&gt;   &lt;tbody&gt;     &lt;tr .../&gt;   &lt;/tbody&gt; &lt;/table&gt;</pre>	<table><tr><th colspan="5">Table 1: Clearance and Half-Life for the "Typical" Patient</th></tr><tr><th>Age</th><th>Clearance Men (L/hr/m<sup>2</sup>)</th><th>Clearance Women (L/hr/m<sup>2</sup>)</th><th>Half-Life<sup>a</sup> (min)</th><th>Half-Life<sup>a</sup> (min)</th></tr><tr><td>29</td><td>92.2</td><td>69.4</td><td>42</td><td>49</td></tr><tr><td>45</td><td>75.7</td><td>57</td><td>48</td><td>57</td></tr><tr><td>65</td><td>55.1</td><td>41.5</td><td>61</td><td>73</td></tr><tr><td>79</td><td>40.7</td><td>30.7</td><td>79</td><td>94</td></tr></table> <p><sup>a</sup> Half-life for patients receiving a short infusion (&lt;70 min).</p>	Table 1: Clearance and Half-Life for the "Typical" Patient					Age	Clearance Men (L/hr/m <sup>2</sup> )	Clearance Women (L/hr/m <sup>2</sup> )	Half-Life <sup>a</sup> (min)	Half-Life <sup>a</sup> (min)	29	92.2	69.4	42	49	45	75.7	57	48	57	65	55.1	41.5	61	73	79	40.7	30.7	79	94
Table 1: Clearance and Half-Life for the "Typical" Patient																															
Age	Clearance Men (L/hr/m <sup>2</sup> )	Clearance Women (L/hr/m <sup>2</sup> )	Half-Life <sup>a</sup> (min)	Half-Life <sup>a</sup> (min)																											
29	92.2	69.4	42	49																											
45	75.7	57	48	57																											
65	55.1	41.5	61	73																											
79	40.7	30.7	79	94																											

Note that the SPL schema enforces the positioning of <tfoot> before <tbody>

Always start with this standard table and test to see whether it is unambiguous and interpretable. Use the rule control codes 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.





<sup>25</sup> A complete description of the XHTML document model is available at <http://www.w3.org/TR/xhtml1-modularization/Overview.html>. Specific defaults regarding the XHTML table model can be found at [http://www.w3.org/TR/xhtml1-modularization/abstract\\_modules.html#s\\_tablemodule](http://www.w3.org/TR/xhtml1-modularization/abstract_modules.html#s_tablemodule).

## (a) Table Rules (Gridlines)

The standard stylesheet defined by HL7 for SPL allows the user to control rules for each cell by setting the styleCode attribute for the <td> element.<sup>26</sup> The styleCode attribute can refer to more than one rule control.

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

**Table 11. Optional Table Rules**

<u>Rule Placement</u>	<u>styleCode Attribute</u>	<u>Appearance</u>
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	

As noted earlier, more than one rule control may be used in a styleCode. To ensure proper display, the rule control attributes must be separated by a single space (for example, ,<td splx:styleCode="Botrule Lrule">).

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 row and column.

## (b) Horizontal rules

To make rowgroups appear with horizontal rules, first put *splx:styleCode="Botrule"* on the <tr> element. The *Botrule* attribute is rarely needed on the <td> element.

**Comment:** Explain rowgroups and colgroups, give 1-2 examples.

## (c) Vertical rules

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

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

<sup>26</sup> As described below, the standard stylesheet is not part of the SPL schema and is defined only to ensure uniform rendering of SPL to users.

## (d) Cell text alignment

Similar to XHTML tables, the preferred method for aligning cell content within the margins is to use `<col align="." />` in the `<colgroup>` element. Valid values for *align* are "left", "center", "right", "justify" (for full justification of contents within the cells), and "char" (for character alignment within the cells). Using the `<col align="." />` markup ensures that the contents for all cells in the column share the same alignment.

For 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>`. Thus it is possible, but not recommended, to change the alignment for each cell. The following example, while not recommended, 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>&#160;&#160;Male</td>
  <td align="left">182</td>
  <td align="right">186</td>
</td>
  <td>64</td>
  <td>61</td>
</td>
</tr>
<tr>
  <td>&#160;&#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

## (e) Footnotes

Markup for table footnote is the `<tfoot>` tag, as is common practice. Other than this, table footnotes are substantially the same as all footnotes in SPL. See the Footnotes section earlier in this document.

## (f) 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

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 (&#160;) 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>&#160;&#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&#160;of&#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

## 6. 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 MMID (multimedia 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 (GIF, JPEG). Note also that ObservationMedia is always contained within a component1 element.

```

<component1>
  <documentBodyEntry>
    <ObservationMedia MMID="MM1">
      <value xsi:type="ED" mediaType="image/jpeg">
        <reference value="gemzar_structure.jpg"/>
      </value>
    </ObservationMedia>
  </documentBodyEntry>
</component1>

```

For example:

```

...
<paragraph>
  <content emphasis="underline">Quality of Life (QOL)</content>:
  QOL was a secondary endpoint in both randomized studies. In the Gemzar plus
  cisplatin versus cisplatin study, QOL was measured using the FACT-L, which
  assessed physical, social, emotional and functional well-being, and lung cancer
  symptoms. In the study of Gemzar plus cisplatin versus etoposide plus cisplatin,
  QOL was measured using the EORTC QLQ-C30 and LC13, which assessed physical
  and psychological functioning and symptoms related to both lung cancer and
  its treatment. In both studies no significant differences were observed in
  QOL between the Gemzar plus cisplatin arm and the comparator arm.
</paragraph>
<renderMultiMedia referencedObject="MM1">
...

```

would display image MM1 defined by `<ObservationMedia MMID="MM1">` in the document as a block image (see below)..

The actual image file is enclosed by an `<ObservationMedia>` element, contained in any `<component1>` in any section, e.g.,

```

<section>
  .....
  <text>..... </text>
  <component1>
    <documentBodyEntry>
      <ObservationMedia MMID="MM2">
        <value xsi:type="ED" mediaType="image/jpeg">
          <reference value="gemzar_2.jpg"/>
        </value>
      </ObservationMedia>
    </documentBodyEntry>
  </component1>
</section>

```

#### (a) 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 required, the graphic file should be edited to a dimension appropriate for its presentation within the browser. Also, graphics files should be saved at a resolution appropriate for screen viewing, not printing. One common appropriate resolution for screen graphics is 72 dpi.



## (b) File type

The file type for images should be appropriate for the intended use of the SPL document. For SPL files to be viewed in a browser according to the standard stylesheet, best practice is to save all images as JPEGs or GIFs.

## (c) Image placement

If an image is *inline* (i.e., should appear alongside text), insert the `renderMultimedia` tag in the text of a `<paragraph>` as appropriate. If an image is a *block image* (i.e., should appear in its own space), insert the `renderMultimedia` tag after the closing `</paragraph>` tag.

Note: Include any company or product logos as image files; do not attempt to recreate a logo with font effects in the XML document. The standard stylesheet controls the font family and effects for all text in an SPL-compliant package insert, so any font information in the XML will be lost.

## 7. Hypertext Links

SPL offers hypertext linking capabilities similar to those found in the HTML specification, although the tags in SPL are different. For the following, the first example is of a link reference in SPL, while the second example is of the reference's link anchor:

```
<link><linkHtml href="#table_1">Table 1</linkHtml></link> shows plasma clearance and half-life of
gemcitabine following short infusions for typical patients by age and gender.
...
...
<link><linkHtml name="table_1">Table 1:</linkHtml></link> Gemcitabine Clearance and Half-Life for
the &#8220;Typical&#8221; Patient
```

FDA currently does not recommend or support hypertext links in SPL documents.

## V. 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<sup>27</sup>. Future releases of SPL may include data elements covering other areas of the content of labeling.

At the present time, 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 (strength is optional)
- Drug product: Proprietary name
- Drug product: Nonproprietary (Established) name
- Container type(s)
- Quantity per container (and number of containers per container in a combination product)
- National Drug Code(s) (NDC)
- Drug Enforcement Administration (DEA) schedule
- Labeled route(s) of administration
- Imprinting<sup>28</sup>:

<sup>27</sup> 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.

<sup>28</sup> Imprinting is described in Title 21 CFR part 206. This applies to solid dosage forms though may be used for other dosage forms.

- Color
- Shape
- Size
- Coating
- Scoring
- Logo (the graphic/figure that may appear on a solid preparation)
- Imprint Code (any alphanumeric information on a solid preparation)

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

The following discussion addresses how to author the data elements section of the SPL. It is expected that most SPL authors will have automated tools to construct the data elements section of SPL from a template, especially if several different dosage forms or strengths of a product exist.

Information on the drug listing data elements is in 21 CFR 207 and associated guidance documents. See <http://www.fda.gov/cder/drfs/default.htm> for detailed information on the drug listing process. Information on imprinting is in 21 CFR 206.

#### A. 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.)

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:

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	Established Name	Active Ingredients & strength	Inactive Ingredients & strength <sup>b</sup>	Dosage Form	Imprinting	Package Type & Quantity <sup>a</sup>	NDC <sup>b,c</sup>
		List of Active ingredients	List of inactive ingredients		List of characteristics	Package/Qty 1	NDC 1
						Package/Qty 2	NDC 2
						Package/Qty ...	NDC ...

<sup>a</sup> There may be one or more package/quantity/NDC triads for a proprietary name; if only one exists then there would be only one minor row in this model.

<sup>b</sup> Including the strength of inactive ingredients is optional unless required by regulations, e.g., in intravenous preparations.

<sup>c</sup> Every NDC code is unique in this model.

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

A single drug product with one strength and one dosage form (e.g., a 75 mg tablet) would have one proprietary name and one nonproprietary (established) 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.<sup>29</sup>

<sup>29</sup> 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, i.e., drug 'sample' configurations used for marketing purposes should not be included in SPL, even if associated with an NDC code.

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

Proprietary name <sup>a</sup>	Established Name	Active Ingredients & strength	Inactive Ingredients & strength	Dosage Form	Imprinting	Package Type & Quantity <sup>b</sup>	NDC <sup>c</sup>
Name 1		List of Active ingredients	List of inactive ingredients		List of characteristics	Package/Qty 1	NDC 1a
						Package/Qty 2	NDC 1b
						Package/Qty etc.	NDC ...
Name 2		List of Active ingredients	List of inactive ingredients		List of characteristics	Package/Qty 1	NDC 2a
						Package/Qty 2	NDC 2b
						Package/Qty etc....	NDC ...
Name 3		List of Active ingredients	List of inactive ingredients		List of characteristics	Package/Qty 1	NDC 1c
						Package/Qty 2	NDC 2c
						Package/Qty etc.	NDC ...

<sup>a</sup> 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 established name, i.e., it is expected that the established name will be identical for all rows in the table.

<sup>b</sup> 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.

<sup>c</sup> Every NDC is unique in this model.

In this model, each unique drug product will be a separate major row in the table and translate to a <component2><section> block (i.e., will be contained within one section) in the actual SPL document (see [Need to create link] below). This includes the case where the drug product is a combination of two or more products – the overall packaged product corresponds to a separate major row in the table.<sup>30</sup>

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

Table 14 - Sample Drug Product Table

Proprietary name	Established name	Active Ingredients	Inactive Ingredients	Dosage Form & Route	Package Type & Quantity	Imprinting	NDC
Gemzar	gemcitabine HCl	• Gemcitabine HCl; 200 mg	• Manitol; 200 mg • sodium acetate; 12.5 mg	Injection, Powder, Lyophilized, For Solution; Intravenous	Vial, Single Dose; 10 ml		0002-7501-01
Gemzar	gemcitabine HCl	• Gemcitabine HCl; 1 g	• Manitol; 200 mg • sodium acetate; 62.5 mg	Injection, Powder, Lyophilized, For Solution; Intravenous	Vial, Single Dose; 10 ml		0002-7502-01

<sup>30</sup>

The most complex example is where there are two drug products provided as components of a single drug product even if names do not exist for the individual components, e.g., oral contraceptives or ribavirin/interferon combinations. 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 Established Name	Proprietary Name <sup>a</sup>	Established Name	Active Ingred. & strength	Inactive Ingred. & strength	Dose Form	Imprinting	Comp. Pack. Type & Quan. <sup>b</sup>	NDC	Overall Pack. Type & Quan.	NDC <sup>c</sup>
		Comp 1		List of Active ingredients	List of inactive ingredients		List of characteristics				
		Comp 2		List of Active ingredients	List of inactive ingredients		List of characteristics				
		Comp 3.		List of Active ingredients	List of inactive ingredients		List of characteristics				

<sup>a</sup> 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, in this setting it is unlikely. in this setting.

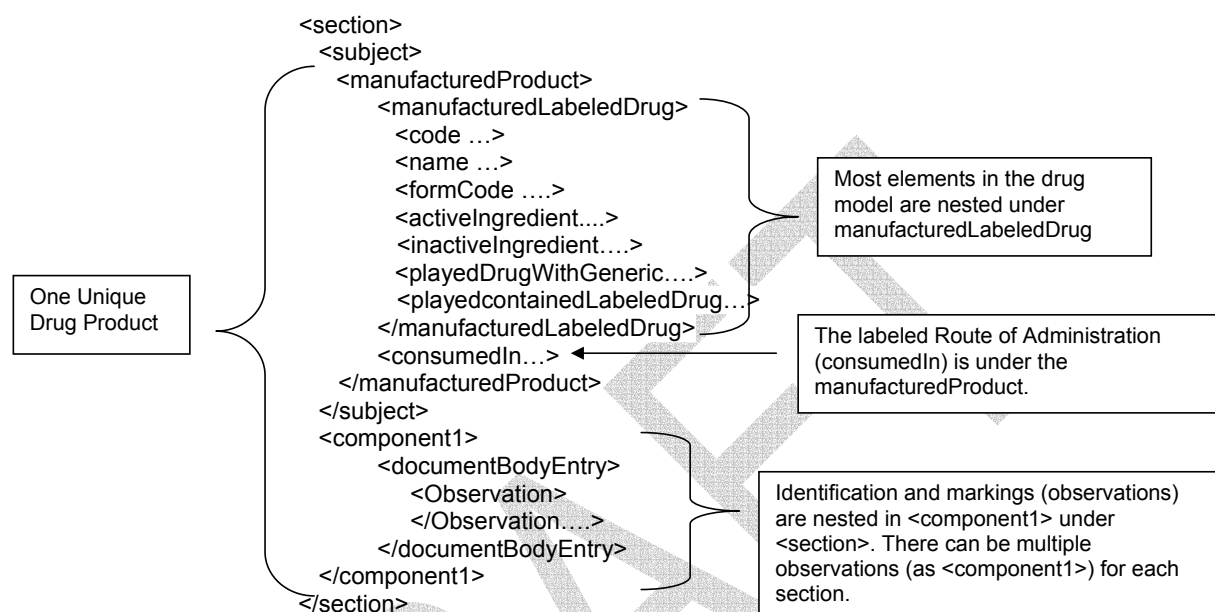
<sup>b</sup> Package type is also unlikely for a component; the overall product should have this property.

<sup>c</sup> This is the NDC for the overall product; individual components may or may not have an NDC code.

In this example, there is an overall brand proprietary name and an overall nonproprietary (established) 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.<sup>31</sup>

Shown below is the structure of the SPL elements for each of the conceptual elements described above. The values for the actual elements in the SPL document that match the conceptual elements described above are in Table 16 below. (Route of administration is also included in the example though this is not necessary for the conceptual view of the model.)

<sup>31</sup> An example of coding the data elements for this situation, i.e., multiple drug products forming one drug product with a separate NDC code is not included in this version of the implementation guide. An example of the coding for this type of product will be included in the next version of this guide.



**Figure 7: 'Schema' Model of SPL Data Elements section.**

Table 16 below describes the actual coding of elements in an SPL document for the elements described in the conceptual view earlier. For this table, the following definitions have been used:

**Active Ingredient:** substance responsible for effects of a medicinal product defined by the complete molecular structure (e.g., with any counter ion) or, if the precise molecular structure is not known, by an unambiguous definition (e.g., the process used to create the substance), e.g. codeine phosphate. As discussed below, this is coded in SPL by a UNII (Unique Ingredient Identifier) provided by FDA.

**Active Moiety:** portion of the active ingredient responsible for the effect, if applicable (e.g., without counter ion), e.g., codeine. As discussed below, this is also coded in SPL by a UNII (Unique Ingredient Identifier) provided by FDA.

**Proprietary Medicinal Product:** includes one or more established medicinal products along with inactive ingredients and appearance and manufacturer or marketing authorization holder name, country and registration number, proprietary name, established number, marketing status, drug product type, and distributor. This is reflected by the proprietary medicinal code value under Proprietary name (the first row in the table below. An example would be Amoxil 500 mg tablet. There can be multiple packages (e.g., NDC codes) for a given proprietary medicinal package. A *Packaged Medicinal Product* is a Proprietary Medicinal Product in a specific package/quantity, i.e., a Packaged Medicinal Product will have an associated NDC code.<sup>32</sup>

<sup>32</sup> Although not discussed in the table below, an Established Medicinal Product is defined as columns 2, 3 and 5 of table 1, i.e., the active ingredients and dose form but without imprinting, inactive ingredients, etc.

Table 16: Mapping and Coding of Data Elements in the Conceptual View to SPL Elements (including labeled Route of Administration)

Element Name	Schema/ FDA req. <sup>a</sup>	Example	Comments
<b>Proprietary name</b>	No/Yes	<pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;code code=" 0002-7501 [labeler and product code from NDC code]" codeSystem="FDA code system" codeSystemName="FDA code name"/&gt;     &lt;name&gt;Gemzar&lt;/name&gt;   .....   .....   &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre>	<p>The proprietary name is the actual text string for the proprietary name and code for the drug product is described in the drug listing regulations (21CFR207) and guidance.</p> <p>The code system for the <b>&lt;code&gt;</b> element under <b>&lt;manufacturedLabeledDrug&gt;</b> is the first two components of the NDC, i.e., the labeler code and the product code.</p> <p>The value for the code attribute of the <b>&lt;code&gt;</b> element (i.e., <b>&lt;code code = "value"&gt;</b>) is the Proprietary Medicinal Product (MP) code. This code is the product and labeler codes from the NDC, i.e., the first 4 or 5 digits of the NDC that make up the labeler code, then the 4 or 5 digits that make up the NDC product code.(e.g., 0002-7501). (Note: a Proprietary Medicinal Product represents the first 6 columns of Table 1 above, i.e., the full description of a medicinal product without the packaging information).</p> <p>At this juncture the codeSystem and codeSystemName are pending; therefore, this element is optional until these values are resolved (which should be very shortly).</p> <p>In the SPL document proprietary name is in the <b>&lt;name&gt;</b> element, a child of the <b>&lt;manufacturedLabeledDrug&gt;</b>, e.g.,</p> <pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;code ...&gt;     &lt;name&gt;proprietary medicinal product name here&lt;/name&gt;     &lt;formCode ....&gt;     &lt;activeIngredient.....&gt;     &lt;inactiveIngredient.....&gt;     &lt;playedDrugWithGeneric....&gt;     &lt;playedContainerLabeledDrug....&gt;   &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre>

<b>Established Name</b>	No/Yes	<pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     ... &lt;!-- name, form code, etc. --&gt;     &lt;playedDrugWithGeneric&gt;       &lt;genericGenericDrug&gt;         &lt;code code="to be determined" code" codeSystem=" " codeSystemName=" "/&gt;         &lt;name&gt;gemcitabine <b>HCI</b>&lt;/name&gt;       &lt;/genericGenericDrug&gt;     &lt;/playedDrugWithGeneric&gt;     ...   &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre>	<p>The actual text string for the established name for the drug as would exist in package labeling should be included in the name field under &lt;genericGenericDrug&gt;.</p> <p>The code system for this element has not been implemented and, therefore, the &lt;code&gt; element under &lt;genericGenericDrug&gt; should not be included in SPL.</p> <p>The established name is a child of &lt;playedDrugWithGeneric&gt; and &lt;genericGenericDrug&gt;, e.g.,</p> <pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;code ...&gt;     &lt;name ...&gt;     &lt;formCode ....&gt;     &lt;activeIngredient....&gt;     &lt;inactiveIngredient....&gt;     &lt;playedDrugWithGeneric&gt;       &lt;genericGenericDrug&gt;         &lt;code....&gt;         &lt;name&gt;established name&lt;/name&gt;       &lt;/genericGenericDrug&gt;     &lt;/playedDrugWithGeneric&gt;     &lt;playedContainerLabeledDrug....&gt;   &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre> <div data-bbox="1333 568 1596 695" style="border: 1px solid black; padding: 5px; width: fit-content;"> <p>The code element in green should not be included in SPL at the present time.</p> </div>
<b>Active Ingredients (Active Moieties)</b>	No/Yes	<pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;!-- name, form code, etc. --&gt;     ...     &lt;activeIngredient&gt;       &lt;quantity&gt;         &lt;numerator value="500" unit="mg"/&gt;         &lt;denominator value="1"/&gt;       &lt;/quantity&gt;       &lt;activeIngredientIngredientEntity&gt;         &lt;code code="SRS determined code" codeSystem="FDA SRS system" codeSystemName="SRS code name"/&gt; </pre>	<p>The active ingredient name is part of a complex structure. &lt;activeIngredient&gt; is a child of &lt;manufacturedLabeledDrug&gt;. &lt;activeIngredient&gt; has several children. The &lt;quantity&gt; is a direct descendent of the &lt;activeIngredient&gt;, and represents the strength of the active ingredient. HL7 has a table of standard units of measure that may be used for the <i>unit</i> attribute. The &lt;activeIngredientIngredientEntity&gt; child contains the name of the activeIngredient and SRS code for the ingredient; it also contains the &lt;activeMoiety&gt; child, which has its own code and name. (Note: the &lt;activeMoiety&gt; tag is repeated twice in the schema and is correct below.)</p> <p>Active ingredient, active moiety and inactive ingredient are defined in the SPL specification.</p>

	<pre> &lt;name&gt;ingredient 1&lt;/name&gt; &lt;activeMoiety&gt; &lt;activeMoiety&gt; &lt;code code="SRS determined code" codeSystem="FDA SRS system" codeSystemName="SRS code name"/&gt; &lt;name&gt;ingredient 1 active moiety&lt;/name&gt; &lt;/activeMoiety&gt; &lt;/activeMoiety&gt; &lt;/activeIngredientIngredientEntity&gt; &lt;/activeIngredient&gt;  &lt;activeIngredient&gt; ***** </pre>	<p>The code system for this element and all nested elements will be the FDA Substance Registration System (SRS), which is under development; until SRS is completed, the &lt;code&gt; element should not be used for activeIngredientIngredientEntity or activeMoiety. If either element is included in SPL, this information will not be processed by FDA. The value for the codes will be the UNII (unique ingredient identifier).</p> <pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;code ...&gt;     &lt;name ...&gt;     &lt;formCode ....&gt;     &lt;activeIngredient&gt;       &lt;quantity&gt;         &lt;numerator&gt;&lt;denominator&gt;       &lt;/quantity&gt;     &lt;/quantity&gt;     &lt;activeIngredientIngredientEntity&gt;       &lt;code ...&gt;       &lt;name&gt;active ingredient 1 name&lt;/name&gt;       &lt;activeMoiety&gt;         &lt;activeMoiety&gt;           &lt;code&gt;           &lt;name&gt;active moiety name&lt;/name&gt;         &lt;/activeMoiety&gt;       &lt;/activeMoiety&gt;     &lt;/activeIngredientIngredientEntity&gt;   &lt;/activeIngredient&gt; &lt;!-- next active ingredient follows if present --&gt;   &lt;inactiveIngredient....&gt; &lt;!-- inactive ingredients... ..&gt;   &lt;playedDrugWithGeneric....&gt;   &lt;playedContainerLabeledDrug....&gt; &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre> <p>Strength of active ingredient</p> <p>Ingredient name</p> <p>Active moiety name</p> <p>Strength is indicated by the &lt;quantity&gt; tag, with a &lt;numerator&gt; and &lt;denominator&gt;. The numerator and denominator each have 'value' and 'unit' attributes. The unit attribute is optional as in the example to the left. Commonly used quantity units are: <b>mg, ug, g, mL, uL, and dL</b>. (It is recommended that the standard set of units of measure provided in The Unified Code for Units of Measure (<a href="http://aurora.regenstrief.org/UCUM">http://aurora.regenstrief.org/UCUM</a>) be used. For a solution, an example could be &lt;numerator value = "30" unit="mg"&gt;&lt;denominator value="5" unit="mL"&gt;</p>
--	--	--



<b>Inactive ingredients</b>	No/Yes	<pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;!-- name, form code, etc. --&gt;     ...     &lt;activeIngredient ....&gt;     &lt;inactiveIngredient&gt;       &lt;quantity&gt;         &lt;numerator value="200" unit="mg"/&gt;         &lt;denominator value="1"/&gt;       &lt;/quantity&gt;       &lt;inactiveIngredientIngredientEntity&gt;         &lt;code code="SRS determined code" codeSystem="FDA SRS system" codeSystemName="SRS code name"/&gt;         &lt;name&gt;mannitol&lt;/name&gt;       &lt;/inactiveIngredientIngredientEntity&gt;     &lt;/inactiveIngredient&gt;     ..... </pre>	<p>The Inactive Ingredients element description parallels the Active Ingredient element exactly. (In the SPL model, both active and inactive ingredients are examples of 'Ingredient entities' and are therefore identical.) However, an 'active moiety' child is not applicable for an inactiveIngredientIngredientEntity. In addition, quantity is optional for inactive ingredients.</p> <p>The code system for this element and all nested elements in inactive ingredients will be the FDA SRS system; until SRS is completed, the &lt;code&gt; element should not be used, if used, this information will not be processed by FDA</p> <pre> &lt;inactiveIngredient&gt;   &lt;quantity&gt;     &lt;numerator/&gt;&lt;denominator/&gt;   &lt;/quantity&gt;   &lt;inactiveIngredientIngredientEntity&gt;     &lt;code....&gt;     &lt;name&gt;inactive ingredient name &lt;/name&gt;   &lt;/inactiveIngredientIngredientEntity&gt; &lt;/inactiveIngredient&gt; &lt;!-- next inactive ingredient .....&gt; </pre> <div data-bbox="1255 475 1541 613" style="border: 1px solid black; padding: 5px; width: fit-content;"> Strength is optional for inactive ingredients in non-intravenous products </div>
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<b>Dosage Form</b>	No/Yes	<pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;name...&gt;       &lt;formCode displayName="Injection, Powder, Lyophilized, For Solution" /&gt; </pre>	<p>Dosage form is coded in the 'formCode' element, a direct child of the manufacturedLabeledDrug element. The coding system for dosage form is described in the drug listing regulation (21CFR207) and guidance (see <a href="http://www.fda.gov/cder/drls/default.htm">http://www.fda.gov/cder/drls/default.htm</a>). There is no codeSystem for this coding scheme, i.e., no associated code value for the formCode element (i.e., code=""). The value in displayName should be the appropriate value from the table at <a href="http://www.fda.gov/cder/dsm/drg/drg00201.htm">http://www.fda.gov/cder/dsm/drg/drg00201.htm</a> e.g.,</p> <div data-bbox="842 321 1598 634" style="border: 1px solid black; padding: 10px;"> <pre> &lt;formCode displayName="Injection, Powder, Lyophilized, For Solution" /&gt; </pre> <p>Note: there are currently plans to request an OID for the FDA Dosage form table; this should be available shortly. When available, the element will take the form:</p> <pre> &lt;formCode codeSystem="OID for FDA table 201" code="value from table at <a href="http://www.fda.gov/cder/dsm/drg/drg00201.htm">http://www.fda.gov/cder/dsm/drg/drg00201.htm</a>" displayName="translation' column in table"&gt; </pre> </div> <pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;code ...&gt;     &lt;name ...&gt;     &lt;formCode displayName=""/&gt;     &lt;activeIngredient....&gt;     &lt;inactiveIngredient....&gt;     &lt;playedDrugWithGeneri....&gt;     &lt;playedContainerLabeledDrug....&gt;   &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre>
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<b>Labeled Route of Administration</b>	No/Yes	<pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug....&gt;     &lt;consumedIn&gt;       &lt;substanceAdministration&gt;         &lt;routeCode displayName="ENTERAL"/&gt;       &lt;/substanceAdministration&gt;     &lt;/consumedIn&gt;   &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre>	<p>Labeled route of administration (see definition in the SPL specification) is coded in the routeCode element, a child of the &lt;manufacturedProduct&gt;, &lt;consumedIn&gt;, &lt;substanceAdministration&gt; elements. (It is NOT a child of manufacturedLabeledDrug because it is the "labeled" route of administration for the product as a whole). The coding system for dosage form is described in the drug listing regulation (21CFR207) and guidance (see <a href="http://www.fda.gov/cder/drls/default.htm">http://www.fda.gov/cder/drls/default.htm</a>).</p> <p>There is no codeSystem for this coding scheme, i.e., no associated code value in the routeCode element. The value in displayName should be the appropriate value from the table at <a href="http://www.fda.gov/cder/dsm/DRG/drg00301.htm">http://www.fda.gov/cder/dsm/DRG/drg00301.htm</a>, e.g.,</p> <div data-bbox="842 456 1541 719" style="border: 1px solid black; padding: 10px; margin: 10px 0;"> <pre> &lt;routeCode displayName="ENTERAL" /&gt; </pre> <p>Note: there are currently plans to request an OID for the FDA route of administration table. When available, this element will take the form:</p> <pre> &lt;routeCode codeSystem="OID for FDA table" code="value from table at http://www.fda.gov/cder/dsm/DRG/drg00301.htm" displayName="'translation' column in table"&gt; </pre> </div> <pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug....&gt;     &lt;consumedIn&gt;       &lt;substanceAdministration&gt;         &lt;routeCode displayName="..." /&gt;       &lt;/substanceAdministration&gt;     &lt;/consumedIn&gt;   &lt;/manufacturedProduct&gt; </pre> <p>If more than one route of administration is approved, &lt;consumedIn&gt; blocks are repeated, e.g.,</p> <pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug....&gt;     &lt;consumedIn&gt; &lt;!-- first route or administration --&gt;        &lt;&lt;&lt;&lt;     &lt;/consumedIn&gt;     &lt;consumedIn&gt; &lt;!-- second route of administration--&gt;        &lt;&lt;&lt;&lt;     &lt;/consumedIn&gt;     etc.....   &lt;/manufacturedProduct&gt; </pre>
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<b>Imprinting</b>			Imprinting are the characteristics of a drug product (e.g., shape, color, logo, etc.) that are included as observations in the data elements section of SPL. These are described separately in Table 17: Imprint Codes.
<b>Package Type and Quantity</b>		<pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;code ...&gt;     &lt;playedcontainedLabeledDrug&gt;       &lt;quantity&gt;         &lt;quantity&gt;           &lt;numerator value="100" unit="mg"/&gt;           &lt;denominator value="1"/&gt;         &lt;/quantity&gt;       &lt;containerPackage&gt;         &lt;code displayName="VIAL" /&gt;         &lt;regulator&gt;           &lt;code code="0002-7502-01" codeSystem="2.16.840.1.113883.6.69" codeSystemName="NDC"/&gt;         &lt;/regulator&gt;       &lt;/containerPackage&gt;     &lt;/playedcontainedLabeledDrug&gt;   &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre>	<p>The package type and quantity are children of the &lt;manufacturedLabeledDrug&gt;&lt;playedcontainedLabeledDrug&gt;&lt;containerPackage&gt; elements. Quantity has the same structure as &lt;quantity&gt; when used with other elements (e.g., active ingredients). Package Type is a value in the &lt;code&gt; element under &lt;containerPackage&gt;</p> <p>The coding system for package type is described in the drug listing regulation (21CFR207) and guidance (see <a href="http://www.fda.gov/cder/drls/default.htm">http://www.fda.gov/cder/drls/default.htm</a>). There is no codeSystem for this coding scheme, i.e., no associated code value in the code element. The value in displayName should be the appropriate value from the table at <a href="http://www.fda.gov/cder/dsm/drg/Drg00907.htm">http://www.fda.gov/cder/dsm/drg/Drg00907.htm</a>, e.g.,</p> <div data-bbox="848 565 1587 792" style="border: 1px solid black; padding: 5px;"> <pre> &lt;code displayName="VIAL" /&gt;  An OID for the FDA route of administration table is being requested. When available, this element will take the form:  &lt;code codeSystem="OID for FDA table" code="value from table at http://www.fda.gov/cder/dsm/drg/Drg00907.htm" displayName="name" column in table"&gt; </pre> </div> <p>The structure is as follows:</p> <pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;code ...&gt;     &lt;name ...&gt;     &lt;formCode...&gt;     &lt;activeIngredient....&gt;     &lt;inactiveIngredient....&gt;     &lt;playedDrugWithGeneric....&gt; </pre>

			<pre> &lt;playedcontainedLabeledDrug&gt;   &lt;containerPackage&gt;     &lt;quantity&gt;       &lt;numerator value="numerator value" unit="units value"/&gt;&lt;denominator value="denominator value"/&gt;     &lt;/quantity&gt;     &lt;code codeSystem="OID for FDA table" code="value from table at http://www.fda.gov/cder/dsm/drg/Drg00907.htm" displayName="name' from table"&gt;       &lt;regulator&gt;         &lt;code code="0002-7502-01" codeSystem="2.16.840.1.113883.6.69" codeSystemName="NDC"/&gt;       &lt;/regulator&gt;     &lt;/containerPackage&gt;   &lt;/playedcontainedLabeledDrug&gt; &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre>
DEA number			<p>DEA number is included in the SPL model; discussion of how to incorporate this value in SPL will be included in the next revision of this implementation guide.</p>

<b>NDC Number</b>	<pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;playedcontainedLabeledDrug&gt;       &lt;quantity....&gt;       &lt;containerPackage&gt;         &lt;code ....&gt;         &lt;regulator&gt;           &lt;code code="0002- 7502-01" codeSystem="2.16.840.1.113883.6.69 " codeSystemName="NDC"/&gt;         &lt;/regulator&gt;       &lt;/containerPackage&gt;     &lt;/playedcontainedLabeledDrug&gt;   &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre>	<p>NDC number is contained as the value in the &lt;code&gt; child of the &lt;regulator&gt; element where NDC is the codeSystemName. &lt;regulator&gt; is a child of &lt;playedcontainedLabeledDrug&gt; and &lt;containerPackage&gt;; the former is a child of &lt;manufacturedLabeledDrug&gt;.</p> <p>The structure is:</p> <pre> &lt;manufacturedProduct&gt;   &lt;manufacturedLabeledDrug&gt;     &lt;code ...&gt;     &lt;name ...&gt;     &lt;formCode ....&gt;     &lt;activeIngredient....&gt;     &lt;inactiveIngredient....&gt;     &lt;playedDrugWithGeneric....&gt;     &lt;playedcontainedLabeledDrug&gt;       &lt;containerPackage&gt;         &lt;code codeSystem="OID for FDA table" code="value from table at http://www.fda.gov/cder/dsm/drg/Drg00907.htm" displayName=""name' from table"&gt;         &lt;regulator&gt;           &lt;code code="NDC number" codeSystem="2.16.840.1.113883.6.69" codeSystemName="NDC"/&gt;         &lt;/regulator&gt;       &lt;/containerPackage&gt;     &lt;/playedcontainedLabeledDrug&gt;   &lt;/manufacturedLabeledDrug&gt; &lt;/manufacturedProduct&gt; </pre> <p>The codeSystem for regulator is HL7 and is always "2.16.840.1.113883.6.69". The codeSystemName is always "NDC" The only variable in &lt;regulator&gt;&lt;code code="..." codeSystem="2.16.840.1.113883.6.69" codeSystemName="NDC"/&gt; &lt;/regulator&gt; is the code attribute (i.e., code="..."), which is the NDC number.</p> <p>An NDC code with the associated information in the entire row of the conceptual models presented above represents a Packaged Medicinal Product.</p>
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<sup>a</sup> Whether the element is required by the schema and/or FDA.

Imprinting and other descriptive information for solid dosage forms is captured by means of nested elements descending separately from a <component1> element in the body of SPL. These elements are sub-elements of the <Observation> element, which is related to a document section through the component1 relationship (i.e., <section> <component1> <documentBodyEntry> <Observation> <id><code>). The values for the <code> element are the codes that describe the physical markings and identification of the product, if available. If no code is available, the <text> field may be used.

For color, where a code system exists:

```
<section>
  <subject>
    <manufacturedProduct>
      .....
    </manufacturedProduct>
  </subject>
  <component1>
    <documentBodyEntry>
      <Observation classCode="OBS">
        <code code="FDACOLOR"/>
        <value code="white" codeSystem="OID for SVG color system">
          </value>
        </Observation>
      </documentBodyEntry>
    </component1>
  </section>
```

For a characteristic (e.g., shape), where no code system exists:

```
<section>
  <subject>
    <manufacturedProduct>
      .....
    </manufacturedProduct>
  </subject>
  <component1>
    <documentBodyEntry>
      <Observation classCode="OBS">
        <code code="imprint code, e.g., FDASHAPE"/>
        <text>ROUND</text>
      </Observation>
    </documentBodyEntry>
  </component1>
</section>
```

The second form should be used for an item with a code system (e.g., color) but where no acceptable value exists for that code system.

The required characteristics include:

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

Each of these has a corresponding HL7 code, i.e.,

- FDACOLOR
- FDASHAPE
- FDASIZE
- FDACOATING
- FDASCORING
- FDAIMPRINTCD
- FDALOGO

It is expected that each characteristic will be present for every solid dosage form. If a characteristic is not applicable, then it can be omitted (e.g., shape of a suspension).

Since the values for some of these characteristics are not standardized yet, authors should use discretion in describing the characteristics with terms that communicate readily, e.g., round is preferred to circular, oval to ovoid or elliptical, etc.

Table 17: Imprint Codes

Color	FDACOLOR	<p>For color, the code system at <a href="http://www.w3.org/TR/SVG/types.html#ColorKeywords">http://www.w3.org/TR/SVG/types.html#ColorKeywords</a> should be used. The value for the code should be the color name, not the rgb value. An OID for this code system is pending.</p> <p>An example of the use of FDACOLOR is:</p> <pre> &lt;component1&gt;   &lt;documentBodyEntry&gt;     &lt;Observation classCode="OBS"&gt;       &lt;code code="FDACOLOR"/&gt;       &lt;value code="lightcyan" codeSystem="OID for SVG color system"/&gt;     &lt;/value&gt;   &lt;/Observation&gt; &lt;/documentBodyEntry&gt; &lt;/component1&gt; </pre> <p>The use of this system is to generally identify the color of the solid dosage form; it is expected that only a relatively few codes will be needed. An 'exact' match is not needed, i.e., it is not expected any analytic tools will be used to 'exactly' characterize the color of a dosage form.</p> <p>The identifying OID for the SVG code system is pending. Until an OID is assigned, it is recommended that value from the name from the SVG table be used, but as 'text' as in the example for shape below, e.g.,</p> <pre> &lt;Observation classCode="OBS"&gt; </pre>
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		<pre> &lt;id root="78AF9883-92D3-4028-8AFB-B00BC8220117"/&gt; &lt;code code="FDACOLOR"/&gt; &lt;text&gt;lightcyan&lt;/text&gt; &lt;/Observation&gt; </pre>
Scoring	FDASCORING	<p>For <b>scoring</b>, there is no FDA code system. However, the following values should be used in the text field:</p> <p>0 - non solid dose forms, powders, etc.  1 - a solid dosage form that is not scored.  2 or greater - The number of possible equal pieces that a dosage form could result in based on the scoring.</p>
Shape	FDASHAPE	<p>There are no code systems for shape. Values should be entered as follows:</p> <pre> &lt;component1&gt; &lt;documentBodyEntry&gt; &lt;Observation classCode="OBS"&gt; &lt;id root="23AF9883-92D3-4028-8AFB-B00BC8220117"/&gt; &lt;code code="FDASHAPE"/&gt; &lt;text&gt;oval&lt;/text&gt; &lt;/Observation&gt; &lt;/documentBodyEntry&gt; &lt;documentBodyEntry&gt; &lt;Observation classCode="OBS"&gt; &lt;id root="78AF9883-92D3-4028-8AFB-B00BC8220117"/&gt; &lt;code code="FDAIMPRINT"/&gt; &lt;text&gt;921&lt;/text&gt; &lt;/Observation&gt; &lt;/documentBodyEntry&gt; &lt;/component1&gt; </pre>
Size	FDASIZE	<p>There are no code systems for size. Values should be entered as &lt;text&gt; elements. See the example for shape above,.</p>
Coating	FDACOATING	<p>There is no code system for coating. Values should be entered as &lt;text&gt; elements. See the example for shape above,.</p>
Logo	FDALOGO	<p>There is no code system for logo. Values should be entered as &lt;text&gt; elements. See the example for shape above.</p> <p>The value for logo should be a text description of the logo. In the future the logo observation may refer to an image file.</p>
Imprint	FDAIMPRINTCD	<p>There is no code system for logo. Values should be entered as &lt;text&gt; elements. See the example for shape above.</p> <p>The value for Imprint should be the actual text that appears on a solid dosage form, e.g.,</p> <pre> &lt;component1&gt; &lt;documentBodyEntry&gt; &lt;Observation classCode="OBS"&gt; &lt;id root="89AF9883-92D3-4028-8AFB-B00BC8220117"/&gt; &lt;code code="FDAIMPRINT"/&gt; &lt;text&gt;50&lt;/text&gt; &lt;/Observation&gt; &lt;/documentBodyEntry&gt; &lt;/component1&gt; </pre>

All data elements for one unique product (corresponding to a major row in the conceptual view table) are contained within a single <component2><section> in the SPL body; each unique product (<ManufacturedProduct>) will have its own section. This means that machine processable information about a drug product 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 (such as 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 example of the XML markup of machine processable structured data elements that describe a drug product (one section per product) 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>

<documentBodyChoice>

<StructuredBody>

<component><!-- this component/section contains all the data elements -->

<section>

<id root="81E32825-5BC8-46EB-8043-AE607B3819FA " />

GUID for section

<!-- Each proprietary drug product is a separate nested component 2 -->

<component2>

<section>

<id root="5708BCA0-8189-4331-83BA-08C7BDBD5C03"/>

<subject>

<manufacturedProduct>

<manufacturedLabeledDrug>

....

....

</manufacturedLabeledDrug>

<consumedIn>

....

</consumedIn>

</manufacturedProduct>

</subject>

<component1>

<documentBodyEntry>

<Observation>

....

</Observation>

</documentBodyEntry>

<component1>

</section>

</component2>

Drug information  
(see above) for  
drug product 1

Labeled Route of Administration  
for drug product 1

Identification and Markings (Imprinting)  
for drug product 1

<!-- ----- start of drug product 2 ----- -->

<component2>

<section>

<id root="GUID">

<subject>

Start of Drug Product 2

```

.....
</subject>
<component1>
  <documentBodyEntry>
    <Observation>
      .....
    </Observation>
  </documentBodyEntry>
</component1>
</section>
</component2>
</component>
<!------- end of drug products/data elements ----->

<!------- Now start Narrative section ----->
<!------- e.g., Description section ----->
<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"
      codeSystemName="LOINC" displayName="Description"/>
    <title>DESCRIPTION</title>
    .....
  </section>
</component>

```

Identification and Markings (Imprinting)  
for drug product 2

end of drug products/data elements ----->

Now start Narrative section ----->  
e.g., Description section ----->

This component contains all the content of labeling -->

**Figure 8: Detailed Model 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.

```

<component2>
  <section>
    <id root="675D3B70-0457-4F92-AA4A-8B30928A32A9"/>
    <subject>
      <manufacturedProduct>
        <manufacturedLabeledDrug>
          <code code="0004-2601" codeSystem="FDA code system"
            codeSystemName="FDA code name"/>
          <name>ExampleDrug</name>
          <formCode displayName="TAB COATED"/>
          <activeIngredient>
            <quantity>
              <numerator value="87.5" unit="mg"/>
              <denominator value="1"/>
            </quantity>
          </activeIngredient>
        </manufacturedLabeledDrug>
      </manufacturedProduct>
    </subject>
  </section>
</component2>

```

Product Code  
(See Proprietary Name in  
Table 16)

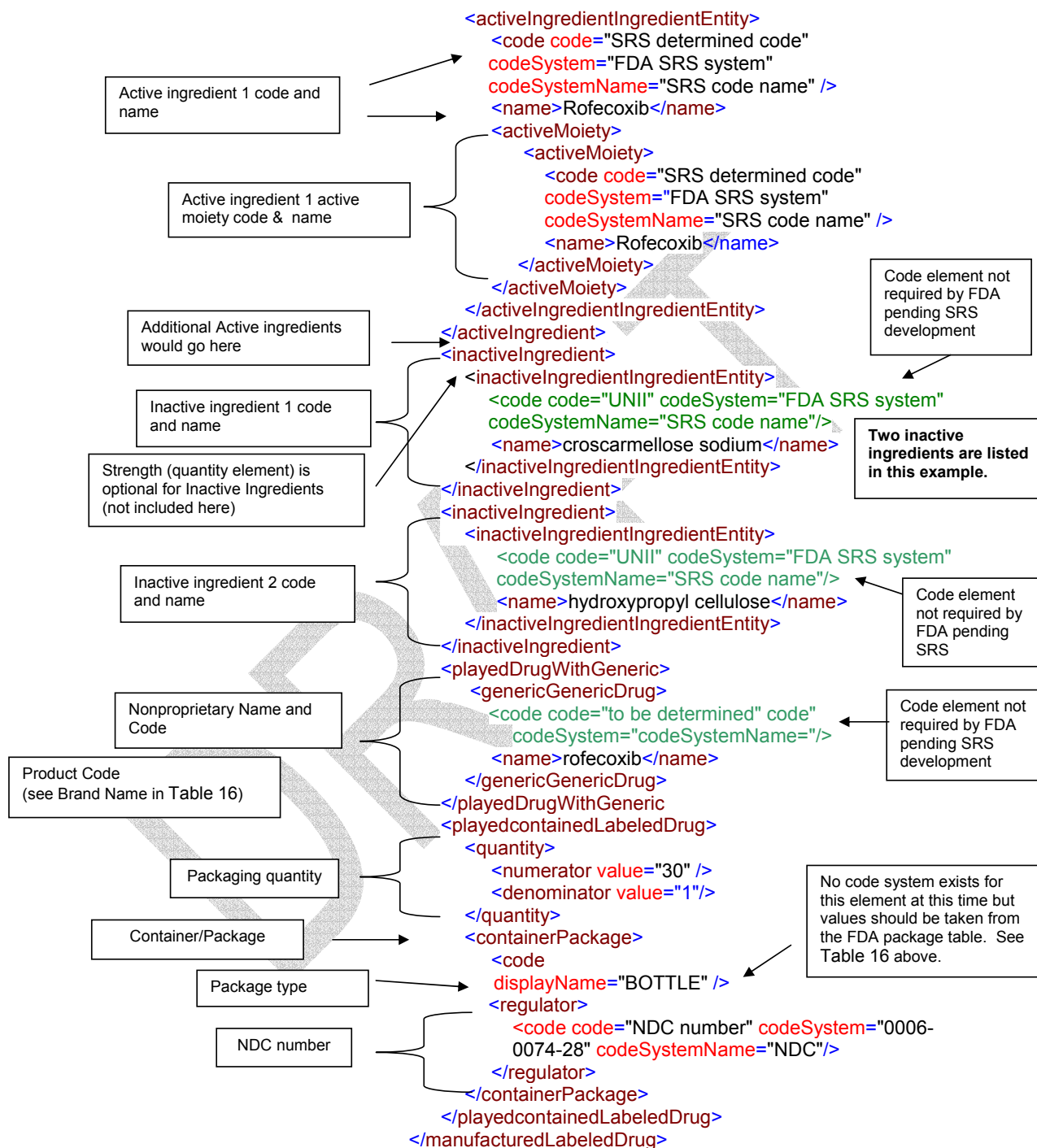
Proprietary  
Name

Dosage Form Name

Active Ingredient 1  
strength

See Table 16  
above. (OID to  
identify this code  
system is  
pending.)

The acceptable value for  
units comes from  
The Unified Code for  
Units of Measure



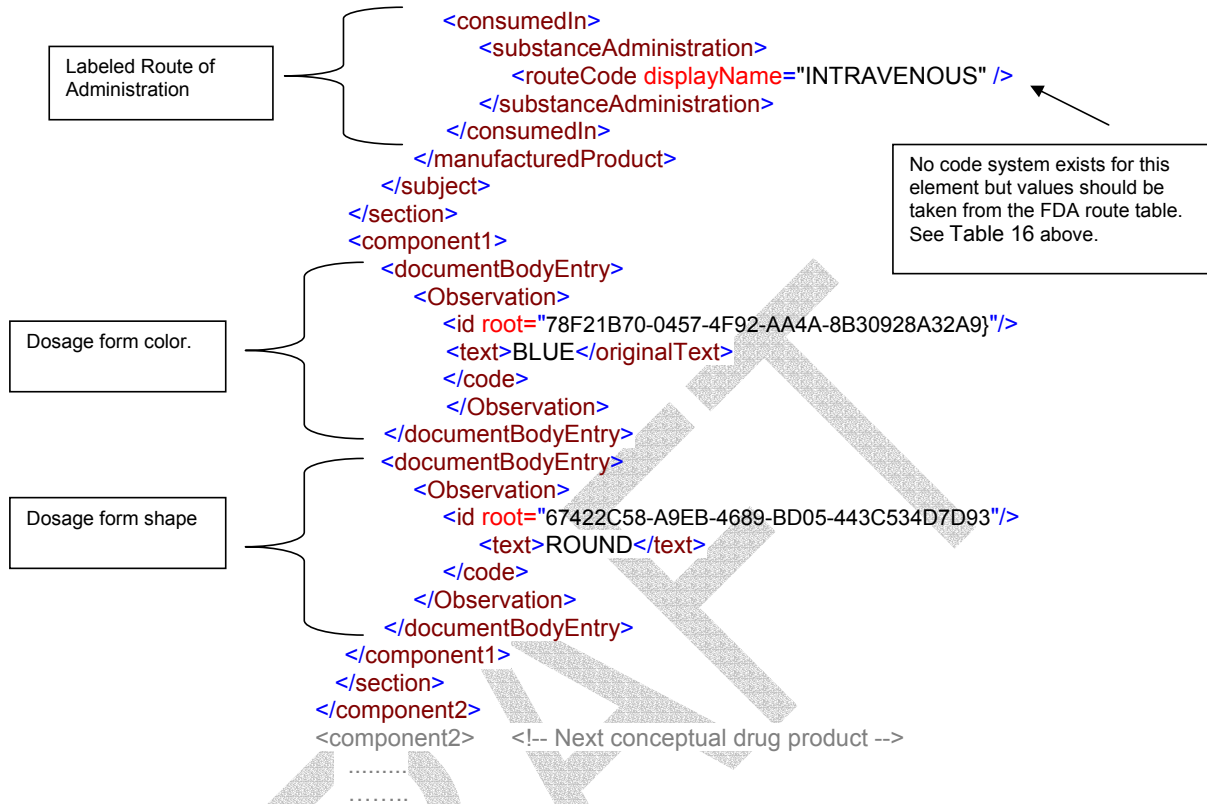


Figure 9: Annotated Example of SPL 'Drug Product' section.

The following example shows a drug product section for an SPL document when there is a combination product involved. This example addresses the case of a kit in which two separate drugs are combined in a single carton – and the combination product has its own brand name and NDC. The example used is Rebetron which contains two separate products, Rebetol and Intron A.

```
<section>
  <subject>
    <manufacturedProduct>
      <manufacturedLabeledDrug>
        <name>Rebetron</name>
        <playedDrugWithGeneric>
          <genericGenericDrug>
            <code code="TBD" codeSystem="OID TBD" codeSystemName="FDA established name"/>
            <name>ribavirin and interferon alfa-2b</name>
          </genericGenericDrug>
        </playedDrugWithGeneric>
        <containerPackage>
          <containedPackage>
            <code> code="TBD" codeSystem="OID TBD" codeSystemName="carton"/>
            <regulator ... NDC code for the combination product />
          </containedPackage>
        </containerPackage>
      </manufacturedLabeledDrug>
    </manufacturedProduct>
  </subject>
  <subject>
    <manufacturedProduct>
      <manufacturedLabeledDrug>
        <name>Rebetol</name>
        <formCode code="From_FDA_vocabulary" displayName="capsule" codeSystem="1.2.3.4" codeSystemName="FDA"/>
        <activeIngredient>
          <quantity>
            <numerator value="200" unit="mg"/>
            <denominator value="1"/>
          </quantity>
          <activeIngredientIngredientEntity>
            <code code="CodeForRibavirin" codeSystem="1.2.3.4" codeSystemName="FDA"/>
            <name>ribavirin</name>
          </activeIngredientIngredientEntity>
        </activeIngredient>
        <playedDrugWithGeneric>
          <genericGenericDrug>
            <code code="TBD" codeSystem="OID TBD" codeSystemName="FDA established name"/>
            <name>ribavirin</name>
          </genericGenericDrug>
        </playedDrugWithGeneric>
        <inactiveIngredient>
          <inactiveIngredientIngredientEntity>
            <code code="CodeForLactoseMonohydratel" codeSystem="1.2.3.4" codeSystemName="FDA"/>
          </inactiveIngredientIngredientEntity>
        </inactiveIngredient>
      </manufacturedLabeledDrug>
    </manufacturedProduct>
  </subject>
</section>
```

```

        <name>lactose monohydrate</name>
      </inactiveIngredientIngredientEntity>
    </inactiveIngredient>
    <containedLabeledDrug>
      <quantity>
        <numerator value="70"/>
        <denominator value="1"/>
      </quantity>
      <containerPackage>
        <code> code="TBD" codeSystem="OID TBD" codeSystemName="bottle"/>
        <regulator ... NDC code for the component product [if there is one] />
      </containerPackage>
    </containedLabeledDrug>
  </manufacturedLabeledDrug>
  <consumedIn>
    <substanceAdministration>
      <routeCode code="ORAL" codeSystem="2.16.840.1.113883.5.112" codeSystemName="RouteOfAdministration" displayName="oral"/>
    </substanceAdministration>
  </consumedIn>
</manufacturedProduct>
</subject>
<subject>
  <manufacturedProduct>
    <manufacturedLabeledDrug>
      <name>Intron A</name>
      <formCode code="From_FDA_vocabulary" displayName="injectable solution" codeSystem="1.2.3.4" codeSystemName="FDA"/>
      <activeIngredient>
        <quantity>
          <numerator value="3 million" unit="[iU]"/>
          <denominator value="0.5" unit="mL"/>
        </quantity>
        <activeIngredientIngredientEntity>
          <code code="CodeForInterferonAlfa2b" codeSystem="1.2.3.4" codeSystemName="FDA"/>
          <name>interferon alfa-2b</name>
        </activeIngredientIngredientEntity>
      </activeIngredient>
      <playedDrugWithGeneric>
        <genericGenericDrug>
          <code code="TBD" codeSystem="OID TBD" codeSystemName="FDA established name"/>
          <name>interferon alfa-2b</name>
        </genericGenericDrug>
      </playedDrugWithGeneric>
      <inactiveIngredient>
        <inactiveIngredientIngredientEntity>
          <code code="CodeForMannitol" codeSystem="1.2.3.4" codeSystemName="FDA"/>
          <name>mannitol</name>
        </inactiveIngredientIngredientEntity>
      </inactiveIngredient>
    </manufacturedLabeledDrug>
  </manufacturedProduct>
</subject>

```

```

<containedLabeledDrug>
  <quantity>
    <numerator value="3" unit="mL"/>
    <denominator value="1"/>
  </quantity>
  <containerPackage>
    <code> code="TBD" codeSystem="OID TBD" codeSystemName="multi-dose vial"/>
    <regulator ... NDC code for the component product [if there is one] />
  </containerPackage>
</containedLabeledDrug>
</manufacturedLabeledDrug>
<consumedIn>
  <substanceAdministration>
    <routeCode code="IVC" codeSystem="2.16.840.1.113883.5.112" codeSystemName="RouteOfAdministration" displayName="Infusion, intravenous
catheter"/>
  </substanceAdministration>
</consumedIn>
</manufacturedProduct>
</subject>
</section>

```

**Figure 10: Example of SPL 'Drug Product' section for combination (multiple component) drug product.**



## VI. Submitting SPL to FDA

See FDA guidance to industry: *Providing 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> or at <http://www.fda.gov/cder/guidance/6028dft.pdf>.

DRAFT

## VII. Appendices

### A. Benefits of an XML approach to SPL

The benefits that accrue to all stakeholders in the drug regulatory process by adoption of Structured Product Labeling (SPL) make the business case for implementation of SPL overwhelming. The benefits of SPL derive from use of standard, universally adopted information standards such as XML, from the specific aspects of the SPL model for describing prescription drug content, and from adoption of an open standard for SPL:

Specific benefits of SPL include:

- Stakeholders can develop automated, customized presentations of SPL content to reduce medical errors and improve patient care.
- SPL can be used by decision-support systems to improve patient care and reduce medical errors.
- Communication within industry (e.g., business-business communication) is facilitated by the ability to use SPL with XML-compliant tools or services.
- The use of well-defined vocabularies and coding systems within SPL enables uniform and unambiguous description of prescription drug products for data information systems
- XML-based transformations of SPL content by third-parties can increase the information and medical value of SPL documents while ensuring the integrity of FDA-approved labeling content.
- Internal business processes can repurpose the data contained within SPL through the use of XML-compliant databases.
- SPL insures data integrity of labeling content (and other SPL data elements) between industry and FDA databases.
- XML compliant consumer and health practitioner tools can use SPL in multiple settings.
- SPL can be readily integrated with HL7-based hospital information systems due to compliance with CDA architecture.
- Tools or objects that implement the standard can be utilized across all instances of SPL.
- Labeling content in SPL is not tied to proprietary tooling, allowing the development of SPL documents by different tools while retaining compatibility.
- SPL-associated XML stylesheets allow consistent presentation (rendering) of label content across different package inserts.
- Labeling changes and updates can be transmitted and immediately integrated into information systems.
- Non-rendered data elements (e.g., metadata about the SPL document or tagged content abstracted from the content of labeling) can be encompassed by the SPL standard to allow SPL data to integrate with other FD and stakeholder systems.

These benefits represent only a fraction of the extensive benefits that accrue from adoption of SPL. The principles underlying these benefits are discussed below.

#### 1. SPL as an Open Standard:

SPL has been adopted as an open standard by Health Level Seven (HL7), an ANSI-accredited Standards Developing Organization (SDO). SPL development within HL7 has followed a well-defined, rigorous, ANSI-specified set of standards development procedures that has ensured consensus, openness and balance of interest among all participants in the development process. Participants in this process have included representatives of the pharmaceutical industry, regulatory participants from the United States, and observers from other international agencies, domain and technical experts from HL7, health care providers, and software vendors.

The SPL document standard is defined by an XML schema; XML schemas are also an open standard supported by the World Wide Web consortium (W3C).<sup>33</sup> The vast penetration of XML technology in business and consumer products allows SPL to leverage the large number of tools available that support XML and other W3C standards<sup>34</sup>. The use of the HL7 information model and HL7 modeling conventions

<sup>33</sup> See <http://www.w3c.org/XML/>.

<sup>34</sup> For example, XML is supported by all major Internet browsers.

for the development of SPL ensures that SPL documents (also referred to as instances) are universally readable and unambiguously understood to all users of SPL documents and the developers of SPL tooling.<sup>35</sup>

As an open standard, SPL facilitates interoperability between systems. This provides substantial benefits to users through the reduced cost of software applications due to marketplace competition and the decreased need to customize applications around a proprietary standard. As an open standard, developers benefit substantially by full, immediate access to the information necessary to implement SPL systems. As noted earlier, adherence to a standard dramatically improves integration different software applications and permits increased sophistication of software systems based on SPL.

The HL7 ANSI-mandated open development process ensures that all stakeholder concerns are addressed during the process of future enhancements to the standard. The publicly-open HL7 consensus process allows the contribution from a far greater array of participants than would be accessible to FDA in a more restricted standards-development approach. This permits a substantial number of individuals to contribute to the standard who otherwise would be excluded.

Overall, the use of an open standard such as SPL enables direct and predictable industry-to-FDA communication of package insert information, with subsequent direct communication of content to health care professionals and other third parties in a manner previously not possible with earlier FDA standards, e.g., PDF.

## 2. Machine Processability & Data Integration

As an XML standard SPL contains machine-readable context (i.e., tagged) information. Using XML enables the textual content to also be represented as data, i.e., "entries," in a data layer not visible to the human reader in the document but machine readable.

By structurally and semantically identifying content in this fashion, standardized data exchange between systems can occur. It permits business-to-business, industry-to-regulatory agency, and regulatory agency-to-public data transfer in a seamless manner. Knowledge of the sending or receiving system is not needed as long as there is conformance to the standard; in addition, since the definition of SPL (i.e., the XML schema for SPL) is an open standard, others systems can readily integrate structured information from SPL documents. During the exchange across systems, the need for additional transformation steps is eliminated.

Through use of XML, SPL can contain machine processable information separate from labeling content, i.e., 'data elements' related to or derived from label content but not strictly present in an identical format in current label content. For example, a tagged list of inactive ingredients may not appear as such in the content of a package insert but could be included as machine-processable data elements included by the SPL author. Data elements (or any tagged information) can serve as data for other systems separate from SPL, e.g., drug registration systems.<sup>36</sup>

The structure and machine readability of SPL also enables certain previously manual review functions within FDA and industry to become machine processable activities, e.g., identifying changes to the content of individual package inserts or comparing information across a broad range of SPL instances.

<sup>35</sup> SPL embodies syntactic interoperability through the use of XML schemas and semantic interoperability (i.e., unambiguous interpretation of the XML tags in SPL) through derivation from the HL7 RIM model. See <http://www.hl7.org> for more information or [http://www.healthcare-informatics.com/webinars/05\\_20\\_04.htm](http://www.healthcare-informatics.com/webinars/05_20_04.htm) for a web-based discussion of HL7 and semantic interoperability.

<sup>36</sup> This converse may also be supported, i.e., SPL could be populated with information from other information systems (rather than supplying information), ensuring data integrity across data systems. However, in either role (i.e., as receiver or supplier of 'data'), SPL serves as an envelope for this information.

### 3. Human Readability & Data Presentation

SPL expresses the content of drug labeling separately from its presentation. A uniform presentation (or rendering) of content across all package inserts can be supported by FDA; this is an important benefit to potential end-users of SPL content.

Equally valuable is the ability to have customized presentations (renderings) for end users and within regulatory agencies and industry. Such renderings may exist for a single SPL instance or across multiple SPL documents. Customized rendering should permit use of the content of pharmaceutical labeling by both the health care industry and regulatory agencies in medically and regulatory important ways that were previously inaccessible.

As an XML-based document, an SPL document retains human-readability in its native document form; sections of SPL can be easily comprehended, displayed, and edited without transformation or special rendering.

### 4. Streamlined Processing

SPL has significant advantages for internal processing of documents. XML-based documents permit separation of content for different purposes, e.g., for generating different regulatory submissions by pharmaceutical companies or for entry into different database systems by FDA, e.g., drug listing. SPL itself can be directly constructed via database systems. Modular use of document sections promotes consistency of content in company-generated documents and the reduction or elimination of redundancies; this similarly aids FDA in maintaining consistency across documents..

SPL facilitates the comparisons of document content (both narrative and data elements) across documents or between current and earlier versions of the same document. Document revision histories can be automated and viewed.

The use of a structured standard would permit processes developed by one organization to be used seamlessly by others; for examples, objects to "test" whether an SPL meets certain regulatory criteria (e.g., CBE) developed by a regulatory agency could be distributed for use by pharmaceutical companies. (Similar functionality could also be provided as web services.)

SPL also permits automated insertion and deletion of sections while confirming and maintaining the data integrity of non-altered content.

### 5. Scalability & Flexibility

The SPL format permits scalable implementation of document markups that may be of varying complexities. Such markups are flexible, i.e., naming or nesting of sections are not imposed upon the document, and permits integration of XML and non-XML sources with common metadata. Lastly, multiple data types (e.g. images, tables, and/or text) may be embedded into SPL.

As a schema-based standard, evolution of SPL can occur in a backward-compatible fashion that maintains compatibility with earlier versions of the standard. Similarly, transformations of XML documents can permit third parties to easily convert non-SPL defined information into clinical products and data sources while insuring integrity of the SPL content.

### 6. Tool independence

SPL as a non-proprietary open standard is compatible with a wide range of XML document creation applications while remaining independent of underlying storage mechanisms and/or document management systems. It is available to vendors who can apply the standard to any XML-based product they currently market. Vendors can build new tools or modify any current tools they may have to work with the standard.

Each business may define their own processes to incorporate SPL and choose the tools which will best complement the way they do their work, recognizing that SPL documents will be compatible with any other system.

The development of SPL as an open standard within the HL7 standards development process ensures that future development of the standard reflects a consensus process among industry, regulatory authorities, and the general health care community.

Use of SPL as an unambiguous, standardized markup (including use of standard controlled vocabularies and coding systems) should ultimately facilitate use of the content of a text document as data, permitting accurate database-like searches across SPL documents to improve patient care and safety. With data in SPL format, there may be opportunities to eliminate redundant data collection and manual processing that are used in other submissions, such as drug listing. Additionally, process efficiencies may surface with other organizations which use package insert information.

The potential benefits of SPL apply to every stakeholder who implements SPL. Even without the obvious benefit for use within FDA, benefit to other organizations that will serve as information-providers (such as the National Library of Medicine [NLM]), and information-consumers such as health care professionals and the general public make the transition to SPL by FDA necessary.

## 7. Security of documents

Need section on security added once defined.

## B. SPL Standard Stylesheet and FDA Implementation of Stylesheets

### 1. Introduction

SPL is a form of document markup that is based on the HL7 clinical document architecture that will enable the standardization of the structure and semantics of the required content of drug product labeling as described in FDA regulations and guidance. While the SPL document is human readable, there are minimal formatting structures (e.g., 'bold' or 'italics' font effects via the <content emphasis="..."> tag) available under the SPL-schema definition. The process of generating a formatted human readable display or presentation of an SPL document (instance) is referred to as rendering.<sup>37</sup>

This HL7 SPL standard stylesheet is used for the display of an SPL document. It consists collectively of two files, an SPL extensible stylesheet language file (currently spl-1.1.xsl ) and an SPL cascading stylesheet file (currently spl-1.1.css). These files are W3C standard-compliant file types that define the baseline set of style conventions for viewing an SPL XML file in a current browser, such as Microsoft Internet Explorer 6.0, Mozilla 1.7, Netscape Navigator 7.1, or Opera 7.54 or greater.<sup>38</sup> File spl-1.1.xsl transforms an SPL document to a W3C standard-compliant XHTML document. spl-1.1.css defines cascading stylesheet classes for rendering the XHTML-transformed SPL document. Both files were created to be "browser-independent," meaning software products that support the W3C standards should render a valid SPL document similarly.<sup>39</sup>

Examples of rendering via the SPL standard stylesheet are shown in Sec. IV.A.4

If additional styles are needed for the proper display of the FDA content of labeling that have not been adopted in the HL7 standard stylesheet, these will be included in a FDA-specific stylesheet that will add, or cascade, with the HL7 stylesheet. The file is named similarly to spl-1.1.css, i.e., FDA-1.1.css. The FDA SPL standard stylesheet will be available at [www.fda.gov/oc/dataacouncil/spl/](http://www.fda.gov/oc/dataacouncil/spl/).

It should be noted that the css files are coded in the xsl file, i.e., in the actual coding of the SPL file the names of the active css files are unnecessary. Specifying the current xsl file in the SPL document will automatically select the css files current at the time the SPL is created.

### 2. SPL Stylesheet Components

The files collectively referred to as the SPL Standard Stylesheet (i.e., the separate xsl and css files) define the baseline set of style conventions for viewing an SPL-compliant XML file in a browser.

To illustrate how they are used, the following code represents a snippet from the gemcitabine demonstration SPL document cited earlier:

```
<component>
  <section>
    <id root=" A856E13A-8AA7-4C45-B378-97957CDFFC81"/>
    <code code="34090-1" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
      displayName="Clinical pharmacology"/>
    <title>CLINICAL PHARMACOLOGY</title>
    <component2>
      <section>
        <id root="DD761815-06CE-47CA-A2D2-EFB2F24EFA44"/>
        <code displayName="Mechanism of action" nullFlavor="OTH"/>
        <text>
```

<sup>37</sup> In this discussion, 'presentation,' 'display,' and 'rendition' are used synonymously.

<sup>38</sup> Support for a W3C-complaint XML stylesheet transformation is not necessarily for properly rendering SPL. Server-based implementations of SPL may transform SPL via the standard XSL file and transmit the transformed XHTML document for rendering on a local device. In this model, only software support for rendering an XML/XHTML document with stylesheet classes is necessary for display.

<sup>39</sup> The end-user display/presentation is the XHTML transformed SPL document. Direct viewing of the SPL document, although possible via a specific CSS file, is not supported or recommended.

```

<paragraph>
  Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin <content
  emphasis="italics">in vitro</content>. No effect of cisplatin on gemcitabine triphosphate
  accumulation or DNA double-strand breaks was observed. <content emphasis="italics">In
  vivo</content>, gemcitabine showed activity in combination with cisplatin against the LX-1
  and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or
  NCI-H520 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine
  xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the
  greatest interaction.
</paragraph>
.....
.....

```

These excerpts of SPL-compliant XML are transformed by the following code in spl-1.1.xsl:

```

.....
<xsl:template match="v3:section/v3:title">
  <xsl:param name="sectionLevel" select="count(ancestor::v3:section)"/>
  <xsl:element name="h{$sectionLevel}">
    <xsl:apply-templates select="@*" />
    <xsl:apply-templates mode="mixed" select="node()" />
  </xsl:element>
</xsl:template>
.....

<xsl:template match="v3:paragraph">
  <p>
    <xsl:apply-templates select="@*[v3:caption]" />
    <xsl:apply-templates mode="mixed"
      select="node()[not(self::v3:caption)]" />
  </p>
</xsl:template>
.....

<xsl:template mode="mixed" match="v3:content">
  <span>
    <xsl:apply-templates mode="mixed" select="@*[node()]" />
  </span>
</xsl:template>
<xsl:template mode="mixed" match="v3:content[@emphasis='yes']">
  <em><xsl:apply-templates mode="mixed" select="@*[node()]" /></em>
</xsl:template>
<xsl:template mode="mixed" match="v3:content[@emphasis='italics']">
  <em class="Italics{@splx:styleCode}">
    <xsl:apply-templates mode="mixed"
      select="@*[not(local-name()='styleCode')][node()]" />
  </em>
</xsl:template>
.....

```

into this HTML-compliant markup:

```

<h1>CLINICAL PHARMACOLOGY</h1>
<p>
  Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin <em class="Italics">in
  vitro</em>. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was
  observed. <em class="Italics">In vivo</em>, gemcitabine showed activity in combination with cisplatin against
  the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520
  xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure
  to gemcitabine 4 hours before cisplatin produced the greatest interaction.

```

</p>

The HTML <p> element is rendered according to the CSS classes defined in the css file. For example, the <p> element is displayed by this class definition:<sup>40</sup>

```
p {
  text-indent: 0em;
  margin-top: 0em;
  margin-bottom: 0ex;
  line-height: 2.2ex;
}
```

with default styles inherited from the body element:

```
body {
  background-color: white;
  color: black;
  font-family: Arial Unicode MS
  margin-left: 4em;
  margin-right: 4em;
}
```

Therefore, in a compliant browser supporting CSS formatting, the snippet above would be presented as black text on a white background. There would be 4 cm left and right margins, and a line-height of 2.2 ex.

When displayed in a W3C complaint browser, the text would appear similar to the following<sup>41</sup>:

#### CLINICAL PHARMACOLOGY

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin *in vitro*. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, gemcitabine showed activity in combination with cisplatin against the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction.

The cascading stylesheet defines a default CSS class for each XHTML element resulting from the transformation of SPL to XHTML. Because SPL permits reference to an external namespace, additional formatting choices are available to render SPL content in specific ways. If necessary, these additional formatting choices would be available in the FDA SPL stylesheet for the display of the FDA content of labeling (see the next section for more details). For example, the following SPL snippet:

```
.....
<tr splx:styleCode="Botrule">
  <td>&#160;&#160;Range</td>
  <td>36 to 88</td>
  <td>35 to 79</td>
</tr>
<td>33 to 76</td>
<td>35 to 75</td>
```

<sup>40</sup> Note: the unit 'em' is a measure of horizontal space (width) that depends on the currently effective font (approximately the width of the lower case m). The unit 'ex' is a measure of vertical space (height) that depends on the currently effective font (approximately the height of a lower case x). For example, the 4 em value indicates that for the margin-left and margin-right properties, the left and right margins will be four times the height of the default font rendering the document. The sans-serif value for the font-family property specifies the default non-serif font for the browser, e.g., Arial or helvetica fonts.

<sup>41</sup> The margins are inaccurate in this example, having been reformatted for this specific document.



```

</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>7%</td>
<td>7%</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
....

```

will render as two rows in the following table.<sup>42</sup>

**Table 2: Randomized Trials of Combination Therapy with Gemzar plus Cisplatin in NSCLC**

Trial	28-day Schedule <sup>a</sup>		21-day Schedule <sup>b</sup>	
	Gemzar/ Cisplatin	Cisplatin	Gemzar/ Cisplatin	Cisplatin/ Etoposide
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
Stage IIIA	7%	7%	N/A	N/A
Stage IIIB	26%	23%	48%	52%
Stage IV	67%	70%	52%	49%
Baseline KPS <sup>c</sup> 70 to 80	41%	44%	45%	52%
Baseline KPS <sup>c</sup> 90 to 100	57%	55%	55%	49%
Survival	p=0.008		p=0.18	
Median, months	9.0	7.6	8.7	7.0
(95%,C.I.) months	8.2, 11.0	6.6, 8.8	7.8, 10.1	6.0, 9.7
Time to Disease Progression	p=0.009		p=0.015	
Median, months	5.2	3.7	5.0	4.1
(95%,C.I.) months	4.2, 5.7	3.0, 4.3	4.2, 6.4	2.4, 4.5
Tumor Response	26%	10%	33%	14%
	p<0.0001 <sup>d</sup>		p<0.01 <sup>d</sup>	

<sup>a</sup> 28-day schedule – Gemzar plus cisplatin: Gemzar 1000 mg/m<sup>2</sup> on Days 1, 8, and 15 and cisplatin 100 mg/m<sup>2</sup> on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m<sup>2</sup> on Day 1 every 28 days.

<sup>b</sup> 21-day schedule – Gemzar plus cisplatin: Gemzar 1250 mg/m<sup>2</sup> on Days 1 and 8 and cisplatin 100 mg/m<sup>2</sup> on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m<sup>2</sup> on Day 1 and I.V. etoposide 100 mg/m<sup>2</sup> on Days 1, 2, and 3 every 21 days.

<sup>c</sup> Karnofsky Performance Status.

<sup>d</sup> p-value for tumor response was calculated using the two-sided Fisher's exact test for difference in binomial proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.

In this example, specifying "Botrule" for the styleCode attribute to the first <tr> element creates a horizontal rule below the first row in the table (bottom rule)

The complete list of available CSS formatting classes is discussed in the Section IV.A.5 Tables.

### 3. Creation and Use of SPL Stylesheets

To the extent possible, users should adopt the CSS classes available in the HL7 standard css stylesheet for creating SPL documents. If specific requirements necessitate additional stylesheet classes to accommodate the proper display of a valid SPL document, HL7 permits authorized agencies to define a local cascading stylesheet that extends the existing HL7 standard stylesheet.

FDA is responsible for defining the local SPL practices for regulatory submissions in the United States. Additional classes available for SPL submissions in the U.S. (fda-1.1.css) can be found at [http://www.fda.gov/cder/spl\\_classes.htm](http://www.fda.gov/cder/spl_classes.htm). By cascading fda-1.1.css with spl-1.1.css, users have access to a superset of CSS formatting classes beyond that available in spl-1.1.css alone. No classes are defined in fda-

<sup>42</sup> In a browser supporting CSS1 and certain class properties available in CSS2.

1.1.css that override existing classes in spl-1.1.css, meaning that no identical class names are used in fda-1.1.css and spl-1.1.css. The addition of local classes to spl-1.1.css provides a means for supplementing the standard stylesheet in those circumstances for which this is necessary. Local classes are not intended to fundamentally alter the appearance of a rendered SPL document as defined by the HL7 standard stylesheet through, for example, extensively modifying common elements, such as the <paragraph> or <list> elements.

FDA will maintain fda-1.1.css. Use of local classes permits FDA to act independently from HL7 when the rapid addition of CSS classes is necessary to meet an immediate needs. FDA will forward any added classes to the HL7 for consideration in adding to the HL7 SPL standard stylesheet with the goal of minimizing locally (i.e., FDA) defined classes. All added classes adopted in the HL7 SPL standard stylesheet will be removed from the locally defined stylesheets.

Formatting classes not present in the HL7 SPL standard stylesheet (spl-1.1.css) or in FDA-specific additional classes defined in fda-1.1.css will not be supported by FDA and should not be used in SPL documents submitted to FDA.

The SPL transformation stylesheet is maintained by HL7 and is designed to render an XHTML-compliant document formatted for human readability according to standard document constructs. It is anticipated that virtually all formatting accommodations necessary for rendering SPL will be accommodated through HL7 or realm-specific CSS classes as opposed to alterations in the transformation (xsl) stylesheet.

C. Gemcitabine Sample SPL document

D. Second Sample SPL document

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E. Glossary (under development)

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. ( <a href="http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html">http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html</a> )
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." ( <a href="http://access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html">http://access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html</a> )
Active ingredient	1) An active ingredient in a product is defined in regulations 2) HL7: A role representing a therapeutically active ingredient (player) in a mixture (scoper), where the mixture is typically a manufactured pharmaceutical. Active Ingredients in SPL are modeled by the <activeIngredient> data element described in Table 16.
Active moiety	1) The molecular structure responsible for the physiological or pharmacological action of the drug substance. 2) The active moiety as describe in regulations. Active moiety is included in SPL as a child element (activeMoiety) of the Active ingredient element and is described in Table 16.
ANSI	American National Standards Institute
Approved Labeling	Labeling content that has been officially approved by the FDA. This does not refer to labeling content that is implemented by the sponsor (and not formally FDA approved) through CBE or annual report changes, etc.
Architecture	An architecture for structured documents defines relationships between documents and document specifications in terms of specialization and inheritance (see also CDA architecture)
ASCII	American Standard Code for Information Interchange, a common 8-bit character encoding of printed (and some non-printed characters) for electronic communication.
Association	
Attribute	A name-value pair included inside an XML element tag
CDA	HL7 Clinical Document Architecture
Class	
Clinical document	An HL7 clinical document is a documentation of clinical observations and services, with the following characteristics: <ul style="list-style-type: none"> <li>• Persistence – A clinical document continues to exist in an unaltered state, for a time period defined by local and regulatory requirements.</li> <li>• Stewardship – A clinical document is maintained by a person or organization entrusted with its care.</li> <li>• Potential for authentication – A clinical document is an assemblage of information that is intended to be legally authenticated.</li> <li>• Wholeness – Authentication of a clinical document applies to the whole and does not apply to portions of the document without the full context of the document.</li> <li>• Human readability – A clinical document is human readable.</li> </ul> <p>In HL7, Clinical Documents are derived from the Clinical Document Architecture (see xxxx). SPL is derived from the HL7 Clinical Document Architecture.</p>
Clinical Document Architecture	ANSI/HL7 CDA R1.0-2000. Specification for the structure and semantics of "clinical documents" for the purpose of exchange. Defined by HL7. See <a href="http://xxxx">http://xxxx</a>
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).

Term or Abbreviation	Definition
	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.
Data Model	
Dosage Form	1) Form of product, (e.g., tablet, capsule, solution, etc.) that contains an active drug ingredient or placebo. Dosage Form is modeled as an Observation in SPL using the FDA CDER Data Standards Table (see Table 16.) 2) A finished dosage form as described in regulations
Drug	1) Articles recognized in the Official United States Pharmacopoeia, Official Homeopathic Pharmacopoeia of the United States, or Official National Formulary 2) Articles intended for the use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals
Electronic Labeling Rule	
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. See VII.G, XML Primer.
Entity	
ELIPs	FDA's Electronic Labeling Information Processing System.
Established name	1) The official name of a drug substance 2) In US FD&C Act, the term "established name", with respect to a drug or ingredient thereof, means (A) the applicable official name designated pursuant to section 508 of the FD&C Act, or (B), if there is no such name and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in such compendium, or (C) if neither clause (A) nor clause (B) of this subparagraph applies, the common or usual name, if any, of such drug or of such ingredient, except that where clause (B) of this subparagraph applies to an article recognized in the United States Pharmacopoeia and in the Homeopathic Pharmacopoeia under different official titles, the official title used in the United States Pharmacopoeia shall apply unless it is labeled and offered for sales as a homeopathic drug, in which case the official title used in the Homeopathic Pharmacopoeia shall apply.
Established Medical Product	
FD&C Act	Food, Drug and Cosmetic Act – <a href="http://www.fda.gov/opacom/laws/fdact/fdctoc.htm">http://www.fda.gov/opacom/laws/fdact/fdctoc.htm</a>
FDA	Food and Drug Administration.
Granularity	The relative size of a defined 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.
Harmonization	
Health Level Seven	An ANSI-accredited States Developing Organization (SDO) operating in the healthcare arena. "Level Seven" refers to the highest level of International Standards Organization's (ISO) communications model for Open Systems Interconnection (OSI) – the application level. The application level addresses definition of the data to be exchanged, the timing of the interchange and the communication of certain errors to the application. The seventh level supports such functions as security checks, participant identification, availability checks, exchange mechanism negotiations and, most importantly, data exchange structuring. (See <a href="http://www.hl7.org">http://www.hl7.org</a> )
HL7	See Health Level Seven above. The "7" stands for the Application level of the ISO communication model – ISO level 7.
HTML	Hypertext Markup Language, a specification of the W3C that provides markup of documents for display in a web browser
Inactive ingredient	Any component of a drug product other than an active ingredient, as described in

Term or Abbreviation	Definition
	regulations
Ingredient	Any component of a drug product
Label	Label is considered identical to the FDA-defined package insert or Final Printed Labeling (FPL).
Labeling	
Legal authentication	A completion status in which a document has been signed manually or electronically by the individual who is legally responsible for that document
Level	
LOINC	LOINC® (Logical Observations, Identifiers, Names, and Codes, <a href="http://www.regenstrief.org/loinc.htm">http://www.regenstrief.org/loinc.htm</a> ). 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. LOINC codes within SPL identify specific values, e.g., sections within the FDA package insert (see Appendix H).
Markup	Computer-processable annotations within an XML document not meant to be displayed but needed to structure the document,, e.g., element names such as <section>.
MD5 Check Sum	
MedID	
Normative	
National Library of Medicine	(NLM) is the world's largest biomedical library. The Library acts as a supplemental resource after local, regional, and other national resources have been contacted (such as the FDA). NLM also creates and maintains databases (including all US marketed products or Approved labeling) and databanks for general use.
Package	Container for holding a product, as described in US FDA regulations. Package in SPL is modeled in the <containerPackage> element. (See Table 16: Mapping and Coding of Data Elements in the Conceptual View to SPL Elements (including labeled Route of Administration)
Package Insert	
Package quantity	The net quantity of contents of a product in package form
Patient Package Insert	
Processing Instruction	
Proprietary Medical Product	
Proprietary name	1) A name that a company uses for the commercial distribution of a drug product; may also be known as the brand name 2) The brand name as described in regulations
Realm	The geographical, organizational, or political environment where the HL7 standard is being used. For SPL, the US realm is used as this reflects a United States regulatory document.
Reference Information Model (RIM)	An information model used as the base model for deriving all HL7 messages and clinical documents. Since all HL7 documents are derived from a common model, interoperability and consistency between documents is assured.
Regulated product	A drug product that is subject to regulatory requirements.
RIM	Reference Information Model
Role	
Schema	A formal definition of the structure and content of a type of XML document. (See also W3C Schema)
Section	
SGML	Standard Generalized Markup Language, ISO 8879:1986(E) as amended and corrected. XML is derived from SGML.
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

Term or Abbreviation	Definition
	information on the owner of the marketing authority for the product, the author, legal authenticator, and reviewers
SPL Instance	
SPL specification	The Structured Product Labeling (SPL) specification is a document markup standard that specifies the structure and semantics for the regulatory requirements and content of product labeling.
Strength	1) The concentration of a substance (e.g., the concentration of drug in a dosage form) 2) The measurement of the drug substance as described in regulations
Stylesheet	A file that describes how to display an XML document of a given type. See XSL below.
Template	
UNII	
URI	Uniform Resource Indicator
Valid document	A document which 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. See VII.G.8, Well formed and Valid XML Documents.
Value set	In HL7, a vocabulary domain that has been constrained to a particular realm and coding system.
Vocabulary domain	In HL7, the set of all concepts that can be taken as valid values in an instance of a coded field or attribute
W3C	The World Wide Web Consortium, an international industry consortium ( <a href="http://www.w3.org">http://www.w3.org</a> )
W3C Schema	The three-part schema specification issued by the W3C XML Schema Part 0: Primer, W3C Recommendation 2-May-2001, <a href="http://www.w3.org/TR/xmlschema-0/">http://www.w3.org/TR/xmlschema-0/</a> XML Schema Part 1: Structures, W3C Recommendation, 2-May-2001, <a href="http://www.w3.org/TR/xmlschema-1/">http://www.w3.org/TR/xmlschema-1/</a> XML Schema Part 2: Datatypes, W3C Recommendation, 2-May-2001, <a href="http://www.w3.org/TR/xmlschema-2/">http://www.w3.org/TR/xmlschema-2/</a>
XML	Extensible Markup Language, specification of the W3C, a formal subset of SGML ( <a href="http://www.w3.org/TR/REC-xml">http://www.w3.org/TR/REC-xml</a> ). See Appendix VII.G, XML Primer.
XML declaration	Markup stating that that document is an XML document and stating to which version of the XML specification the document is conformant
XML document	SPL is an XML document. An XML consists of a prolog (processing instructions), a root document element, and other objects. See Appendix VII.G, XML Primer.
XML schema	See W3C Schema
XSL	Extensible Style Language, a specification of the W3C ( <a href="http://www.w3.org/Style/XSL/">www.w3.org/Style/XSL/</a> ) An XSL stylesheet in SPL collectively consists of several files, a transformation file (spl-xxx.xsl) and a cascading style sheet (spl-xxx.css). These files 'transform' SPL into an HTML files that can be viewed by a standard Web browser. See Appendix VII.B, SPL standard stylesheet.
XSLT	XSL transformation language, a specification of the W3C ( <a href="http://www.w3.org/TR/xslt">http://www.w3.org/TR/xslt</a> ). XSLT is one part of what is collectively considered the XSL stylesheet (see XSL above).

#### F. Viewing SPL Files

Spl\_viewer.zip is available at <http://www.fda.gov/oc/datacouncil/spl/>. This zip file, when unzipped, contains the 2 example files shown above and a viewing application for rendering SPL on a Windows-compatible computer. *Spl Viewer.htm*, one of the files available when spl\_viewer.zip is unzipped, permits viewing SPL files in either their original XML or rendered forms.

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## G. XML Primer

### 1. Introduction

XML (Extensible Markup Language) provides a method for structuring electronically transmitted information. There are general conventions for describing the structure of the document that apply to all XML documents, e.g., that XML elements have a start tag and an end tag (see below), but they do not specify the exact structure a particular document must take. Instead, the XML standard addresses this by a mechanism that permits specific rules to be written for specific XML document types (such as SPL) that list and define the components that make the document XML-compliant. The rules for a specific type of XML document define the structure for the information in that particular document type, e.g., an 'address' in a particular document type may be specified to consist of a 'street name', a 'city', and a 'zip code'. The zip code may be further specified to exist only as a 5 digit number.<sup>43</sup> In more technical terms, the rules of an XML document type, or the 'schema' for that document type, unambiguously specify the 'syntax' that a document can take.

Information in an XML document may be intended for display to be read by humans (e.g., in print or on a computer screen); many of the documents on the World Wide Web are XML documents that are read through web browsers. Other XML documents primarily contain 'data' that is not meant for reading but for processing by another computer. In both cases XML provides the structure where both the 'sender' and the 'receiver' can understand the information, regardless of whether the 'receiver' is a human or another computer. XML documents such as SPL contain both types of information in one document, i.e., the 'content of labeling' meant for display and reading by humans, and 'data elements' meant to be 'interpreted' by computers and used in database systems (where they may be subsequently presented to a reader in a different form).

SPL is a type of XML document defined by a schema, or rules, for creating this specific type of XML document. The schema for a specific type of document (or the document itself) is not part of the XML standard but must be written following rules of the XML standard. This is analogous to FDA regulations or to the CTD; regulations define the rules of how to create a New Drug Application, but do not specify the actual content of any specific application. Similarly, the CTD describes how a submission should be organized but does not specify the content of a particular submission. The CTD specifies the 'rules' how to organize a submission.

The following is an abbreviated introduction to aspects of XML terminology used in this implementation guide. Should you wish to learn more about XML, Internet or printed resources regarding XML are readily available.

### 2. Elements and Tags

An element is the basic building block of an XML document. Element names are defined by whoever wrote the schema for the document; in some cases they may be standardized (e.g., elements used for web pages, SPL elements based on the HL7 information model). The basic format of an XML element is: <tag>information</tag> (i.e., a set of tags wraps a particular piece of the information being structured), as shown in the following example:

```
<model>Ford Mustang</model>
```

Every XML element has a start tag (<model> in this example), an end tag </model>, and the element content ("Ford Mustang"). A start tag always has a left angle bracket (<), the element name (model), and a right angle bracket (>). The end tag is identical to the start tag with the addition of a slash (/) after the left angle bracket to indicate "close tag".<sup>44</sup> Start tags and end tags are considered *markup*, i.e., the information in an XML document that is not meant to be displayed but identifies the structure of the document. Processing instructions, as well as comments (both described later in this section) are other examples of markup.

A schema consists of defined elements in a particular order, possibly with other elements nested inside them. The root element is the first element in an XML document. All the other elements in an XML document are nested

<sup>43</sup> **The rules could have just as easily specified a 9 digit zip code -- the form an XML document takes is dependent on the rules that were written for that document type by the author of that document type.**

<sup>44</sup> Because of this, a left angle bracket (<) cannot be used in the content of an XML element since this will be misinterpreted as the start of a new element. To include a left angle bracket as an in SPL content an entity reference must be used, e.g., <model>Ford &#lt;car &#gt;</model> which would be displayed as "Ford <car>" in a browser.

inside the root element, also referred to as being children of the root element. Each child element may consist of other elements, content information (i.e., text), or a combination of text and other elements. A special type of element is the empty element which may contain attributes (see below) but neither text nor other elements. An empty tag has a special form where there is no close tag (essentially a start and end tag combined). `<emptyTag/>` is an example of the form an empty tag would take.

Since the first element in an XML document is always the root element, e.g., `<Document>`, the last tag is always the end tag for the root element, e.g., `</Document>`. Element names (and therefore tags) are case sensitive, i.e., `<document>` is a different tag from `<Document>`.<sup>45</sup>

For example, if *car* is the “parent” or root element of an XML document, sub-elements or children of *car* might include *make*, *model* and *color* so, in XML markup, the car: a red Ford Mustang would appear as:

```
<car>
  <make>Ford</make>
  <model>Mustang</model>
  <color>RED</color>
  <vin vinNumber="12335566699"/>
</car>
```

*car* is an element which contains only other elements; these elements are the *make*, *model*, *color*, and *vin* elements. Another way of expressing this is that *make*, *model*, *color* and *vin* are children of the *car* element, or ‘nested’ within the *car* element. ‘*vin*’ is an empty element with the attribute *vinNumber* (see below).<sup>46</sup>

### 3. Attributes

Attributes are name/value pairs that are associated with a particular element; they may further define or modify the element. Attributes appear inside start tags or empty tags. Attributes must have a “value” (including a possible default value) assigned; this value will always be enclosed by quotes.<sup>47</sup> The name/value pair is always expressed as:

```
<element attribute name="value">content</element>
```

For example, one method to identify a person’s age via an attribute in an XML document could be:

```
<person age="18">toni</person>
```

In this example, the element *person* has an attribute *age* with a value of 18.<sup>48</sup> In SPL, an example of an element containing an attribute could be:

```
<paragraph>This drug is <content emphasis="bold">contraindicated </content> with food.</paragraph>
```

<sup>45</sup> The distinction between elements and tags is frequently confusing and some people use them interchangeably. For example, *car* is an element, with child elements *make*, *model*, etc. Another element in the example below is *make*, where the value is Ford and is identified by `<make>Ford</make>`. A tag is specific markup in an XML document, e.g., `</make>` is an end tag for the element *make*. Elements may be referred to simply by their name whereas a tag always has brackets, e.g., `<car>` is the start tag for the *car* element. However, a common convention in narrative about XML is to surround element names with angle brackets (this convention was used in the SPL specification). If the example of *car* above were a complete XML document (rather than being part of another document), then *car* would be the root element.

<sup>46</sup> An important point is illustrated by comparison of the element `<model>` in this and the earlier example. Although the element names are identical, they may have different meanings. In the earlier example, *model* referred to the manufacturer and *model* together. In the latter example, *model* was used only for the specific model, e.g., *mustang*. Although the rules, or schema, for a specific XML document specify the syntax of the document, they can’t ensure the ‘semantic’ interpretation of a document, i.e., exactly what the elements mean. Elements should be unambiguously defined in something like a data dictionary; alternatively, an information model such as the HL7 information model will convey explicit semantics to element names based on it.

<sup>47</sup> A default value would be assigned in the schema, or rules, for that particular type of XML document.

<sup>48</sup> The reader may ask why this isn’t an element, e.g., `<person><name>Toni</name> <age>18</age></person>`. How to make the decision as to whether a certain value should be specified as an attribute or element in the structure of an XML document is beyond the scope of this primer.

The element *content* has the attribute: *emphasis*, with a value of "bold". When displayed, this code would likely be displayed as follows:

This drug is contraindicated with food

Empty elements may be used to hold attributes and values, e.g.,

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

In this example there is no content for the *renderMultiMedia* element since it is an empty element. However the attribute *referencedObject* contains the value MM1; MM1 is the information necessary for the *renderMultiMedia* element to convey where to place some information stored in a file that is external to the document. The name of appropriate file in this instance (MM1) could point to a file that contains an image of the molecular structure of a drug.

#### 4. The Structure of an XML Document

XML documents generally consist of two parts, one of which contains the 'processing instructions' at the start of an XML document, and the other the body or content of the document. Within the body lies the root element and all its "children" or sub-elements. This document hierarchy is often depicted using the metaphor of a tree. As described previously, elements can contain textual content (called PCDATA in the XML standard), other elements (sub-elements or children) or both (known as mixed content). In XML, it is imperative that the children or sub-elements be nested properly.<sup>49</sup> If we use the previous example:

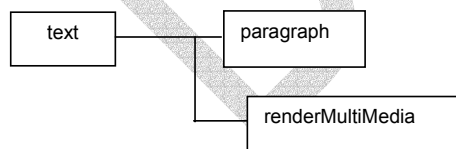
```
<paragraph>this drug is <content emphasis="bold">contraindicated </content> with food.</paragraph>
```

The *paragraph* element is mixed: it contains text content as well as other elements. The element *content* is nested within *paragraph*.

The element *text* in SPL is an example of an element that contains only other elements<sup>50</sup>:

```
<text>
  <paragraph>This is just the paragraph content</paragraph>
  <renderMultiMedia referencedObject="MM5"/>
</text>>
```

In this example, the element *text* element contains the elements *paragraph* and *renderMultimedia*. *paragraph* and *renderMultimedia* are sub-elements or children of *text*. Using the tree metaphor to depict this relationship, another way to show the relationship is:



#### 5. XML Instructions and the Root Element

<sup>49</sup> Nesting in this context refers to the order of the children of an element, i.e., that an actual XML document follows the structure permitted in the rules (or schema) for that document.

<sup>50</sup> Text is being used in different contexts in this discussion. Text refers to the content, or value of an element (e.g., the text, or value, or content of the *paragraph* element in `<paragraph>green olive</paragraph>` is 'green olive'. *text* is also an element name in SPL as in `<text><paragraph>green olive</paragraph></text>`. In XML, textual content is usually referred to as PCDATA (parsed character data).

XML documents contain instructions that do not contain either content or data elements, but are used by the program processing the XML document for different purposes (e.g., a web browser opening an XML document). The XML declaration at the start of an XML document identifies the document as an XML document and specifies the version of the XML standard used when creating the document. Other processing instructions may be included that, for example, specify a transformation file that will aid in displaying the XML content. The following is an example of a declaration plus processing instructions in an XML document that specifies a transformation file:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="spl-1.1.xsl"?>
```

The ? after the left angle bracket identifies each line of this markup as an XML instruction.

The root element of an XML document is a required and critical aspect of an XML document as it contains all the other elements that constitute the document (i.e., it defines the starting point and ending point for the document). The root element uses a special syntax and identifies the schema(s) that will be used to validate an XML document.

The root element has many optional attributes, the description of which is beyond the scope of this primer, and may often appear quite complex. The specific form of the root element to be used with SPL is specified in the implementation guide above. However, the general order of XML document is:

```
<?xml version="1.0" encoding="UTF-8"?>
<? Other Processing instructions... ">
<rootElement>
....
....
</rootElement> <!-- end tag for root element -->
```

## 6. XML Comments

Comments may exist anywhere in an XML document except inside tags. Comments are ignored by the XML processor. Comments are identified by the special character sequence <!-- (start comment) and --> (end comment). For example:

```
<example><!-- this is a comment --></example>
```

A more detailed example of valid XML comments is:

```
<text>
  <!-- this was written to address Matt's concerns -->
  <paragraph>drug x may cause.... </paragraph>
  <paragraph><!-- another comment, but this time mixed in the content of an element -->drug x
  may also cause.... </paragraph>
</text>
```

The following would not be permissible because the comment is inside the tag:

```
<text>
  <paragraph <!-- this is a comment -->>this is invalid since the comment is in markup (in this case
  the start tag for paragraph).....</paragraph>
</text>
```

## 7. XML Schemas

A schema is a separate XML document that describes the rules, or syntax, of an XML document type (e.g., SPL). A schema defines the permissible elements and attributes in a document, the order in which they occur in an XML document, and possible values for these elements<sup>51</sup>. For example, a schema might permit:

```
<text><paragraph>this is OK</paragraph></text>
```

but not permit:

```
<paragraph><text>this is not OK</text></paragraph>
```

or just as easily, the schema could permit the reverse.

The schema also specifies the values that can be used for attributes, where the value is restricted, and can even specify the type of content that is acceptable for the value (the data type), e.g., specifying certain attributes to be dates and others only as numbers.

XML schemas can be straightforward or extremely complex depending on the document type the schema is intended to address. Creating schemas is beyond the scope of this primer. However, it should be noted that authors of XML documents (e.g., SPL authors) would not alter a schema in creating a document; changes to a schema can only be made by the creator of the schema. Authors, however, may frequently refer to the schema to understand the structure of a document and determine what elements and attributes are permissible for that document type.

## 8. Well formed and Valid XML Documents

An XML document must be well-formed, and if well-formed, can then be tested for validity. A well-formed document is an XML document that follows the basic rules of every XML document, e.g., that all elements have a start tag and end tag (excepting empty tags), that nesting is correct, that attribute values are in quotes, etc. For example,

```
<test><paragraph>paragraph content...</test>
```

is not well-formed since there is a missing end tag for the paragraph element; similarly,

```
<test><paragraph>paragraph content...</test></paragraph>
```

is not well-formed since the tags are improperly nested. These are rules of the XML standard and are independent of the schema used for a particular document type. They apply to all XML documents.

If a document is well-formed it can then be tested for validity. Validity tests whether an XML document follows the rules of the specific schema for that document type; if it does, then it is considered a valid document. For example, in SPL:

```
<text><paragraph>this is a paragraph</paragraph></text>
```

is valid but:

```
<paragraph><text>this is an invalid paragraph</text></paragraph>
```

<sup>51</sup> Another means of specifying the rules, or the syntax of XML document is a DTD, or document type definition. Both are similar in that they define the rules of an XML document, (a DTD is actually a type of schema) but the details of each differ substantially. Discussion of the details of both schemas and DTDs is beyond the scope of this primer, although it is important to note that schemas rather than DTDs are used to define the structure of an SPL document.

is invalid since the order of elements in the latter example is not permitted by the SPL schema. However, both examples are well-formed XML.

## 9. Tables

Tables are not part of the XML standard; they are defined by the schema of a document type that has decided to include tables. (There is no need to even call these 'tables'; a schema could have named this element anything else. However, a 'table' element is familiar since this element is commonly used in HTML documents on the World Wide Web.) Tables can also take different forms in different document types, i.e., the permitted children of the table element can be different in different schemas. Because tables are so important in SPL, the structure of the *table* element in SPL is discussed briefly here.<sup>52</sup>

The table element in SPL is identified by the `<table>` tag. A table may contain rows and columns. The number of columns in a table is defined by the number of cells in a row. *tr* identifies row elements and cells in a row are *td* elements. An empty cell would be `<td/>`.

A simple table (including comments) could be:

```
<table>
  <tr> <!-- row 1 -->
    <td>col1 value for this row</td><td>col2 value for this row</td>
  </tr> <!-- end tag for row 1 -->
  <tr> <!-- row 2 -->
    <td>col1 value for this row</td><td>col2 value for this row</td>
  </tr> <!-- end tag for row 2 -->
</table>
```

A heading row in a table is the *th* element. Use is identical to the *td cell* element, e.g.,

```
<table>
  <thead>
    <tr> <!-- a heading row (there can be more than 1 -->
      <th>column 1 heading</th><th>column 2 heading</th>
    </tr> <!-- end tag for heading row 1 -->
  </thead>
  <tbody>
    <tr> <!-- row 1 -->
      <td>col1 value for row</td><td>col2 value for this row</td>
    </tr> <!-- end tag for row 1 -->
    <tr> <!-- row 2 -->
      <td>col1 value for row</td><td>col2 value for this row</td>
    </tr> <!-- end tag for row 2 -->
  </tbody>
</table>
```

When a heading is used, it is good practice to divide a table into heading and body sections by use of the *thead* and *tbody* elements, as shown in the example above, although these elements are optional.

Footnotes are included as a separate section at the start of the table, even if they are displayed at the end of the table. The structure is the same. For example:

```
<thead>.....
</thead>
<tfoot>
```

<sup>52</sup> Although the *table* element in SPL is very similar to the *table* element in HTML, it is not identical. The SPL schema must be used for constructing tables in SPL.

```

<tr>
  <td align="left" colspan="5">
    <paragraph splx:styleCode="Footnote">
      <caption>a</caption> Half-life for patients receiving
      a short infusion (&lt;70 min).
    </paragraph>
  </td>
</tr>
</tfoot>
<tbody>.....
</tbody>

```

This more realistic example illustrates several aspects of the SPL table model in addition to use of the footnote (*tfoot*) element: (1) Cells in a row, header, or footnote can contain an *align* attribute, (2) cells can contain the *colspan* attribute, and (3) cells can contain *paragraph*. Colspan allows a cell to span multiple columns. In a five column table, 5 'footnote' columns would make little sense; colspan also allows the footnote to appear as anticipated, i.e., across all columns of a table in a separate row. Colspan is also frequently used in the body of a table where a particular row may need to combine columns for presentation. For example:

Column header for 1 and 2		Column head 3	Column head 4	Column head 5
Male <sup>a</sup>	Female			
4	5	100	300	500
6	7	388	887	543
P = .007		P=.34		
<sup>a</sup> This is an example of a footnote				

The table has two header rows; in the second header row, the code that yields merging, or spanning the last 3 columns is: `<th align="center">male<sup>a</sup></th><th align="center">female</th><th colspan="3"></th>`. For the fifth row, similar code is: `<tr><td align="center" colspan="2">P=.007</td><td colspan="3">P=.34</td></tr>`. The *colspan* attribute exists for spanning rows of a table. Use is similar to *rowspan*, e.g., `<td colspan="2">this spans 2 columns</td>`.

A table may have a caption by use of the *caption* element, e.g., `<table><caption>This is the caption for this table</caption><thead>..... </table>`.

Two additional elements are available for organizing the structure of SPL tables: *colgroup*, with the associated *col* element. Colgroup is used to organize the columns of a table so they can be presented as a group, e.g., with a heavier vertical rule between groups. Colgroup can be used as follows:

```

<table>
  <colgroup>
    <col align="left"/>
    <col align="center"/>
  </colgroup>
  <colgroup>
    <col align="right"/>
    <col align="left"/>
  </colgroup>
  <thead>
    .....
    .....
  </thead>

  <tbody>
    .....
    .....
  </tbody>
</table>

```

This defines a table with 4 columns, 2 column groups with 2 columns each. The default alignment for each column is specified (optionally) by the align attribute. Note that the *col* element can appear without a *colgroup* element, e.g., `<table><col/><col/>.....`

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## H. LOINC codes for SPL

LOINC code	displayName
	Document type
34391-3	HUMAN PRESCRIPTION DRUG LABELING
	Section type
34066-1	BOXED WARNING SECTION
34067-9	INDICATIONS & USAGE SECTION
34068-7	DOSAGE & ADMINISTRATION SECTION
34069-5	HOW SUPPLIED SECTION
34070-3	CONTRAINDICATIONS SECTION
34071-1	WARNINGS SECTION
34072-9	GENERAL PRECAUTIONS SECTION
34073-7	DRUG INTERACTIONS SECTION
34074-5	DRUG &OR LABORATORY TEST INTERACTIONS SECTION
34075-2	LABORATORY TESTS SECTION
34076-0	INFORMATION FOR PATIENTS SECTION
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
34083-6	CARCINOGENESIS & MUTAGENESIS & IMPAIRMENT OF FERTILITY SECTION
34084-4	ADVERSE REACTIONS SECTION
34085-1	CONTROLLED SUBSTANCE SECTION
34086-9	ABUSE SECTION
34087-7	DEPENDENCE SECTION
34088-5	OVERDOSAGE SECTION
34089-3	DESCRIPTION SECTION
34090-1	CLINICAL PHARMACOLOGY SECTION
34091-9	ANIMAL PHARMACOLOGY &OR TOXICOLOGY SECTION
34092-7	CLINICAL STUDIES SECTION
34093-5	REFERENCES SECTION
34391-3	HUMAN PRESCRIPTION DRUG LABELING
TBD	SUPPLEMENTAL PATIENT MATERIAL