Structured Product Labeling

ANSI/HL7 SPL R1.0 2004

August 17, 2004

Editors:

Sandy Boyer
Consultant
Editor, Clinical Document Architecture
Co-chair, HL7 Structured Documents Technical Committee
slboyer@attglobal.net

Robert H. Dolin, M.D.
Kaiser Permanente
Editor, Clinical Document Architecture
Co-chair, HL7 Structured Documents Technical Committee
Robert.H.Dolin@kp.org

HL7 Steward:

Regulatory Clinical Research Information Management (RCRIM) Technical Committee

Co-chairs:

Randy Levin
Linda Quade
Barbara Tardiff

IMPORTANT NOTES:

HL7 licenses its standards and select IP free of charge. **If you did not acquire a free license from HL7 for this document,** you are not authorized to access or make any use of it. To obtain a free license, please visit http://www.HL7.org/implement/standards/index.cfm.

If you are the individual that obtained the license for this HL7 Standard, specification or other freely licensed work (in each and every instance "Specified Material"), the following describes the permitted uses of the Material.

A. HL7 INDIVIDUAL, STUDENT AND HEALTH PROFESSIONAL MEMBERS, who register and agree to the terms of HL7's license, are authorized, without additional charge, to read, and to use Specified Material to develop and sell products and services that implement, but do not directly incorporate, the Specified Material in whole or in part without paying license fees to HL7.

INDIVIDUAL, STUDENT AND HEALTH PROFESSIONAL MEMBERS wishing to incorporate additional items of Special Material in whole or part, into products and services, or to enjoy additional authorizations granted to HL7 ORGANIZATIONAL MEMBERS as noted below, must become ORGANIZATIONAL MEMBERS of HL7.

B. HL7 ORGANIZATION MEMBERS, who register and agree to the terms of HL7's License, are authorized, without additional charge, on a perpetual (except as provided for in the full license terms governing the Material), non-exclusive and worldwide basis, the right to (a) download, copy (for internal purposes only) and share this Material with your employees and consultants for study purposes, and (b) utilize the Material for the purpose of developing, making, having made, using, marketing, importing, offering to sell or license, and selling or licensing, and to otherwise distribute, Compliant Products, in all cases subject to the conditions set forth in this Agreement and any relevant patent and other intellectual property rights of third parties (which may include members of HL7). No other license, sublicense, or other rights of any kind are granted under this Agreement.

C. NON-MEMBERS, who register and agree to the terms of HL7's IP policy for Specified Material, are authorized, without additional charge, to read and use the Specified Material for evaluating whether to implement, or in implementing, the Specified Material, and to use Specified Material to develop and sell products and services that implement, but do not directly incorporate, the Specified Material in whole or in part.

NON-MEMBERS wishing to incorporate additional items of Specified Material in whole or part, into products and services, or to enjoy the additional authorizations granted to HL7 ORGANIZATIONAL MEMBERS, as noted above, must become ORGANIZATIONAL MEMBERS of HL7.

Please see http://www.HL7.org/legal/ippolicy.cfm for the full license terms governing the Material.

Table of Contents

1 Organization of the Specification

1.1 Normative and non-normative sections

Sections 2 through 5 are normative (i.e., prescribe the norm or standard). Sections 1 (Organization) and 6 (Appendices) are non-normative (i.e., informative only).

The normative specification consists of:

- Scope and design principles for the specification – see *2. Introduction*
- Characteristics and major components of a Structured Product Labeling (SPL) document – see *3.1 Characteristics of SPL Documents*
- Background information about the underlying information model (the HL7 Reference Information Model [RIM]) and the Clinical Document Architecture (CDA), a closely related HL7 standard, and general issues related to use of this specification – see *3 General Concepts*
- Requirements for the model – see *4.1 Product Labeling Requirements*
- Description of the model (general concepts, components) – see *4.2 SPL Model*
- Technical specification
    - Refined Message Information Model (RMIM) – see *5.4 SPL RMIM*
    - Hierarchical Description (HD)[1] – see *5.5 SPL Hierarchical Description (HD)*
    - Schema – see *5.6 SPL Schema*

Additional information that may be useful in understanding or implementing the specification is available in the Appendices (including mapping between the data requirements and the model and schema).

1.2 Editorial conventions

This specification uses notations that are standard in Extensible Markup Language (XML) and HL7. Those include:

- XML element names are surrounded by angle brackets (e.g., <Document>). (Because names of classes in this Structured Product Labeling (SPL) specification become the XML element names, they are also surrounded by angle brackets in this document.)
- Names of HL7 attributes that involve two or more words follow camelCode convention, i.e., the first word is lowercase and the following words begin with uppercase (e.g., classCode).
- HL7 attributes that are specific to a RIM class are named by concatenation of the class and the RIM attribute (e.g., Act.code).

In this specification, RIM attribute names are surrounded by single quotation marks (e.g., ‘code’ or ‘Act.code’). (Note that many RIM attributes become XML elements in the SPL Schema, as a result of HL7 schema creation rules.)

Vocabulary domain names are italicized (e.g., *ActClass*).

Terms defined in the glossary (see *6.1 Glossary*) are cited in double quotes on first mention within this document. Acronyms are not quoted but are expanded in the glossary.

[1]Although the HD is the same as the structure called the HMD (Hierarchical Message Description) in other parts of the HL7 Version 3 specification world, we have chosen HD in this document because we didn’t want to imply that this structure is limited to messages. In fact, in the emerging HL7 Development Framework (HDF), this same structure will be used, as it is in this specification, for “abstract information structures” other than “just” messages.

2 Introduction

2.1 What is the Structured Product Labeling 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 the authorized published information that accompanies any medicine licensed by a national or international medicines licensing authority. Like most documents, an SPL document has sections and sections contain text (paragraphs, lists, tables); SPL documents can be rendered and published in these standard narrative presentations. At the same time, the SPL specification provides semantic markup that permits extraction of relevant data embedded in the narrative so that it can be used for other purposes. In other words, SPL markup of a product labeling document both preserves the human readability of the content and facilitates machine processing of that content.

This specification includes a detailed description of an information model for structured product labeling documents as well as the XML representation of that model. The information model is based on the HL7 Reference Information Model (RIM) and uses the HL7 Version 3 Data Types.

SPL is based on the HL7 Clinical Document Architecture (CDA), which specifies the structure and semantics of "clinical documents" for the purpose of exchange (see *3.1.1 Relationship of the SPL Specification to CDA*). The SPL Schema is defined as an XML entity. An SPL document references the SPL Schema.

For this version of the specification, document analysis focused primarily on labeling for drug products. It is important to note that the name for this type of document is highly variable. While “product labeling” was chosen for this specification, other names include package insert, prescribing information, product information, medicines information, and summary of product characteristics, among others. The precise definition and content of product labeling may also vary depending on the country. (For example, in the U.S., all written, printed, or graphic matter accompanying a drug product is called “labeling”. For human prescription drugs, the “content of labeling” includes all text tables and figures in the labeling described in 21CFR 201.57.) Implementers of this standard should refer to applicable regulations and definitions in the realm in which the standard will be used.

2.2 Purpose of the SPL specification

The major purpose of the SPL specification is to facilitate the review, editing, storage, dissemination of, and access to product labeling document content. It is intended to:

- Facilitate provision of the content of product labeling both electronically and in a human readable format. SPL documents can be exchanged across systems without the need for additional transformation steps.
- Improve dissemination of product labeling (both new product labeling and product labeling updates) to users of product labeling. The ability to provide the most up-to-date product labeling in a timely manner is considered to be critical to improving risk management of regulated products.
- Facilitate more efficient evaluation of labeling changes by allowing more effective use of computer technology to compare different versions of labeling on a section by section basis.
- Promote more coordinated data collection throughout the regulatory agency and improve processing, storage and archiving capabilities. Reduce or eliminate redundancies in data collection.
- Improve access to information and enhance the ability to query and report on the content of labeling, allowing better support for specific analyses such as sub-population assessments of differences in products based on gender, race, age, and geographic location.
- Improve interoperability of the regulatory agency’s systems with other clinical information systems.
- Use standards to improve integration of clinical data.
- Enhance patient safety by helping to provide prescribers and consumers with improved access to information needed to make better risk management decisions in a format that will enhance integration with other technical and clinical applications.
- Support retention of legacy product labeling in databases.

2.3 Scope of the SPL specification

The scope of the SPL specification is the standardization of the markup of the content of product labeling documents for the purpose of review, editing, storage, dissemination, analysis, decision-support, and other re-use.

The SPL specification is a markup specification for the regulatory content of a product labeling document. This specification is not specific to the U.S. realm, but does fulfill identified regulatory requirements for the content of drug product labeling described in U.S. regulations 21CFR201.56 and 21CFR201.57 for prescription drug labels and 21CFR201.66 for over-the-counter drug labels. The specification can be extended to accommodate the requirements of drug product labeling in other realms. However, it is also not necessarily restricted to use for drug labeling. This specification is extensible such that future versions could accommodate specifications for other product labeling document types (e.g., blood, vaccine, veterinary drug, food, dietary supplements, and device labeling).

It is important to note that the SPL specification models the structure and semantics of labeling content and not the presentation found in printed labeling such as package inserts and promotional labeling. It standardizes the markup of the required content, specifically the structure and semantics of that content. Although the human readability requirement specifies that the content must at the very least be readable using a generic stylesheet that applies to all HL7 structured documents, the use of specialized stylesheets for specific presentation purposes is not prohibited

The SPL specification does not specify the creation or management of documents, only their storage and exchange markup. Document management is critically interdependent with the product labeling specification, but the specification of document management messages is outside the scope of the SPL specification.

This specification does not address the transfer mechanism for product labeling documents. The specification for messages that might carry the product labeling document is outside the scope of the SPL specification, although the CDA standard does specify how to package clinical documents within HL7 messages (see *3.2.4 Sending an SPL document in an HL7 message*). An SPL document may be transmitted in an HL7 message that is designed to transfer clinical documents. Alternatively, several other mechanisms may be used to transfer product labeling including physical media, PDF, electronic transfer of word processing applications, among many others.

2.4 Goals and Design Principles

2.4.1 Goals

In general, this specification shares the goals of the CDA, which are:
1. Give priority to delivery of patient care.
2. Allow cost effective implementation across as wide a spectrum of systems as possible.
3. Support exchange of human-readable documents between users, including those with different levels of technical sophistication.
4. Promote longevity of all information encoded according to this architecture.
5. Enable a wide range of post-exchange processing applications.
6. Be compatible with a wide range of document creation applications.
7. Promote exchange that is independent of the underlying transfer or storage mechanism.
8. Prepare the design reasonably quickly.
9. Enable policy-makers to control their own information requirements without extension to this specification.

Although SPL does not give priority to delivery of patient care in the same way as clinical documents (CDA documents) which are directly associated with patient encounters, the goal of providing timely information about medical products ultimately serves patient care.

Additional goals of the SPL specification include:
1. Facilitate review, storage, and dissemination of product labeling.
2. Maximize timeliness of availability of product labeling.

2.4.2 Design Principles

This specification follows the design principles of CDA, including:
1. The specification must be compatible with XML and the HL7 RIM.
2. Technical barriers to use of the specification should be minimized.
3. The specification specifies the schemas required for exchange.
4. The specification should impose minimal constraints or requirements on document structure and content required for exchange.
5. Document specifications based on this specification should accommodate such constraints and requirements as supplied by appropriate professional, commercial, and regulatory agencies.
6. Document specifications for document creation and processing, if intended for exchange, should map to this exchange specification.
7. CDA documents must be human readable using widely-available and commonly-deployed XML-aware browsers and print drivers and a generic CDA style sheet written in a standard style sheet language.
8. Use open standards.

Regulatory requirements for the SPL specification impose additional design principles that include:
1. Documents may be revised as a whole or on a section-by-section basis.
2. Product labeling documents and document sections should contain sufficient information to enable unique identification for the purposes of:
    - Automation of the processing and review of new and updated product labeling
    - Product labeling document content verification and comparison of updated labeling with existing labeling by reviewers
    - Efficient and secure archiving of product labeling document content in databases
    - Preservation of context and connections between all versions of documents and document sections
    - The potential for querying (including complex queries) and retrieval from databases
    - Aggregation into up-to-date complete approved product labeling documents for dissemination to information providers
    - Support for effective presentation of product labeling
    - Support for dissemination of and access to product labeling documents
3. The model should be extensible. Evolution of the data model and terminology should take place as necessary, keeping in mind issues of backward compatibility.

3 General Concepts

3.1 Characteristics of SPL Documents

3.1.1 Relationship of the SPL Specification to CDA

The SPL specification is based on the HL7 Clinical Document Architecture (CDA). However, there are a number of fundamental differences between the two specifications, for example:
- CDA documents involve a Patient – SPL documents do not.
- CDA documents involve one or more Providers – SPL documents do not.
- CDA documents involve an Encounter – SPL documents do not.

CDA was chosen as the basis for the SPL specification for a number of reasons:
- CDA is the basis for generating consistent human readable documents across different computer systems.
- It is an established standard (HL7- and ANSI-approved) for markup of clinical documents.
- It allows use of simple markup of documents (e.g., sections) and at the same time provides a mechanism for evolution over time to more complex and granular markup (i.e., full encoding of all concepts). This is particularly important as regulatory agencies and product manufacturers must deal with management of legacy

product labeling documents (including paper documents), interim electronic documents (e.g., PDF files), and fully marked up XML documents.
- It facilitates interoperability of data management systems. Documents of varying format and from varying platforms can be exchanged and utilized. Non-CDA XML documents can be converted to CDA for exchange.
- It facilitates exchange of documents of varying markup complexity.
- It is extensible, so that the specification can be expanded in future, if desired, to include other document types (e.g., product labeling for biologics, and possibly device labeling).

Product labeling documents can share many of the following characteristics of clinical documents (as defined by CDA). The characteristics of CDA documents include:
    - Persistence – A clinical document continues to exist in an unaltered state, for a time period defined by local and regulatory requirements.
    - Stewardship – A clinical document is maintained by a person or organization entrusted with its care.
    - Potential for authentication - A clinical document is an assemblage of information that is intended to be legally authenticated.
    - Context - Contents of a clinical document share a common context unless all or part of that context is overridden or nullified.
    - 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.
    - Human readability – A clinical document is human readable.
- The potential for authentication is subtly different for product labeling documents than for CDA documents. While a product labeling document may be authenticated, and may even have a requirement for legal authentication in some realms, this authentication occurs on the official, approved version of the document rather than on each instance (copy) of the document.
- Like a CDA document, an SPL document is a defined and complete information object that can include text, images, sounds, and other multimedia content.

In addition, product labeling documents have the following characteristics:
- Public service – A product labeling document provides information for the safe and effective use of the product.
- Legal standing – A product labeling document legally represents the product to the best of the sponsor's knowledge.

As the healthcare setting moves forward into an increasingly electronic and paperless environment it has become apparent that there are many types of documents used in a healthcare setting that can enhance medical care that are not covered by the current design of CDA. Documents that provide Standard Operating Practices, decision trees and algorithms and other types of guidance are critical to providing a high standard of care to the patient. Similarly, product labeling can be viewed as such a document, providing the prescriber with the essential information for the safe and effective use of a product. Current thinking is that there may be a need to define HL7 structured documents in general and determine the place of CDA, SPL, and other healthcare documents in that context. In the meantime, an SPL document is described as an HL7 structured document that is based on CDA.

Like CDA documents, the SPL document consists conceptually of a Header, referred to in this specification as the "SPL Header", and a Body, which is referred to in this specification as the "SPL Body". The SPL Header identifies and classifies the document and may provide information on the owner of the marketing authority for the product, the author, legal authenticator, and reviewers. The Body contains the product labeling content itself.

Like CDA Release Two, the SPL specification identifies sections, which contain narrative, and also provides some more granular semantic markup of specific data elements contained within sections. For this version of the specification, those data elements are largely related to identification and description of drug products.

3.1.2 Major components of an SPL document

This section serves as a high-level introduction to the major components of an SPL document, all of which are described again and in greater detail later on. The intent here is to familiarize the reader with the high-level concepts to facilitate an understanding of the sections that follow.

Major components of a prototypic SPL document are shown in *Figure 1. Major components of an SPL document*[2].

An SPL document is wrapped by the <Document> element, and contains a header (see *4.2.1 SPL Header*) and a body (see *4.2.2 SPL Body*). The header lies between the <Document> and the <StructuredBody> elements, and identifies and classifies the document and provides information on participants in creation, ownership, and review of the document (such as owner of marketing authority, author, and regulatory agency reviewers).

The body contains the labeling content, and can be either unstructured, or can be comprised of structured markup (see *4.2.2.1 SPL Body Choice*). *Figure 1* shows a structured body, which is wrapped by the <StructuredBody> element, and which is divided up into recursively nestable document sections.

An SPL document section is wrapped by the <Section> element. Each section can contain a single narrative block (see *4.2.2.2.4 SPL Section Narrative Block*), and any number of data elements (see *4.2.2.3 SPL Body Structures*).

The SPL narrative block is wrapped by the <text> element within the <Section> element, and provides a slot for the human readable content needing to be rendered. See also *3.6 "Human Readability" and Rendering SPL Documents* and *3.4 SPL Conformance* for principles governing the representation of the narrative block, and conformance requirements on the part of senders when populating the block, and receivers when rendering it.

Within a document section, the narrative block represents content to be rendered, whereas SPL data elements represent structured content provided for a computer. SPL encodes certain data elements identified as necessary for machine processing and utilization of content of a section. *Figure 1*shows an <Observation> structure, although several other SPL body structures are defined (see *4.2.2.3 SPL Body Structures*). The data elements can reference specific text in the narrative block (see *4.2.2.4 Relationship between SPL Narrative Block and SPL Body Structures*).

Figure 1. Major components of an SPL document

```
<Document>
   … SPL Header …
   <StructuredBody>
       <Section>
       <text> … </text>
       <Observation> … </Observation>
       </Section>
       <Section>
           <Section> … </Section>
       </Section>
   </StructuredBody>
</Document>
```

[2] Many required SPL components are not shown in the figure.

3.2 Relationship of the SPL Specification to Other HL7 Standards

Note: A number of HL7 Version 3 standards and artifacts, which are integral to understanding and/or implementation of SPL, are mentioned in this specification. Copies of all of these are available to HL7 members and authorized licensees. For further information, please contact HL7 headquarters at:

Health Level Seven, Inc.
3300 Washtenaw Ave, Suite 227
Ann Arbor, MI 48104
Telephone: 734-677-7777
Fax: 734-677-6622
E-mail: hq@hl7.org

3.2.1 Reference Information Model (RIM)

The SPL specification, including the Refined Message Information Model (RMIM), Hierarchical Description, and Schema, is based entirely on the HL7 RIM version 2.02. It uses the HL7 "data types" and vocabulary. (See *5.3 HL7 Methodology*.)

The decision to use the RIM as the underlying information model for SPL necessitates use of HL7 Version 3 terminology and conventions. Representation of concepts using the RIM may involve the interrelationship of a number of "classes", as well as inclusion of attributes that put the classes in context (e.g., mood code, determiner code). For information about Version 3 and the RIM, see http://www.hl7.org; for more detailed information or for copies of HL7 Version 3 standards, contact Health Level Seven.

Key RIM concepts that are discussed in the SPL specification include:

- Classes— RIM classes are the people, places, roles, things, and events about which information is kept, as well as the relationships between those. Classes have a name, description, and sets of attributes, relationships, and states. The core RIM classes include Act, Entity, Role, Participation, ActRelationship, and RoleLink. (The root class in the SPL model is an Act named <Document>.) An Entity, playing a Role, Participates in an Act. (For example, a <Person> playing the Role of <AssignedEntity> participates as an <author> in the <Document> Act.) Entities can also be "scopers" of Roles. (For example, an <Organization> may be the scoper of the role that the <Person> is playing – see more on this below.)
- Clones—Classes may be used and re-used multiple times in a RIM-derived model. Class cloning is the creation in any HL7 model (e.g., RMIM) of a class derived from one in a source model (e.g., RIM). Source classes, along with their appropriate attributes, are selected to represent concepts to be included in the new model. The same class may appear multiple times in a model with different names, constraints or "associations" each time. Each of these replicated classes is referred to as a "clone". A clone can be more tightly constrained than its source class (e.g., use fewer attributes, have more restrictive cardinality on attributes or associations, and/or have a restricted vocabulary domain) but it cannot be more loosely constrained (e.g., a required attribute cannot be made optional). The SPL model is made up of a number of clones of Act, Entity, Participation, Role, and ActRelationship.
- Attributes—RIM classes have attributes. The value for coded attributes (data type CD or CE) comes from a "vocabulary domain". Some vocabulary domains exist within HL7 and others are external to HL7.
- Data types— Data types define the structural format of the data carried in the attribute and influence the set of allowable values an attribute may assume. Some data types have very little intrinsic semantic content and the semantic context for that data type is carried by its corresponding attribute. However HL7 also defines quite extensive data types such as one for the person name part, which is provides all the structure and semantics to support a person name. Every attribute in the RIM is associated with one and only one data type, and each data type is associated with zero or many attributes.

In the diagram used to represent an RMIM, each type of RIM class has a defined color and shape. Clones of RIM classes retain the color and shape of the parent RIM class so that their nature and origin can be determined by visual inspection.

Both the structural classes themselves and the classes that show the relationships between them become XML elements in the Schema. In addition, many of the RIM attributes become XML elements in the schema.

An understanding of "player" Entities and scoper Entities will help in understanding the SPL model. In the HL7 V3 model, Entities have roles and those roles may be playing roles or scoping roles. A scoping role helps to determine what the playing role is. As an example:

> The same chemical material may be an active ingredient in one drug product and an inactive ingredient in another. This is expressed in the SPL model by means of separate roles – the chemical material (which is an Entity clone called IngredientEntity) is said to play a role of either an active ingredient or an inactive ingredient. Which role it is playing is determined by the product (i.e., it is scoped by the product), which is another Entity called LabeledDrug. In the HL7 V3 model, this relationship is expressed by saying that the <LabeledDrug> Entity (the product) is the scoper of the <Role> (either <ActiveIngredient> or <InactiveIngredient>) that is played by the <IngredientEntity> (the ingredient).

In RMIM diagrams, player relationships are shown as solid lines and scoper relationships are shown as dotted lines (see *5.4.1 RMIM diagram*).

3.2.2 Data Types

Detailed information about the data types used in the SPL specification can be obtained from "Data Types – Implementation Technology Specification for XML" (see http://www.hl7.org; for more detailed information or for copies of HL7 Version 3 standards, contact Health Level Seven).

See also *6.3.4 Understanding HL7 V3 Data Types*.

3.2.3 Controlled Vocabulary and Coded Elements

Some vocabulary domains represent "value sets" for coded product labeling components. These domains can include HL7-defined concepts or can be drawn from HL7-recognized coding systems such as LOINC. Vocabulary domains have a coding strength that can be "Coded, No Extensions" (CNE), in which case the only allowable values for the SPL component are those in the HL7 vocabulary domain; or "Coded, With Extensions" (CWE), in which case values other than those in the HL7 vocabulary domain (such as local codes) can be used if necessary. Every vocabulary domain has a unique HL7-assigned identifier, and every concept within a vocabulary domain has a unique code (mnemonic). A coded FDA labeling component, for example, may constrain its use of an associated vocabulary domain to a stated subset of codes.

3.2.3.1 Use of HL7 vocabulary domains

HL7 vocabulary domains have been used throughout this specification, except for those that have distinct regulatory descriptions (such as those defined in regulatory policy documents). Creation of the specification necessitated addition of some values to existing HL7 domains; this is accomplished through the process of "harmonization".

Where a coded product labeling component is associated with an HL7-defined vocabulary domain, the standard specifies the coding strength (CWE vs. CNE) and enumerates the allowable concepts with a code, display name, and definition for each concept.

3.2.3.2 Use of external vocabulary domains

A number of vocabulary domains and coding systems already in existence or under development within regulatory agencies (e.g., FDA in the U.S.) or other standards development organizations (e.g., LOINC) may be used to encode concepts in SPL documents (e.g., section name, drug name, dosage form, route of administration). Some of these will be incorporated into the HL7 vocabulary domains through the process of harmonization. Vocabulary domains that will not be incorporated into HL7 vocabulary domains are referenced as external domains according to HL7 V3 processes. When these are used in SPL documents (e.g., when LOINC codes for section names are used), they are referenced as external domains in the document instance.

Where a coded product labeling component is associated with an externally-defined vocabulary domain, the standard specifies the coding strength (CWE vs. CNE), and an example of allowable concepts of that domain (with a code, display name, and code system identifier for each concept).

Specific requirements for the use of vocabulary domains may be specified in regulatory guidance documents.

3.2.4 Sending an SPL document in an HL7 message

The exact process by which SPL documents will be exchanged has not been defined. However, if an SPL document is to be sent in an HL7 message, the following principles apply:

From the perspective of a V2.x or V3 message, an SPL document is a multimedia object, to be exchanged as a Multipurpose Internet Mail Extensions (MIME, RFC 2046) package, encoded as an encapsulated data type (ED).

Any MIME packaging strategy must accommodate the following requirements:

- There is no need to change any of the references within the base SPL document when creating the MIME package.
- There is no need to change any of the references within the base SPL document when extracting the contents of a MIME package.
- All components of a SPL document that are integral to its state of wholeness (such as a non-XML body or an ObservationMedia) are able to be included in a single MIME package.
- There are no restrictions on the directory structure used by receivers. Receivers can place the components of the SPL document into directories of their choosing.

The current recommendation is to follow the approach described in the Internet standard RFC 2557 "MIME Encapsulation of Aggregate Documents, such as HTML (MHTML)" (http://www.ietf.org/rfc/rfc2557.txt), which is the approach for the MIME encapsulations of aggregate documents used by ebXML and DICOM.

In V2.x, SPL documents are to be exchanged in the OBX segment, in any message that can exchange documents (such as MDM). Within the OBX segment, the MIME package is placed in OBX.5 (Field 00573 Observation value), encoded as a V2.x encapsulated data type. The value of OBX.2 (Field 00570 Value Type) should be set to "ED". The value of OBX.3 should be the same as Document.code.

Many fields in the message will overlap in meaning with fields in the CDA document. The following table shows the correspondence between the HL7 V2 MDM message's TXA segment and components of CDA.

Table 1. HL7 V2 TXA Segment to CDA Mapping

TXA Field	CDA Component
TXA-2 Document type	Document.code
TXA-6 Origination date/time	Document.effectiveTime
TXA-9 Originator code/name	author
TXA-12 Unique document number	ClinicalDocument.id

TXA-13 Parent document number	relatedDocument.id
TXA-18 Document confidentiality status	Document.confidentialityCode
TXA-22 Authentication person, time stamp	legalAuthenticator

In V3, SPL can be exchanged in any message that can exchange documents. The Act.text RIM attribute contains the MIME package, encoded as an encapsulated data type.

For examples, see *6.6 Sample MIME Encapsulation of an SPL Document in an HL7 Version 2.x and Version 3 Message*.

3.3 XML Markup of SPL Documents

XML markup of SPL documents is prescribed in this specification. SPL instances are valid against the SPL schema and may be subject to additional validation (see *3.4 SPL Conformance*). There is no prohibition against multiple schema languages (W3C, DTD, RELAXNG, etc.), as long as conforming instances are compatible.

Design Principles of the SPL Schema include:

- **General Requirements:** The design of the SPL Schema follows the more general requirements for SPL (see *2.4 Goals and Design Principles*).

- **CDA Schema and V3 ITS:** The SPL Schema will follow the general V3 XML ITS.

- **RIM Mapping:** The SPL Schema describes the style of XML markup of SPL instances for the purpose of exchange. It cannot be understood outside the context of this defining specification including the normative RMIM and Hierarchical Description.

  At the same time, the SPL Schema should be evaluated on its own and is not intended to replicate or take the place of the RMIM and HD. The SPL Schema, then, is not, in and of itself, an adequate map between conforming instance and the HL7 RIM. Semantic interoperability of SPL instances requires use and knowledge of the SPL Schema, RMIM and HD as well as the corresponding RIM.

- **Document Analysis:** The SPL Schema and conformant instances should adhere to the requirements of document analysis in derivation of the content model.

  Note on Document Analysis:
  Document analysis is a process that might be thought of as the document equivalent of a use case. Document analysis looks at a single instance or class of documents and analyzes their structure and content, often representing this as a tree structure "elm" notation. Document analysis also looks at the business rules for the lifecycle of that document or document class. Traditionally, document analysis determines the content model and overall structure and style of XML. Document analysis is an iterative step in content model derivation -- the "bottom up" approach to complement the "top down" derivation from the RIM. This will ensure that schemas and instances are not only RIM-derived, but represent recognizable artifacts in a simple manner.

- **Nesting:** The SPL Schema should not use unnecessary nesting of elements. Specifically, nested elements that have a fixed and required relationship to each other should be expressed as a single element.

- **Naming:** While XML markup, by definition, is for machine processing, it should be optimized for human review, debug, design. The SPL Schema is not "self-documenting", but meaning should be clear from tag name and documentation (e.g., mapping to RIM). The human-language sense of a tag name should not be counterintuitive.

The SPL Schema tag and attribute naming will follow V3 camelCase convention and will strive to be neither verbose nor cryptic. Tag naming can be independent of RIM class and attribute names providing a buffer from changes.

> Note on naming as a buffer: As the RIM evolves, we need a level of indirection between naming in XML instances and naming in the RIM that supports continuity over time and backward compatibility. Ideally, the RIM can change and the instances persist and, to some extent, naming within instances can persist. Allowing a disconnect, with a defined derivation, can allow the RIM to morph while instances retain both consistent tagging and a rigorously defined derivation.

- **Vocabulary:** Vocabulary can be enumerated within the SPL Schema or in an external, referenced source. It is preferable to enumerate it when the vocabulary terms are both limited (not too large in number) and stable (not subject to change between ballot cycles). Where vocabulary is either too large or is subject to change, it is preferable to maintain it external to the SPL Schema and incorporate it by reference. In these cases, obviously, XML validation will not suffice for conformance.

3.4 SPL Conformance

A conformant SPL document is one that at a minimum validates against the SPL Schema, and that restricts its use of coded vocabulary to values allowable within the specified vocabulary domains. However a computer cannot validate many aspects of conformance. The focus of this section is to highlight these aspects of SPL that cannot be machine validated - particularly those aspects related to the SPL human readability requirements.

A document originator is an application role that creates a document. SPL documents can be created via transformation from some other format, as a direct output of an authoring application, etc. The document originator often is responsible for communicating with a persistent storage location. The document originator is responsible for ensuring that generated SPL documents are fully conformant to this specification.

A document recipient is an application role that receives status updates and documents from a document originator or document management system. The document recipient is responsible for ensuring that received SPL documents are rendered in accordance to this specification.

Because SPL is an exchange standard and may not represent the original form of a document, there are no persistent storage requirements for SPL documents defined in this standard. However, as noted below (see *3.5 SPL Documents and Document Management*), document management is critically interdependent with the SPL specification.

3.4.1 Recipient responsibilities

- **Assume default values where they are defined in this specification, and where the instance does not contain a value:** Where SPL defines default values, the recipient must assume these values in the event that no value is contained in an SPL instance. This holds regardless of whether or not the SPL Schema supplies the recipient with the default values.

- **Parse and interpret the complete SPL header:** A recipient of an SPL document must be able to parse and interpret the complete SPL header. Because applications may choose to display demographic and other SPL header data drawn from a central master directory, the rendering of the SPL document header is at the discretion of the recipient.

- **Parse and interpret the SPL body sufficiently to be able to render it:** A recipient of an SPL document must be able to parse and interpret the body of an SPL document sufficiently to be able to render it, using the following rendering rules:

- If the SPL Body is non-XML, it will need to be rendered with a software tool that recognizes its particular MIME media type.

- If the SPL Body is structured, the label of a section, as conveyed in the 'Section.title' component, must be rendered. The absence of the 'Section.title' component signifies an unlabeled section.

- If the SPL Body is structured, the contents of the 'Section.text' field must rendered per the rules defined in *4.2.2.2.4 SPL Section Narrative Block.*

- A recipient of an SPL document is not required to parse and interpret the complete set of SPL body structures contained within the SPL body. Within a local implementation, trading partners may ascribe additional recipient responsibilities to parse and interpret various entries.

- A recipient of an SPL document is not required to validate an SPL document against referenced templates. Within a local implementation, trading partners may ascribe additional recipient responsibilities for template validation.

3.4.2 Originator responsibilities

- **Properly construct SPL Narrative Blocks:** An originator of an SPL document must ensure that the content of the document body is structured such that a recipient, adhering to the recipient responsibilities above, will correctly render the document. This includes:

    - If the SPL Body is structured, the label of a section must be conveyed in the 'Section.title' component. The absence of the 'Section.title' component signifies an unlabeled section.

    - If the SPL Body is structured, the rendered contents of a section must be placed in the 'Section.text' field, regardless of whether information is also conveyed in SPL body structures within a section.

    - If the SPL Body is structured, the contents of the 'Section.text' field must be created per the rules defined in *4.2.2.2.4 SPL Section Narrative Block.*

- An originator of an SPL document is not required to fully encode all narrative into SPL body structures within the SPL body. Within a local implementation, trading partners may ascribe additional originator responsibilities to create various entries.

3.5 SPL Documents and Document Management

Product labeling can be revised, and the corresponding SPL document or section is then replaced by a new version. Ideally, in a document management system an updated document or section would declare itself as obsolete, and would contain an explicit pointer to a more recent version, limiting dissemination to the healthcare community to the most recent version of the labeling. This would lessen the chances of a healthcare provider basing treatment decisions on outdated or erroneous data. In practice, however, it is impossible to guarantee an explicit forward pointer from an outdated version to the newer version. Without a process that tracks the chain of custody of documents/sections and all of their copies, there can be no way to guarantee that a document or section being viewed has not been subsequently revised. However, SPL documents do have the ability to state that the given document (or section) is replacing a previous document (or section).

To minimize the risk of viewing superseded information, there is a critical interdependence between documents/sections and document management systems. If SPL documents are viewed outside the context of a document management system, it cannot be known with certainty whether or not the viewed document has been revised. HL7 messages that carry SPL documents may convey critical contextual information that ensures accurate viewing of the data.

3.6 "Human Readability" and Rendering SPL Documents

The SPL requirement for human readability guarantees that a receiver of an SPL document can readily display the content of the document on a standard Web browser. SPL, with its blend of narrative and structured data elements, presents some challenges to this requirement.

Among the requirements affecting the design of SPL are the following:

- There must be a deterministic way for a receiver of an arbitrary SPL document to render the content.
- Human readability shall not require a sender to transmit a special style sheet along with an SPL document. It must be possible to render all SPL documents with a single style sheet and general-market display tools.
- Human readability applies to the regulatory content. There may be additional information conveyed in the document that is there primarily for machine processing that need not be rendered (e.g., ingredient codes).
- When structured content is derived from narrative, there must be a mechanism to describe the process (e.g. by author, by human coder, by natural language processing algorithm, by specific software) by which machine-processable portions were derived from a block of narrative.
- When narrative is derived from structured content, there must be a mechanism to identify the process by which narrative was generated from structured data.

These principles and requirements have led to the current approach, where the material to be rendered is placed into the 'Section.text' field (see *4.2.2.2.4 SPL Section Narrative Block*). The content model of this field is specially hand crafted to meet the above requirements, and corresponds closely to the content model of narrative in CDA. Structured data elements can reference narrative content in the 'Section.text' field. Multimedia observations are encoded outside the 'Section.text' field, and the <renderMultiMedia> tag within the 'Section.text' field provides an outgoing pointer that indicates where the referenced multimedia should be rendered.

3.7 Security, Confidentiality, and Data Integrity

Application systems sending and receiving SPL documents are responsible for meeting any legal requirements for document authentication, confidentiality, and retention. For communications over public media, cryptographic techniques for source/recipient authentication and secure transport of encapsulated documents may be required, to be addressed by mechanisms outside the scope of this standard.

Control of access to and ability to modify document content is outside the scope of this standard.

The SPL document does include confidentiality status information to aid application systems in managing access to sensitive data, if necessary. Confidentiality status may apply to the entire document or to specified segments of the document.

3.8 SPL Extensibility

Locally-defined markup may be desired when local semantics have no corresponding representation in the SPL specification. SPL seeks to standardize the highest level of shared meaning while providing a clean and standard mechanism for tagging meaning that is not shared.

SPL uses the extensibility mechanism specified in the HL7 Version 3 XML Implementation Technology Specification (ITS) for extensions in the HL7 namespace. For additional information, see http://www.hl7.org or contact Health Level Seven.

Extensions in a foreign namespace are not part of the normative standard and must be specified in a local implementation guide.

When these extension mechanisms mark up content of general relevance, users are encouraged to submit them to HL7 for adoption in subsequent versions of the standard so as to maximize the use of shared semantics.

3.9 SPL Context Inheritance

SPL context inheritance is managed in much the same way as CDA context inheritance. SPL context is set in the SPL header and applies to the entire document. Context can be overridden at the level of the document section.

3.9.1 Overview of SPL Context

A document, in a sense, is a contextual wrapper for its contents. Assertions in the document header are typically applicable to statements made in the body of the document, unless overridden. For instance, the author of the document (identified in the header) is assumed to be the author of all sections of the document, unless a different author is explicitly stated. The objective of the SPL context rules is to make these practices explicit in relationship to the RIM, such that a computer will understand the context of a portion of a document the same way that a human interprets it.

At the same time, there is no guarantee that machine processing will identify a mistaken application of contextual rules. From some errors of encoding, there is no recovery other than human review.

SPL's approach to context, and the propagation of that context to nested document components, follows these design principles established in CDA:

- SPL uses the RIM context mechanism (contextControlCode for Participations; contextConductionInd [context conduction indicator] for ActRelationships), and assigns fixed values to these attributes to accomplish the design objectives below, thus constraining the RIM context model. SPL extends the context propagation property to designated attributes of the SPL Header, which also propagate through any ActRelationship for which contextConductionInd=TRUE.

- The SPL Header sets context for the entire document. A propagating value specified in the document header holds true for the entire document, unless explicitly overridden, refined, or nullified in the document <Section>. This principal applies to both Participations and to designated attributes of the SPL Header. Contextual header components (i.e., those that have propagating components) include, but are not limited to:
    - Author
    - Confidentiality
    - Human language

- Context propagates from outer tags to nested tags. Context that is specified on an outer tag holds true for all nested tags, unless overridden on a nested tag. Context specified on a tag within the SPL body always overrides context propagated from an outer tag. For instance, the specification of authorship at a document section level overrides all authorship propagated from outer tags.

- Context is sometimes known precisely, and is sometimes unknown, such as in the case where a document is comprised of a large unparsed narrative block that potentially includes statements that contradict outer context. Because SPL context always propagates unless overridden, the representation of unknown context is achieved by overriding with a null value.

3.9.2 Technical aspects of SPL context

The RIM defines the context of an act as those participants of the act that can be propagated to nested acts. In the RIM, whether or not contextual participants do propagate to nested acts depends on whether or not the intervening act relationship between parent and child act allows for conduction of context. The explicit representation of context, and whether or not the context on an act can propagate to nested acts, is expressed via these attributes:

- Participation.contextControlCode

- ActRelationship.contextConductionInd.

SPL constrains the general RIM context mechanism such that context always overrides and propagates, as shown in the following table:

Table 2. SPL constraints on RIM context attribute

RIM attribute	Cardinality	Conformance	Default Value
Participation.contextControlCode	1..1	NULL values not permitted	"OP" (overriding, propagating)
ActRelationship.contextConductionInd	1..1	NULL values not permitted	"TRUE"

Where the context of a nested component is unknown, the propagated context must be overridden with a null-valued component, as shown in the following table.

Table 3. Blocking context propagation with null values

Context	Null value representation
Author	AssignedEntity.id = NULL; No playing entity; No scoping entity.
Confidentiality	confidentialityCode = NULL.
Human language	languageCode = NULL.

4 SPL Overview

4.1 Product Labeling Requirements

4.1.1 Document requirements

Product labeling documents should be both human readable and machine processable.

Precise requirements regarding metadata for document management have not been established. Therefore, the model contains information that would be required regardless of document management processes (e.g., document identifier [id]) as well as information that may be desired in some realms (e.g., author, legal authenticator).

Required document header information includes:

- document identifier (id)
- code (document type)
- effective time (when the document was authored)

Optional document header information includes:

- Name of the document (title)
- Owner of the marketing authority (organization)
- Author
- Legal authenticator
- Reviewer (verifier)
- Set id
- Version number
- Availability time (Release date)
- Confidentiality code
- Language code

Product labeling documents may be revised or replaced. One document may be a transformation from another.

Formatting of documents may vary from one realm to another or one implementation to another.

4.1.2 Section requirements

HL7 structured documents contain sections. Product labeling documents tend to be organized into commonly understood sections (e.g., indications for drugs). While there may be a standard set of section names and hierarchies for a product labeling document in a given realm, at this time there is no single international standard product labeling document structure. Product labeling document content and structure is usually specified in regulations. Therefore, the SPL model is deliberately flat and non-hierarchical – the ability to identify and name sections has been provided, but the exact names, order, and nesting of sections are not specified. This provides a high level of flexibility in the model.

Product labeling document sections may be revised or replaced on a modular basis.

Sections contain narrative text.

Sections may contain data elements. Sections may contain images (e.g., chemical structure of a drug).

4.1.3 Data element requirements

In order to facilitate machine processing of data contained within the narrative of product labeling document sections, it is necessary to provide markup of these data, which are referred to in this specification as data elements. The primary intent of data elements defined to date is to facilitate document indexing, search and retrieval, and to provide a standard convention for insertion of codes in order to identify required data elements.

For this version of the SPL specification, a number of data elements related to drug product labeling have been identified. These include:

- Imprint information for solid dosage form:
    - Imprint code
    - Size
    - Shape
    - Color
    - Coating
    - Scoring
    - Logo
- Drug product code (e.g., NDC code in the U.S.)
- Package type
- Package quantity
- Controlled substance classification or schedule (e.g., DEA number in the U.S.)
- Active ingredient (name, code, strength)
- Active moiety (code)
- Inactive ingredient (name, code, strength)
- Labeled route of administration
- Proprietary name (sometimes known as brand name)
- Nonproprietary (generic) name

4.2 SPL Model

A graphical picture of the SPL model is provided by the RMIM (see *5.4.1 RMIM diagram*), the creation of which is the first step in the creation of the XML Schema using HL7 tooling. See *5.4.2 RMIM diagram walk-through* for additional technical details about the classes in the SPL model and their relationships to one another.

Because this model is based on the HL7 RIM and relies on HL7 Version 3 processes in its creation, discussion of the components cannot be separated from references to Version 3 concepts (e.g., classes, clones, entities, roles, participations). As a result, the descriptive text below may contain references to the classes from which elements in the model were derived. See *3.2.1 Reference Information Model (RIM)* for discussion of some basic Version 3 concepts. For more detailed background information on these concepts and HL7 processes for model creation, see http://www.hl7.org or contact Health Level Seven.

See *6.5.1 Mapping between SPL data elements and RMIM* for a detailed description of how each of the required drug product data elements (described in *4.1.3 Data element requirements*) has been captured.

As mentioned earlier, the SPL document consists conceptually of a Header and a Body, which are described in detail below.

4.2.1 SPL Header

The purpose of the SPL Header is to enable product labeling storage and exchange across and within institutions and to facilitate document management.

The SPL Header contains metadata about the document. There are two logical components of the SPL Header:
(1) Document information
(2) Information about participants in creation, ownership, and review of the document (such as owner of marketing authority, author, and regulatory agency reviewers)

Document information identifies the document, defines confidentiality status, and describes relationships to other documents. Potential "participants" in the document process include document originators (authors), manufacturers (owners of marketing authority), those who legally authenticate the document, and regulatory agency reviewers of the document. All of the participants are optional in the SPL model.

4.2.1.1 SPL Header Attributes

Information about both the document as a whole and sections contained within it is necessary to fulfill the requirement for modular updating and utilization of product labeling.

4.2.1.1.1 Document classification

A <Document> is an Act in the HL7 V3 model. Every <Document> has a 'classCode', which identifies the type of Act it represents. For the SPL document, the value is DOC (structured document), which is drawn from a subset of the *ActClass* HL7 vocabulary domain that classifies documents in general.

4.2.1.1.2 Document identification

Every <Document> has a required, globally-unique instance identifier, 'id' (which is different from the XML element identifier; see the HL7 Data Types specification for more information about use of globally-unique instance identifiers); an optional identifier, 'setId', that remains constant across all document revisions that derive from a common original document, and an optional version number, 'versionNumber'. These identifiers may be useful in document management, including management of replacements.

Every <Document> has a required document type code, 'code'. This code identifies the type of product labeling document (e.g., prescription drug label or over-the-counter prescription drug label). The externally-defined vocabulary domain for 'Document.code' is preferentially drawn from LOINC.

NOTE:

Within the LOINC database, beginning with version 2.09, May 2003, document type codes are those that have a value of "DOC" in the Scale component. This subset of LOINC is included in the appendix (see *6.4 LOINC Document Codes and Document Section Codes*).

The hierarchical relationship among LOINC document codes is in evolution. Per the June 20, 2003 Clinical LOINC meeting minutes: "… all of the parts of the LOINC document names will be mapped to a standard reference terminology. Mapping to a reference terminology will provide definitions for the terms used, and will also provide relationships and subsumption hierarchies for the parts of the document names".

Every <Document> has an optional 'title', with a data type of ST that allows free text entry of the human readable title of the document. It is the 'title' of a document that is rendered. The title describes (but does not guarantee) the content of the document.

4.2.1.1.3 Document time stamps

Every <Document> has a required 'effectiveTime' that identifies the document origination time, i.e., when the document was created. The attribute 'effectiveTime' has a TS data type.

A <Document> may also have an optional 'availabilityTime', which is equivalent to the release date of the product labeling document.

Other time stamps in the document lifecycle may be recorded through the various participants in the document (see *4.2.1.3 SPL Header Participants* and *4.2.2.2.3 SPL Section Participants* for a description of people and organizations that play a role in a product labeling document). Each Participation class clone has a required 'time' attribute. Thus, there is a time associated with an <author>, <verifier> (reviewer), and <legalAuthenticator>.

4.2.1.1.4 Document confidentiality

The SPL Header makes it possible to indicate document confidentiality status through a 'confidentialityCode' attribute. A single 'confidentialityCode' can be used in the Header that will apply to the entire document unless it is overriden. The value for 'confidentialityCode' may be drawn from the *Confidentiality* vocabulary domain. Values other than those in the HL7 vocabulary domain (such as local codes) can also be used if necessary.

4.2.1.1.5 Document language

The 'languageCode' specifies the human language of character data in the product labeling document (whether they be in contents or attribute values). The values of the attribute are language identifiers as defined by the IETF (Internet Engineering Task Force) RFC 3066: Tags for the Identification of Languages, ed. H. Alvestrand. 1995 (http://www.ietf.org/rfc/rfc3066.txt), which obsoletes RFC 1766. Language is a contextual component of SPL, where the value expressed in the header holds true for the entire document, unless overridden by a nested value (as further described in *3.9. SPL Context Inheritance*).

4.2.1.2 SPL Document Relationships

The SPL Header enables the explicit representation of relationships between documents. These relationships rely on document identifiers described above. For example, an original document is the first version of a document, and gets a new globally unique 'id' value; it can also contain a new value for 'setId' and a value of 'versionNumber' set to equal "1".

The nature of the relationship is captured by means of the 'relatedDocument.typeCode' attribute on the ActRelationship clone.

Whether and how this information is used depends on the document management system in use.

For example, a replacement document replaces an existing document. Identification information in the Header may assist in tracking the replacement document. One example scenario is:

> The replacement <Document> gets a new globally unique 'id' value, and uses the same value for 'setId' as the parent document (<RelatedDocument>) being replaced, and increments the value of 'versionNumber' by 1. (If used, the 'versionNumber' will be incremented by one when a document is replaced, but can also be incremented more often to meet local requirements.) The parent document is considered superseded, but is still retained in the system for historical reference. The parent document being replaced is referenced via an ActRelationship to the <RelatedDocument> with a type code of RPLC (for "replaces").

The value of RPLC for 'relatedDocument.typeCode' is contained in the *x_ActRelationshipDocument* subset of the *ActRelationshipType* vocabulary domain.

4.2.1.3 SPL Header Participants

Possible persons and organizations involved in the creation and review of a product labeling document are associated with the <Document> as participants. (This is based on the fact that, in accordance with the RIM, a clone of the Participation class is used to indicate this relationship.) Participants may include document originators (authors), legal authenticators of the document, organizations that own the marketing authority for the product, and product labeling reviewers at the regulatory agency. Participants are capable of and accountable for their independent decisions. All of these participants are optional in the SPL model but could be constrained to be required for a given realm.

Information about participants is captured by means of clones of several interrelated RIM classes: Participations, Roles, and Entities. In general, an Entity (<Person> or <Organization>) playing a particular Role (in this case, <AssignedEntity>), participates in an Act (e.g., a <Document>). It is the Participation clone that identifies the type of participant. The type of <Participation> (e.g., author) is indicated by a code. The Role played by the Entity establishes that entity's competency or authority to participate as indicated. For example, a person participating as an author of a label is only authorized to do so if assigned by the organization responsible for authorship of the label.

The way in which that a <Person> or <Organization> is participating in the document is specified by the 'typeCode' attribute on the relevant Participation class clone. While the nature of the participation may be suggested by the XML element name, the 'typeCode' values are the definitive indication[3].

See *3.2.1 Reference Information Model (RIM)* for discussion of some basic Version 3 concepts. For more detailed background information on these concepts and HL7 processes for model creation, see http://www.hl7.org or contact Health Level Seven.

4.2.1.3.1 Author

Product labeling documents can be authored by one or more individuals. The SPL Header provides for optional identification of document authors.

Information about the author is captured by means of several interrelated classes:

- <author> – A Participation clone that links the <Document> to the <Person> and <Organization> (through the <AssignedEntity>). The required 'time' attribute is used to indicate the time of participation by the author (usually the time of origination). The value for 'typeCode'which is drawn from the *ParticipationType* vocabulary domain and which describes the nature of the participation, is AUT.
- <AssignedEntity> – A Role clone that links the <author> to the <Person> and <Organization>.

[3] Where there is only one allowable value for typeCode, it is modeled as a single default attribute in the RMIM (which becomes a fixed attribute in the XML Schema).

- <Person> – An Entity clone. Provides details (e.g., name) about the person participating in the document as an <author>.
- <Organization> – An Entity clone. Provides details about the organization (the manufacturer or owner of the marketing authority) for which the author is working.

4.2.1.3.2 Owner of Marketing Authority

The SPL Header can specify the organization from which the document originates and that is in charge of maintaining the document (i.e., the owner of the marketing authority), commonly called the manufacturer. The SPL Header provides for optional identification of the owner of the marketing authority, if desired. This is captured by means of the <Organization> entity.

Information about the owner of the marketing authority is captured by means of several interrelated classes:

- <author> – A Participation clone that links the <Document> to the <Organization> (through the <AssignedEntity>). The required 'time' attribute is used to indicate the time of participation by the author (usually the time of origination). The value for 'typeCode', which is drawn from the *ParticipationType* vocabulary domain and which describes the nature of the participation, is AUT.
- <AssignedEntity> – A Role clone that links the <author> to the <Organization>.
- <Organization> – An Entity clone. Provides details about the organization (the manufacturer or owner of the marketing authority) for which the author is working.

In other words, the same classes are used as are used to capture the author but, because <Person> is optional, it is possible to capture only information about the <Organization>. (The assumption is that the organization for which the author is working will be the holder of the marketing authority.)

4.2.1.3.3 Legal Authenticator

In some realms there may be a requirement to capture a legal authenticator of the labeling content. The SPL Header provides for optional identification of legal authenticators.

A legally authenticated document exists when an individual with the proper legal authority has attested to the accuracy of the document content. A document can be legally authenticated by zero or more people. The required 'time' attribute is used to indicate the time of participation by the legal authenticator (the time at which the document was authenticated). The value for 'typeCode' for the legal authenticator participation is LA.

Requirements for capture of information about a potential legal authenticator have not been defined to date. However, in the case where a local document is transformed into a SPL document for exchange, authentication only occurs on the local document and the fact of authentication is reflected in the exchanged SPL document. An SPL document can reflect the unauthenticated or authenticated state. The unauthenticated state exists when no authentication information has been recorded (i.e., it is the absence of being authenticated).

Authentication involves signing of the document either manually or electronically by the responsible individual. While electronic signatures themselves are not included in the SPL Header information, the SPL Header does document the existence of a signature elsewhere via the 'signatureCode' component. The value for 'signatureCode', which is drawn from the ParticipationSignature vocabulary domain, is S (signed).

Information about the legal authenticator is captured by means of several interrelated classes:

- <legalAuthenticator> – A Participation clone that links the <Document> to the <Person> and <Organization> (through the <AssignedEntity>). The required 'time' attribute is used to indicate the time of participation by the legal authenticator (usually the time of signature). The value for 'typeCode' for the legal authenticator of the document, which is drawn from the *ParticipationType* vocabulary domain, is LA.
- <AssignedEntity> – A Role clone that links the <legalAuthenticator> to the <Person> and <Organization>.
- <Person> – An Entity clone. Provides details about the person playing the role of a <legalAuthenticator> (such as name).

- <Organization> – An Entity clone. Provides details about the organization for which the <legalAuthenticator> is working.

4.2.1.3.4 Reviewer

SPL documents may be reviewed by one or more persons within the regulatory agency. The SPL Header provides for optional identification of regulatory reviewers.

Information about the reviewer is captured by means of several interrelated classes:

- <verifier> – A Participation clone that links the <Document> to the <Person> and <Organization> (through the <AssignedEntity>). The required 'time' attribute is used to indicate the time of participation by the author (usually the time of review). The value for 'typeCode' for the author of the document, which is drawn from the *ParticipationType* vocabulary domain, is VRF (verifier).
- <AssignedEntity> – A Role clone that links the <verifier> to the <Person> and <Organization>.
- <Person> – An Entity clone. Provides details about the person playing the role of a <verifier> (such as name).
- <Organization> – An Entity clone. Provides details about the organization (the regulatory agency) for which the <verifier> is working.

4.2.2 SPL Body

4.2.2.1 SPL Body Choice

The SPL document body can be either unstructured or can be comprised of structured XML markup.

The <NonXMLBody> element represents a document body that is in some format other than XML. NonXMLBody.text is used to reference data that is stored externally to the CDA document, rather than directly encoded inline. Because inline transmission of the non-XML body is not allowed, the use of NonXMLBody.text.BIN and NonXMLBody.text.thumbnail are precluded from use. (To incorporate non-XML data within an XML document [e.g., figures like chemical structures, diagrams], <ObservationMedia> is used.) Rendering of <NonXMLBody> requires a software tool that recognizes the particular MIME media type of the unstructured body.

The <StructuredBody> element represents an XML document body that is comprised of one or more <Section>s.

4.2.2.2 SPL Sections

The purpose of the SPL <Section> element is to provide a means of organizing the product labeling content into the commonly understood sections generally found in these documents.

The element <Section> is a container used to wrap other containers. A <Section> can occur in the <StructuredBody>, or can be nested within another <Section>. A <Section> can also be replaced by another <Section>. A <Section> can contain nested <Section> elements or other structures such as <Observation>s.

The SPL <Section> contains the actual product labeling text and graphics to be rendered. There are three logical components of the SPL <Section>:
(1) General section information.
(2) Information about participants in creation of the section.
(3) The actual product labeling text and graphics to be included in the label section (and which will be rendered), along with structured data elements (that may be used for machine processing).

The mechanisms to uniquely identify a specific product labeling section, to indicate a standard type code and name for the section, and to include a local name for the section (e.g. realm or language specific name; possibly constrained by the type code) are all included.

4.2.2.2.1 SPL Section Attributes

4.2.2.2.1.1 Section classification

Every <Section> has a 'classCode' attribute, the value of which identifies it as a document section. The 'classCode' for <Section> is DOCSECT.

4.2.2.2.1.2 Section identification

Every <Section> has a required, globally-unique instance identifier, 'id' (which is different from the XML identifier; see the HL7 Data Types specification for more information about use of globally-unique instance identifiers).

Every <Section> has a required type code attribute, 'code', that describes (but does not guarantee) the content of the section. The externally-defined vocabulary domain for 'Section.code' may be drawn from LOINC. (See *6.4 LOINC Document Codes and Document Section Codes* for a sample set of LOINC document section codes.) However, because the coding strength is CWE, the code set may be extended locally. Examples of possible section codes include:

Indications and usage
Dosage and administration
Contraindications
Warnings
Drug interactions
Adverse reactions
etc.

NOTE: Version 2.09 (May 2003) of the LOINC database does not provide a ready method for retrieval of section codes from within the larger database. Per the June 20, 2003 Clinical LOINC meeting minutes:

- LOINC will use the same code for sections whether they contain coded information or unstructured text.
- All items in the LOINC database will be classified as to whether each is a document code, a section code, or an individual (single) observation.

Every <Section> has an optional 'title', with a data type of ST that allows free text entry of the human readable title of the section. It is the 'title' of a section that is rendered. The title describes (but does not guarantee) the content of the section.

4.2.2.2.1.3 Section time stamps

Every <Section> has an optional 'effectiveTime' that identifies the section origination time, i.e., when the section was created. The attribute 'effectiveTime' has an IVL <TS> data type.

4.2.2.2.1.4 Section confidentiality

Each <Section> contains an optional 'confidentialityCode' attribute that can override the 'confidentialityCode' attribute in <Document>.

4.2.2.2.1.5 Section language

'Section.languageCode' specifies the human language of character data (whether they be in contents or attribute values), if different from the language at the <Document> level. The values of the attribute are language identifiers as defined by the IETF (Internet Engineering Task Force) RFC 3066: Tags for the Identification of Languages, ed. H. Alvestrand. 1995 (http://www.ietf.org/rfc/rfc3066.txt), which obsoletes RFC 1766. Language is a contextual component of SPL, where the value expressed in the header holds true for the entire document, unless overridden by a nested value (as further described in *3.9. SPL Context Inheritance*).

4.2.2.2.2 SPL Section Relationships

The SPL specification enables the explicit representation of the relationships between versions of sections. These relationships rely on the section identifiers described above. Whether and how this information is used depends on the document management system in use.

A replacement section replaces an existing section. The 'id' attribute in the <Section> may assist in tracking the replacement section.

A section is related to the section it replaces (<sectionReplaced>) through the <replacementOf> relationship (an ActRelationship clone). The value of RPLC for 'replacementOf.typeCode' is contained in the *ActRelationshipType* vocabulary domain.

4.2.2.2.3 SPL Section Participants

4.2.2.2.3.1 Author

If desired, the author(s) of specific sections can be identified (which will override the author(s) specified in the Header). The SPL model provides for optional identification of document section authors.

Information about the author is captured by means of several interrelated classes:

- <author> – A Participation clone that links the <Section> to the <Person> and <Organization> (through the <AssignedEntity>). The required 'time' attribute is used to indicate the time of participation by the author (usually the time of origination). The value for 'typeCode' for the author of the document, which is drawn from the *ParticipationType* vocabulary domain, is AUT.
- <AssignedEntity> – A Role clone that links the <author> to the <Person> and <Organization>.
- <Person> – An Entity clone. Provides details about the person playing the role of an <author> (such as name).
- <Organization> – An Entity clone. Provides details about the organization (e.g., the manufacturer or owner of the marketing authority) for which the <author> is working.

Note: In the SPL RMIM, this class is represented as a "shadow" of the <author> class for <Document>, indicating that this participation is used by both the <Section> and the <Document> classes..

4.2.2.2.4 SPL Section Narrative Block

The 'Section.text' field is used to store narrative to be rendered and is a special hand-crafted content model (the same as 'Section.text' in CDA) that is part of the SPL standard. The SPL schema incorporates the schema for this content model.

The content model for the 'Section.text' field is shown in *Figure 2. Content Model of 'Section.text'*, and is described here.

4.2.2.2.4.1 Content

The SPL <content> element is used to wrap a string of text so that it can be explicitly referenced, or so that it can suggest rendering characteristics. The <content> element can nest recursively, which enables wrapping a string of plain text down to as small a chunk as desired.

The <content> element contains an optional local identifier (represented as an XML ID attribute), serving as the target of a reference. The originalText component of a RIM attribute present in any SPL body structure can make explicit reference to the identifier, thereby indicating the original text associated with the attribute in the SPL body structure (see *4.2.2.4.2 XML ID/IDREF Pointers*). There is no requirement that SPL body structures must reference into the narrative block. The referencing mechanism can be used where it is important to represent the original text component of a coded SPL body structure.

The <content> element contains an optional 'emphasis attribute that can be used to indicate the text decoration or emphasis present in the source document. (Allowed values are bold, underline, italics, and yes.) Emphasis attribution propagates to nested text, unless overridden. When these attributes are used solely to meet local rendering requirements, receivers are not required to render documents using the style hints provided and can present stylized text in accordance with their local style conventions. However, these attributes may also be used in a stylesheet to enforce formatting requirements outlined in regulations.

> **NOTE:** The 'emphasis' attribute does not convey meaning. Shareable semantics are only achieved by the inclusion of SPL body structures, which can make reference to stylized sections of narrative.

The <content> element contains an optional 'revised' attribute (with values of insert or delete), which can be used to indicate narrative changes from the last version of an SPL document. The attribute is limited to a single generation, in that it only reflects the changes from the preceding version of a document. If applied, it needs to be used in conjunction with standard SPL revision tracking. Receivers are required to interpret the 'revised' attribute when rendering by visually distinguishing or suppressing deleted narrative.

4.2.2.2.4.2 Link

The <link> element is a generic referencing mechanism, and contains a single required <linkHtml> element. Its intent is to provide behavior similar to the HTML anchor tag.

Multimedia that is simply referenced by the labeling document and not an integral part of the document can use <link>. Multimedia that is integral to a labeling document, and part of the attestable content of the document requires the use of the <ObservationMedia> SPL class, which is referenced by the <renderMultiMedia> element in the narrative block (see *4.2.2.2.4.5 renderMultiMedia*).

NOTE: SPL links do not convey meaning. Shareable semantics are only achieved by the inclusion of SPL body structures and their associated formalized relationships.

4.2.2.2.4.3 Subscript and superscript

The SPL <sub> and <sup> elements are used to indicate subscripts and superscripts, respectively.

Receivers are required to interpret these elements when rendering by visually distinguishing subscripted and superscripted characters.

4.2.2.2.4.4 Line break

The SPL
 element is used to indicate a hard line break. It differs from the SPL <paragraph> element in that the
 element has no content, and typically is rendered without an intervening blank line.

4.2.2.2.4.5 renderMultiMedia

The <renderMultiMedia> element references external multimedia that is integral to a document, and part of the attestable content of the document, and serves to show where the referenced multimedia is to be rendered.

The <renderMultiMedia> element contains a required 'referencedObject' attribute (represented as an XML IDREFS attribute), the values of which must equal XML ID values of <ObservationMedia> within the same document.

Multimedia that is simply referenced by the document and not an integral part of the document can use <link> (see *4.2.2.2.4.2 Link*).

The expected behavior is that the referenced multimedia be rendered at the point of reference. <renderMultiMedia> can reference a single <ObservationMedia>. If <renderMultiMedia> references a single <ObservationMedia>, that <ObservationMedia> should be rendered at the point of reference.

The <renderMultiMedia> element has an optional <caption> (see *4.2.2.2.4.9 Caption*) which can also be rendered at the point of reference.

4.2.2.2.4.6 Paragraph

A <paragraph> is similar to the HTML paragraph, which allows blocks of narrative to be broken up into logically consistent structures. A <paragraph> element contains an optional caption (see *4.2.2.2.4.9 Caption*).

4.2.2.2.4.7 List

A <list> is similar to the HTML list. A <list> has an optional caption (see *4.2.2.2.4.9 Caption*) and contains one or more <item> elements. The required 'listType' attribute specifies whether the <list> is ordered or unordered (with unordered being the default). Unordered lists are typically rendered with bullets, whereas ordered lists are typically rendered with numbers, although this is not a requirement of a receiver. An <item> also has an optional caption, which if present must come first before any other character data.

4.2.2.2.4.8 Table

The <table> is similar to the HTML table. The table markup is for presentation purposes only and, unlike a database table, does not possess meaningful field names.

SPL modifies the strict XHTML table model (see *Table 4. Changes to the strict XHTML table model in SPL*) by removing formatting tags and by setting the content model of cells to be similar to the contents of other elements in the SPL Narrative Block. The <th> element is modeled analogously to the <caption> element (see *4.2.2.2.4.9 Caption*), and as in the <caption> element, the <localCaptionCode > is optional and non-repeatable, and must occur first. (See *Figure 2. Content Model of 'Section.text'* for the content model of <table>.)

Table 4. Changes to the strict XHTML table model in SPL

Change this:
<!ELEMENT caption %Inline;>
To this:
<!ELEMENT caption (#PCDATA | link | sub | sup | localCaptionCode)*>

Change these XML attributes:
%attrs;
To these:
ID ID #IMPLIED
xml:lang NMTOKEN #IMPLIED

Change this:
<!ELEMENT td %Flow;>
to this:
<!ELEMENT td (#PCDATA | content | link | sub | sup | br | renderMultiMedia | localMarkup | paragraph | list)*>

change this:


```
  <!ELEMENT th %Flow;>
```
to this:
```
  <!ELEMENT th (#PCDATA | link | sub | sup | localCaptionCode)*>
```

4.2.2.2.4.9 Caption

The <caption> is a label for a paragraph, list, list item, table, or table cell. It can also be used within the <renderMultiMedia> element to indicate a label for reference ObservationMedia.

A <caption> contains plain text (which may include subscripts and superscripts) and may contain links (see *4.2.2.2.4.2 Link*), and can be coded using the optional <localCaptionCode> element. The <localCaptionCode> element, if used, must occur directly after the <caption> element, and may not repeat. The <localCaptionCode> element's displayName attribute reflects the name of the code within the code system from which it is drawn. The displayName is not to be rendered. The only rendered text is the plain text within the <caption>.

Local caption codes are provided as a convenience for local implementations, and do not convey shareable semantics. There is no requirement for a receiver of an arbitrary SPL document to interpret or act on the codes.

Figure 2. Content Model of 'Section.text'

The content model of the Section.text attribute is specially hand crafted to meet the requirements outlined above (see *3.6 "Human Readability" and Rendering SPL Documents*)

```
<!ENTITY % textAtts  "
  ID ID #IMPLIED
  lang NMTOKEN #IMPLIED">

<!ELEMENT text  (#PCDATA | content | link | sub | sup | br | renderMultiMedia
    | paragraph | list | table)*>

<!ELEMENT content (#PCDATA | content | link | sub | sup | br |
    renderMultiMedia)*>
<!ATTLIST content
  %textAtts;
  emphasis (bold | underline | italics | yes) #IMPLIED
  revised (insert | delete) #IMPLIED>

<!ELEMENT link (linkHtml) >
<!ATTLIST link  %textAtts;>

<!ELEMENT linkHtml (#PCDATA) >
<!ATTLIST linkHtml
  name    CDATA   #IMPLIED
  href    CDATA   #IMPLIED
  rel     CDATA   #IMPLIED
  rev     CDATA   #IMPLIED
  title   CDATA   #IMPLIED
  %textAtts;>

<!ELEMENT sub (#PCDATA)>

<!ELEMENT sup (#PCDATA)>

<!ELEMENT br EMPTY>

<!ELEMENT renderMultiMedia (caption?)>
<!ATTLIST renderMultiMedia
  referencedObject IDREFS #REQUIRED
  %textAtts;>

<!ELEMENT paragraph (#PCDATA | caption | content | link | sub | sup | br |
    renderMultiMedia)*>
<!ATTLIST paragraph  %textAtts;>
```



```
<!ELEMENT list (caption?, item+)>
<!ATTLIST list
  %textAtts;
  listType (ordered | unordered) "unordered" >

<!ELEMENT item (#PCDATA | caption | content | link | sub | sup | br |
    renderMultiMedia | paragraph | list | table)*>
<!ATTLIST item  %textAtts;>

<!ENTITY % cellhalign
  "align      (left|center|right|justify|char) #IMPLIED
   char       CDATA          #IMPLIED
   charoff    CDATA          #IMPLIED"  >

<!ENTITY % cellvalign
  "valign     (top|middle|bottom|baseline) #IMPLIED"  >

<!ENTITY % Tframe "(void|above|below|hsides|lhs|rhs|vsides|box|border)">

<!ENTITY % Trules "(none | groups | rows | cols | all)">

<!ENTITY % Scope "(row|col|rowgroup|colgroup)">

<!ELEMENT table
     (caption?, (col*|colgroup*), thead?, tfoot?, (tbody+|tr+))>
<!ELEMENT caption (#PCDATA | link | | sub | sup | localCaptionCode)*>
<!ELEMENT thead    (tr)+>
<!ELEMENT tfoot    (tr)+>
<!ELEMENT tbody    (tr)+>
<!ELEMENT colgroup (col)*>
<!ELEMENT col      EMPTY>
<!ELEMENT tr       (th|td)+>
<!ELEMENT th       (#PCDATA | link | localCaptionCode)*>
<!ELEMENT td       (#PCDATA | content | link | renderMultiMedia | paragraph |
    list)*>

<!ATTLIST table
  %textAtts;
  summary     CDATA          #IMPLIED
  width       CDATA          #IMPLIED
  border      CDATA          #IMPLIED
  frame       %Tframe;       #IMPLIED
  rules       %Trules;       #IMPLIED
```

```
  cellspacing CDATA          #IMPLIED
  cellpadding CDATA          #IMPLIED  >

<!ATTLIST caption  %textAtts;>

<!ELEMENT localCaptionCode EMPTY>
<!ATTLIST localCaptionCode
  code CDATA #IMPLIED
  codeSystem CDATA #IMPLIED
  displayName CDATA #IMPLIED
  %textAtts;>

<!ATTLIST colgroup
  %textAtts;
  span        CDATA      "1"
  width       CDATA      #IMPLIED
  %cellhalign;
  %cellvalign;  >

<!ATTLIST col
  %textAtts;
  span        CDATA      "1"
  width       CDATA      #IMPLIED
  %cellhalign;
  %cellvalign;  >

<!ATTLIST thead
  %textAtts;
  %cellhalign;
  %cellvalign;  >

<!ATTLIST tfoot
  %textAtts;
  %cellhalign;
  %cellvalign;  >

<!ATTLIST tbody
  %textAtts;
  %cellhalign;
  %cellvalign;  >

<!ATTLIST tr
  %textAtts;
```

```
  %cellhalign;
  %cellvalign;>

<!ATTLIST th
  %textAtts;
  abbr        CDATA      #IMPLIED
  axis        CDATA      #IMPLIED
  headers     IDREFS     #IMPLIED
  scope       %Scope;    #IMPLIED
  rowspan     CDATA      "1"
  colspan     CDATA      "1"
  %cellhalign;
  %cellvalign; >

<!ATTLIST td
  %textAtts;
  abbr        CDATA      #IMPLIED
  axis        CDATA      #IMPLIED
  headers     IDREFS     #IMPLIED
  scope       %Scope;    #IMPLIED
  rowspan     CDATA      "1"
  colspan     CDATA      "1"
  %cellhalign;
  %cellvalign;  >
```

4.2.2.3 SPL Body Structures

SPL body structures are the remaining classes related to the document <Section>. These classes have been created to capture certain data elements identified as necessary for machine processing and utilization of drug product labeling content. (See 4.1.3 *Date element requirements*.) Some of these data elements can be used to capture information about the drug ingredients, strengths, dosage forms, and packaging that occurs in the narrative of the product labeling document. Additional data elements may be identified in future to accommodate other international or U.S. requirements.

These classes are clones of the core classes in the RIM. The data elements have been modeled, according to HL7 Version 3, as either components or participants of a <Section>. This modeling may involve Participations in Acts, with a number of Entities playing a number of Roles. The role of a particular Entity may also be scoped by another Entity. (See *3.2.1 Reference Information Model (RIM)* for discussion of some basic Version 3 concepts. For more detailed information about Version 3 constructs like entities, participations, and playing and scoping roles, see http://www.hl7.org or contact Health Level Seven.

The <Observation> and <ObservationMedia> classes are grouped together as <documentBodyEntry> (which offers a choice of one or the other) and are described below in the sections bearing their names. Other body structures are described in the context of the data elements that they were designed to represent.

4.2.2.3.1 Observation

The <Observation> class inserts codes and other observations into SPL documents. For the current version of the SPL specification, this entry is utilized to capture a code that classifies the referenced content as one of the data elements of interest (e.g., imprint information for solid oral dosage form). Structured observations can reference narrative content in the 'Section.text' field.

The 'classCode' for <Observation> is OBS.

The 'code' has a data type of CE and the 'value' has a data type of ANY.

There is also a 'text' field that allows entry of free text describing the observation (e.g., a description of the size, shape, color, etc. of a solid oral dosage form.

The vocabulary domain for 'Observation.code' is *ObservationType*, which is a sub-domain within the *ActCode* vocabulary domain (which is a CWE domain and can be extended as necessary). For example, some values that are contained in the *FDALabelData* value set within the *ObservationType* vocabulary domain are shown in the following table:

Table 4. Sample values for 'Observation.code' (CWE)

Code	Display Name	Definition
FDAIMPRINTCD	FDA label imprint code	Identifying marks on product
FDASIZE	FDA label size	Description of size of the product as called for in regulations
FDASHAPE	FDA label shape	Description of shape of the product as called for in regulations
FDACOLOR	FDA label color	Description of color of the product as called for in regulations
FDACOATING	FDA label coating	Description of the coating of the product as called for in regulations
FDASCORING	FDA label scoring	Description of scoring of the product as called for in regulations
FDALOGO	FDA label logo	Description of the logo on the product as called for in regulations

4.2.2.3.2 ObservationMedia

The <ObservationMedia> element represents media that is logically a part of a product labeling document, but is stored outside the document and incorporated by reference. Multimedia that is integral to a document, and part of the attestable content of the document, requires the use of <ObservationMedia>. (An example might be the molecular structure for a drug in a drug product labeling document.) Multimedia that is simply referenced by the document and not an integral part of the document can use <link> (see *4.2.2.2.4.2 Link*). Note that the SPL specification's <ObservationMedia> is used only to reference data that is stored externally.

The SPL Body element <ObservationMedia> is derived from the RIM <Observation> class. An <ObservationMedia> class contains an optional instance identifier, 'ObservationMedia.id', and a 'value', 'ObservationMedia.value', which is modeled as an HL7 encoded data (ED) data type. This 'value' attribute is used only to reference external media; the media itself cannot be stored in the <ObservationMedia> element.

The XML ID attribute on the <ObservationMedia> element is used by the <renderMultiMedia> element to identify the media to be rendered (see *4.2.2.2.4.5 renderMultiMedia*).

4.2.2.3.3 Drug product code (e.g., NDC code)

The drug product code (e.g., National Drug Code [NDC] in the U.S.) is captured by means of the 'code' attribute on the <RegulatedProduct> element. The organization that assigns the drug product code is captured by means of an <Organization> element that scopes <RegulatedProduct> role . (See *3.2.1 Reference Information Model (RIM)* for an explanation of players and scopers.)

4.2.2.3.4 Package type

The package type is captured by means of the ‘code’ attribute on the <Package> element.

4.2.2.3.5 Package quantity

The package quantity is captured by means of the ‘quantity’ attribute on either <containedLabeledDrug> (for packages containing a drug) or <containedPackage> (for packages contained within other packages).

4.2.2.3.6 Controlled substance classification or schedule (e.g., DEA number)

The controlled substance classification or schedule is captured by means of the ‘value’ attribute on the <MonitoringProgramEvent> element. When the classification that is desired is the DEA schedule (U.S.realm), the default value for the ‘code’ attribute of CTLSUB (controlled substance) will be changed to DEADrugSchedule (from the *ActCode* HL7 vocabulary domain) and the ‘value’ will be the DEA number.

4.2.2.3.7 Active ingredient

The established name of an active ingredient is captured by means of the ‘name’ attribute on the <IngredientEntity> element when the <IngredientEntity> is playing the role of <ActiveIngredient>.

The code for the active ingredient is captured by means of the ‘code’ attribute on the <IngredientEntity> element.

The strength of the active ingredient is captured by means of the ‘quantity’ attribute on the <ActiveIngredient> element.

4.2.2.3.8 Active moiety

The name of the active moiety of the active ingredient is captured by means of the ‘name’ attribute on the <ActiveMoietyEntity> element.

The active moiety code is captured by means of the ‘code’ attribute on the <ActiveMoietyEntity> element.

4.2.2.3.9 Inactive ingredient

The established name of the inactive ingredient is captured by means of the ‘name’ attribute on the <IngredientEntity> element when the <IngredientEntity> is playing the role of <InactiveIngredient>.

The code for the inactive ingredient is captured by means of the ‘code’ attribute on the <IngredientEntity> element.

The strength of the inactive ingredient is captured by means of the ‘quantity’ attribute on the <InactiveIngredient> element.

4.2.2.3.10 Labeled route of administration

The ‘routeCode’ attribute on <SubstanceAdministration> is used to capture the labeled route of administration of a drug product.

4.2.2.3.11 Proprietary name

The proprietary or brand name is captured by means of the ‘name’ attribute on the <LabeledDrug> element.

4.2.2.3.12 Generic name

The nonproprietary (generic) name is captured by means of the ‘name’ attribute on the <GenericDrug> element.

4.2.2.4 Relationship between SPL Narrative Block and SPL Body Structures

4.2.2.4.1 General concepts

The relationship between the <Section>’s narrative (‘Section.text’) and its body structures is encoded in the intervening ActRelationship or Participation. An <Observation> or <ObservationMedia> is linked to the <Section> via an ActRelationship with a classCode of ’COMP’ (component). The data elements used for identification and description of the product are linked to the <Section> via a Participation with a typeCode of ‘SBJ’ (subject).

The narrative of each <Section>, together with any multimedia content referenced in the narrative (<ObservationMedia>), comprises the complete content of the <Section>. <ObservationMedia> is referenced by <renderMultiMedia> tags in the ‘Section.text’. This is the only case where the body structures contain content that must be rendered with the narrative.

SPL body structures can reference specific content in the narrative block using XML ID and IDREF pointers. The CV and CE data types have an ‘original text’ component (see *6.3.4 Understanding HL7 V3 Data Types*).

4.2.2.4.2 XML ID/IDREF Pointers

SPL body structures can point in to the <content> element of the SPL Narrative Block, and the <renderMultiMedia> element of the SPL Narrative Block can point out to SPL body structures.

The <content> element (see *4.2.2.2.4.1 Content*) contains an optional local identifier (represented as an XML ID attribute), serving as the target of a reference. The originalText component of a RIM attribute present in any SPL body structure can make explicit reference to the identifier, thereby indicating the original text associated with the attribute in the SPL structure.

Figure 3. Referencing into the SPL Narrative Block

```
<text>
    <paragraph>DRUG X is supplied as a <content ID="a1">round</content>, scored tablet.
    </paragraph>
</text>
<component1>
  <documentBodyEntry>
    <Observation>
        <code code="TBD" codeSystem="2.16.840.1.113883.6.5"
          codeSystemName="FDA" displayName="shape"/>
        <value xsi:type="CD" code="TBD"  displayName="round"
          codeSystem="2.16.840.1.113883.6.5">
            <originalText>
                        <reference value="#a1"/>
            </originalText>
        </value>
    </Observation>
  </documentBodyEntry>
</component1>
```

There is no requirement that SPL body structures must reference into the SPL Narrative Block. The referencing mechanism can be used where it is important to represent the original text component of a coded element.

The <renderMultiMedia> element (see *4.2.2.2.4.5 renderMultiMedia*) contains a required referencedObject attribute (represented as an XML IDREFS attribute), the values of which must equal XML ID values of one ObservationMedia within the same document.

An XML attribute "MMID" (multimedia identifier), of type XML ID, is added to <ObservationMedia> within the SPL Schema.

Figure 4. Referencing out of the SPL Narrative Block

```
<Section>
    <paragraph>Latanoprost is a prostaglandin F<sub>2a</sub> analogue. Its chemical name is
    isopropyl-(Z)-7[(5R,2R,3R,6S)3,5-dihydroxy-2-[(3R)-3-hydroxybutyl-5-phenylpentyl]cyclopentyl]-
    5-heptenoate. Its molecular formula is C<sub>40</sub>26H<sub>40</sub>O<sub>5</sub> and its
    chemical structure is:
    <renderMultiMedia referencedObject="MM1"/>
    </paragraph>
    <component1>
      <documentBodyEntry>
        <ObservationMedia MMID="MM1">
                <id root=”10.23.4567.345”/>
                <value xsi:type="ED" mediaType="image/jpeg">
                <reference value="latanoprost_molecular_structure.jpeg"/>
            </value>
        </ObservationMedia>
      </documentBodyEntry>
    </component1>
</Section>
```

5 SPL Technical Specification

5.1 Contents

The technical specification consists of three representations of the SPL model:

- RMIM – a Visio diagram of the model
- Hierarchical Description (HD) – a graphical representation of the model
- Schema – an XML entity

5.2 Use of XML Schemas

An XML “schema” is a specification or set of constraints for a class of documents[4]. There are several schema languages available with varying ability to express constraints. This release of the SPL specification uses the World Wide Web Consortium (W3C) Schema Language as the basis for the HL7 schema that is the primary expression for the Specification. In this document, “schema” or “Schema” refer to any schema, whether W3C Schema, DTD or alternate schema. The normative SPL schema describes the style of XML. SPL instances are valid against the SPL schema and may be subject to additional validation. There is no prohibition against multiple schema languages (W3C, DTD, RELAXNG, etc.), as long as conforming instances are compatible.

[4] Terminology note: The term “document type” is ambiguous. In XML, “document type” is typically equated with DTD, “document type definition” or schema. In the RIM, “document type” is equated with the type code of a document (such as the code for a “Prescription Drug Label” or a “Discharge Summary”). This specification uses “schema” when referring to XML document types and uses “document type codes” when referring to the type code of a document, and avoids the phrase “document type”.

The SPL specification is specified by the SPL schema, which is defined as an XML entity. This schema incorporates the HL7 Version 3 Data Types schema, and the HL7 vocabulary schema.

An SPL document references the SPL schema (PORR_MT050016).

The element <Document> is the root element of an SPL document. This element contains both SPL Header and Body markup.

5.3 HL7 Methodology

Note: A number of HL7 Version 3 standards and artifacts, which are integral to understanding and/or implementation of SPL, are mentioned in this specification. Copies of all of these are available to HL7 members and authorized licensees. For further information, please contact HL7 headquarters at:

Health Level Seven, Inc.
3300 Washtenaw Ave, Suite 227
Ann Arbor, MI 48104
Telephone: 734-677-7777
Fax: 734-677-6622
E-mail: hq@hl7.org

HL7 V3 methodology and tooling were used in the development of this specification.

Document analysis, regulatory requirements, and review of regulatory policy documents were used to help define requirements for the drug product labeling document. These requirements were used to build the specification (including the necessary vocabulary).

The SPL Schema is generated from the SPL Refined Message Information Model (RMIM) (see *5.4 SPL RMIM*). The RMIM is a Unified Modeling Language (UML) representation of all the data requirements for the SPL specification. It structures those requirements in accordance with HL7 methodology principals, which include the requirement that all classes be derived from (be "clones" of) classes in the HL7 Reference Information Model (RIM). A Visio-based tool is used to generate the RMIM diagram using a design repository containing the RIM.

The RMIM is serialized to create a listing of the classes and attributes in such a way that the relationships among them are preserved, and a hierarchy is created (the Hierarchical Description [HD]).

Using the normative HL7 XML Implementation Technology Specification (ITS), the HD is converted to an XML schema.

Note:

The HL7 XML ITS includes rules for creation of XML element names from classes and attributes in the RMIM. For example, many RIM attributes become XML elements in the schema. In addition, some element names in the schema may differ slightly from the corresponding RMIM name. See the XML ITS for a detailed explanation of the element creation and naming rules for HL7 schemas. For additional information, see http://www.hl7.org or contact Health Level Seven.

See also *6.5.2 Mapping between SPL RMIM classes and XML* Schema for a table that shows the translation between SPL RMIM class names and SPL Schema element names.

Attributes that have default values in the RMIM (e.g., determinerCode, typeCode, contextControlCode, contextConductionInd), which become fixed values in the XML Schema, need not be included in the instance document. However, attributes that have default values and are Mandatory (e.g., classCode, moodCode) must be included in the instance document. (See *5.4.2 RMIM diagram walk-through* for additional discussion about default values.)

The SPL schema package contains a number of schemas:

- The SPL Schema, which incorporates the special handcrafted schema for 'text'
- The HL7 Version 3 Data Types Schema (an XML implementation of the abstract data type specification already in use by the CDA and the HL7 Version 3 message specifications).
- HL7 Version 3 Vocabulary schema

The schema distribution package contains a number of additional schemas (including the RIM classes), based on the HL7 decision to include all possible supporting schemas in the schema package for each message type.

The following HL7 artifacts, tools, and versions were used in the construction of this standard:

- HL7 Reference Information Model, version 2.02
- XML Implementation Technology Specification (ITS), HL7 V3, version 1.11
- Visio R-MIM Stencils, version 2.98
- RoseTree, version 2.9.37

5.3.1 Common XML Attributes

5.3.1.1 XML element identification

Every XML element within an SPL document has an optional identifier, which must be unique within the document. The identifier is an XML "ID" data type[5]. Values of XML attributes of type "IDREF" or "IDREFS" must match the value of an ID attribute on some element within the document.

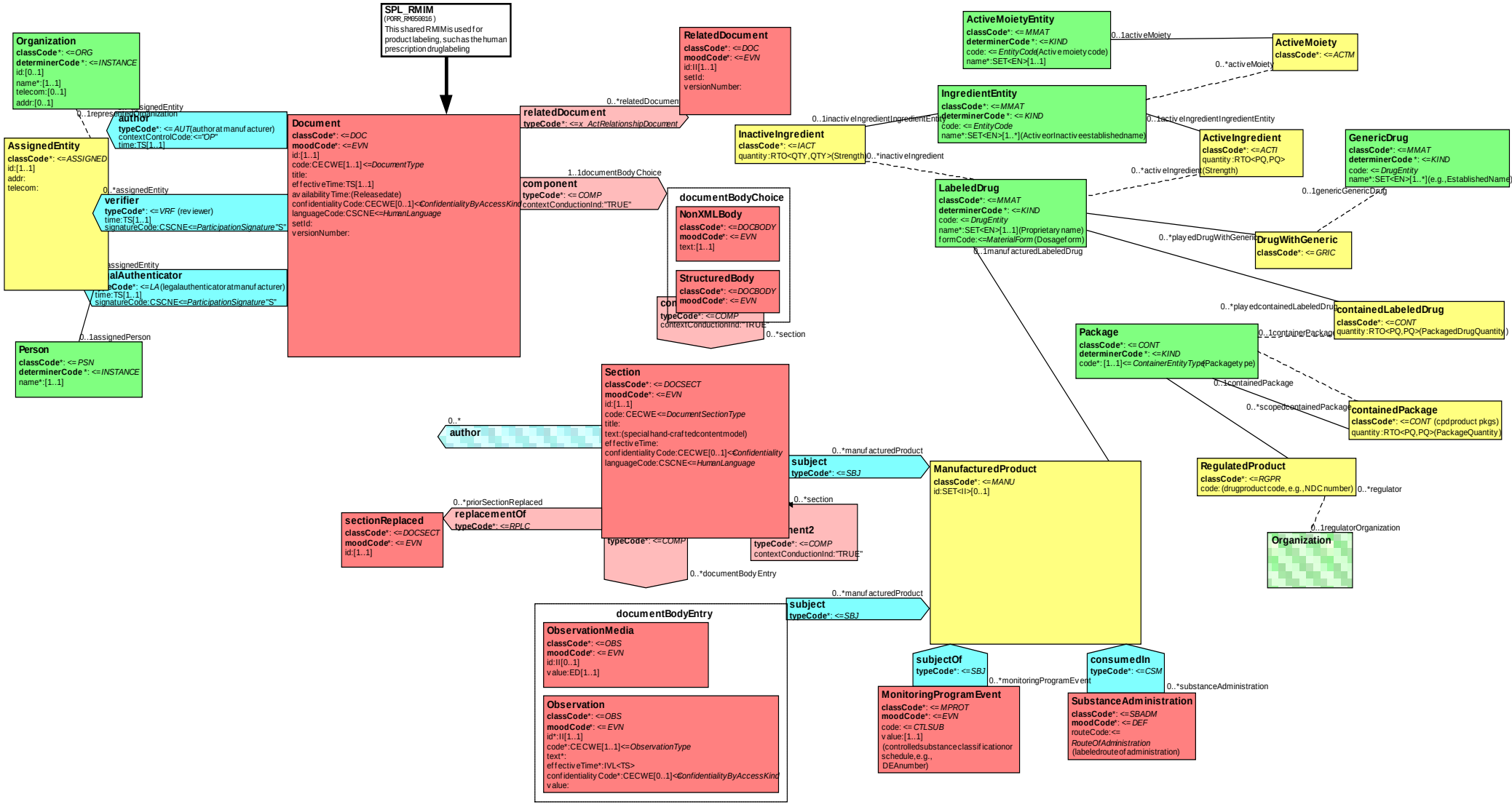
5.4 SPL RMIM

The SPL RMIM is a subset of the RIM that includes a fully expanded set of class clones, attributes and relationships that are used to create SPL documents (see *5.4.2 RMIM diagram walk-through* for details about reading an RMIM).

5.4.1 RMIM diagram

A gif image of the RMIM is included below. In addition, the ballot package contains separate files with both the gif image and the HL7 Visio diagram (see PORR_RM050016.gif and PORR_RM050016.vsd).

[5] This document discusses both XML data types and HL7 Version 3 Data Types, Release 1. Unless otherwise qualified, the term "data type" refers to HL7 Version 3 Data Types.



5.4.2 RMIM diagram walk-through

This section describes the SPL model from the perspective of the RMIM diagram and provides additional information to aid in reading and interpreting the diagram. (See *4.2 SPL Model* for an overview of the model.)

Some of the discussion in this section includes concepts specific to HL7 Version 3 modeling (such as clones, and playing and scoping roles) – for more information on that, http://www.hl7.org or contact Health Level Seven. See also *3.2.1 Reference Information Model (RIM)*.

The section is organized by the RIM classes from which the SPL classes were cloned, in the following order – Act, Role, Entity, arrow classes (ActRelationship, Participation).

The RMIM diagram is generated using a Visio-based HL7 tool. It may include a number of technical details for each class, including:

- Clone name – The Local Name is the name that appears on the diagram and is carried through to the schema.
- Attributes – Name, data type, coding strength (CNE or CWE), cardinality, value (may be default value and/or name of HL7 vocabulary domain), note (in parentheses) about what the attribute is used to represent in this model. If both the HL7 vocabulary domain and a default value are included, the default value is in quotation marks.

Cardinality expresses the minimum and maximum number of occurrences of a class or attribute. The convention used for expressing cardinality is:

- 0..1 (optional, 0 or 1)
- 0..* (optional, 0 to many)
- 1..1 (required, 1 only)
- 1..* (required, 1 or more)

Note: The concept of cardinality in HL7 artifacts (RMIMs, HDs) is distinct from the XML concept. Cardinality is integrally related to the expression of default values for RIM attributes. For example, if an attribute has a default value, it is not necessary to send that value in an instance – if no value is sent, the receiver of the instance must assume that the default value applies. (If there is only one possible value, that value is the default value.) However, if the attribute is designated as Mandatory (e.g., as classCodes are), the value must always be sent in the instance. In the XML schema that is generated from the HD, the HL7 cardinality is translated to XML cardinality according to rules set out in the HL7 XML ITS. If an attribute is required (but not Mandatory) and has a default value, the cardinality in the RMIM and HD will be 0..1 or 0..* (the lower cardinality is 0 because the value does not have to be sent) – in the XML schema, the cardinality will be 1..1 or 1..*. If an attribute is required but has no default value, the cardinality in both the RMIM/HD and the XML schema will be 1..1 or 1..*. For additional information about use of cardinalities and defaults in HL7 artifacts, see the XML ITS and the Conformance chapter of Version 3 (go to http://www.hl7.org or contact Health Level Seven).

For example, a review of the <Document> class (which is an Act clone) in the RMIM diagram will show:

- Local Name is Document
- 'classCode' = DOC (document)
- 'moodCode' = EVN (event)
- 'id' – Data type is SET<II> and cardinality is 1..1
- code – Data type is CE, coding strength is CWE, cardinality is 1..1, vocabulary domain is *DocumentType*
- 'title' – Data type is ST, cardinality is 0..1
- 'effectiveTime' – Data type is TS, cardinality is 1..1
- 'availabilityTime' – Data type is TS, cardinality is 0..1, used to capture the release date of product labeling
- 'confidentialityCode' – Data type is CE, coding strength is CWE, cardinality is 0..1, vocabulary domain is *ConfidentialityByAccessKind*)
- 'languageCode' – Data type is CS, coding strength is CNE, cardinality is 0..1, vocabulary domain is *HumanLanguage*

- ‘setId’ – Data type is II, cardinality is 0..1
- ‘versionNumber’ – Data type is INT, cardinality is 0..1

In the Visio Design Tool, some details are viewable that do not appear in the printed copy of the diagram. See also *5.5 SPL Hierarchical Description (HD)*, which is a graphical representation of all of the technical details of the model. For details about the data types, see the HL7 Data Types specification (go to http://www.hl7.org or contact Health Level Seven).

The content of vocabulary domains mentioned in this specification is available from the Data Models link on the HL7 web site (http://www.hl7.org), either as HTML files in the Reference Information Model section or as part of the design repository under Applications. Vocabulary domains can also be viewed in the HL7 tooling (Visio tool or Rose Tree.)

When RIM classes are cloned, there are certain core attributes that help define the clone – these include ‘classCode’ and ‘code’. The value for ‘classCode’ for each clone is a single default value and the allowed values for ‘code’ further qualify the ‘classCode’.

The following standard HL7 vocabulary domains are used for the class clones:

- *ActClass* – Source of the ‘classCode’ for all Act clones
- *ActCode* – Source of the ‘code’ for all Act clones
- *ActMood* – Source of the ‘moodCode’ for all Act clones
- *ActConfidentiality* – Source of the ‘confidentialityCode’ for all Act clones
- *RoleClass* – Source of the ‘classCode’ for all Role clones
- *RoleCode* – Source of the ‘code’ for all Role clones
- *EntityClass* – Source of the ‘classCode’ for all Entity clones
- *EntityCode* – Source of the ‘code’ for all Entity clones
- *EntityDeterminer* – Source of the ‘determinerCode’ for all Entity clones
- *ActRelationshipType* – Source of the ‘typeCode’ for all ActRelationship clones
- *ParticipationType* – Source of the ‘typeCode’ for all Participation clones

5.4.2.1 Act clones

5.4.2.1.1 Document

The root element of the document and the entry point of the RMIM.

The <Document> may have a number of participants, including <author>, <verifier>, and <legalAuthenticator>.

A <Document> may be related to a <RelatedDocument> through the <relatedDocument> relationship (an ActRelationship clone). The ‘typeCode’ for <relatedDocument> identifies the relationship (e.g., RPLC for replacement).

A <Document> has a required <component>, which links it to a choice of either a <NonXMLBody> or <StructuredBody>.

5.4.2.1.2 RelatedDocument

A <RelatedDocument> may be related to a <Document> through the <relatedDocument> relationship (an ActRelationship clone). The ‘typeCode’ for <relatedDocument> identifies the relationship (e.g., RPLC for replacement).

5.4.2.1.3 NonXMLBody

A <NonXMLBody> may be a <component> of a <Document>. The ‘component.typeCode’ is COMP (component). The classCode is DOCBODY.

The ‘text’ attribute is required and references data that is stored externally to the product labeling document.

5.4.2.1.4 StructuredBody

A <StructuredBody> may be a <component> of a <Document>. The <StructuredBody> contains XML markup of document content. The ‘component.typeCode’ is COMP (component). The classCode is DOCBODY

A <StructuredBody> has optional <component>s, which are <Section>s.

5.4.2.1.5 Section

A <Section> is a <component> of a <StructuredBody>.

A <Section> may be a replacement section. It is related to a <sectionReplaced> through the <replacementOf> relationship (an ActRelationship clone). The ‘typeCode’ for <replacementOf> is RPLC (replacement).

<Section>s can nest. One <Section> is related to another <Section> through the <component2> relationship (an ActRelationship clone). The ‘typeCode’ for <component2> is COMP (component).

A <Section> may contain observations or observation media. A choice of an <Observation> or <ObservationMedia> is a <component1> of a <Section>. The ‘typeCode’ for <component1> is COMP (component).

A <Section> may have a subject that is the <ManufacturedProduct>. A <ManufacturedProduct> is related to the <Section> through the <subject> relationship (a Participation clone). The ‘typeCode’ for <subject> is SBJ (subject).

Note: In the SPL RMIM diagram, the <author> on the <Section> is represented as a shadow of the <author> associated with <Document>.

5.4.2.1.6 SectionReplaced

A <sectionReplaced> is related to a <Section> through the <replacementOf> relationship (an ActRelationship clone). The ‘typeCode’ for <replacementOf> is RPLC (replacement).

5.4.2.1.7 Observation

An <Observation> is contained with a <Section>. An <Observation> is related to a <Section> through the <component1> relationship. The ‘typeCode’ for <component1> is COMP (component).

An <Observation> can reference narrative content in the ‘Section.text’ field.

An <Observation> may have a subject that is the <ManufacturedProduct>. A <ManufacturedProduct> is related to the <Observation> through the <subject> relationship (a Participation clone). The ‘typeCode’ for <subject> is SBJ (subject).

5.4.2.1.8 ObservationMedia

An <ObservationMedia> element is a clone of the RIM Observation class (a sub-type of Act) that represents multimedia that is logically part of the current document (e.g., a molecular structure image). This clone is only for sending multimedia by reference, and only for multimedia that is logically part of the attested content of the document. Because inline transmission of multimedia is not allowed, the use of ObservationMedia.value.BIN and ObservationMedia.value.thumbnail are precluded from use. Rendering a referenced ObservationMedia requires a software tool that recognizes the particular MIME media type.

<ObservationMedia> is related to a <Section> through the <component1> relationship. The 'typeCode' for <component1> is COMP (component).

5.4.2.1.9 MonitoringProgramEvent

The purpose of this element is to capture the controlled substance classification or schedule of a drug (e.g., DEA number in the U.S.), by way of the <ManufacturedProduct> role.

<MonitoringProgramEvent> contains a 'classCode' of MPROT (from the *ActClass* HL7 vocabulary domain) and a 'moodCode' of EVN (event). The default 'MonitoringProgramEvent.code' is CTLSUB (from the *ActCode* HL7 vocabulary domain) and 'MonitoringProgramEvent.value' is the controlled substance classification or schedule. When the classification that is desired is the DEA schedule (U.S.realm), the value for the 'code' attribute will be changed to DEADrugSchedule (from the *ActCode* HL7 vocabulary domain) and the 'value' will be the DEA number.

5.4.2.1.10 SubstanceAdministration

The purpose of this element is to capture the labeled route of administration of a drug.

<SubstanceAdministration> contains a 'classCode' of SBADM (from the *ActClass* vocabulary domain) and a moodCode of DEF (definition). The value for the 'SubstanceAdministration.routeCode', which is a code for the labeled route of administration of the drug, may come from the *RouteOfAdministration* HL7 vocabulary domain.

5.4.2.2 Role clones

5.4.2.2.1 AssignedEntity

The <AssignedEntity> role links persons or organizations participating in the document (author, verifier, legalAuthenticator) to the <Document> or links an author to the <Section> class.

The 'classCode' for <AssignedEntity> is ASSIGNED.

5.4.2.2.2 ManufacturedProduct

The <ManufacturedProduct> role is involved in the capture of information about a product. It provides a link between a <Section> and detailed information about a product that is the subject of that section. For a drug product, that may include proprietary name, nonproprietary (generic) name, ingredients, packaging, labeled route of administration, and controlled substance classification or schedule.

The <ManufacturedProduct> role has a participation relationship to a number of Act clones (including <documentBodyEntry> choices):

- A <ManufacturedProduct> may be the subject of a <Section>. As such, it can be used to capture information about the proprietary name, nonproprietary (generic) name, ingredients, and packaging of a drug.
- A <ManufacturedProduct> may be the subject of an <Observation>. <Observation> can be used to capture descriptive information about a dosage form. For example, it may be used to capture descriptive information required by the U.S. FDA that applies to oral solid dosage forms (imprint code, size, shape, color, coating, scoring, logo).
- A <ManufacturedProduct> is consumed in a <SubstanceAdministration>. <SubstanceAdministration> is used to capture the labeled route of administration of a drug product.
- A <ManufacturedProduct> may be the subject of a <MonitoringProgramEvent>. <MonitoringProgramEvent> is used to capture the controlled substance classification or schedule of a drug (e.g., DEA number in the U.S.).

The 'classCode' for <ManufacturedProduct> is MANU.

There is an optional identifier, 'id' that can be used to facilitate referencing to a product that has been previously defined in the document.

5.4.2.2.3 ActiveMoiety

The <ActiveMoiety> role is part of the structure used to identify the "active moiety" of an active ingredient in a drug product.

The <ActiveMoiety> role is played by an <ActiveMoietyEntity> (shown in the RMIM by a solid line relationship) and scoped by an <IngredientEntity> (shown in the RMIM by a dotted line relationship). (See *3.2.1 Reference Information Model (RIM)* for an explanation of players and scopers.)

The 'classCode' of ActiveMoiety> is ACTM.

5.4.2.2.4 ActiveIngredient

The <ActiveIngredient> role is part of the structure used to identify an "active ingredient" in a drug product, as well as describe the quantity of active ingredient in the product.

The <ActiveIngredient> role is played by an <IngredientEntity> (shown in the RMIM by a solid line relationship) and scoped by a <LabeledDrug> (shown in the RMIM by a dotted line relationship). (See *3.2.1 Reference Information Model (RIM)* for an explanation of players and scopers.)

The 'classCode' of <ActiveIngredient> is ACTI.

The data type of the 'ActiveIngredient.quantity' attribute is RTO<PQ,PQ>.

5.4.2.2.5 InactiveIngredient

The <InactiveIngredient> role is part of the structure used to identify an "inactive ingredient" in a drug product.

The <InactiveIngredient> role is played by an <IngredientEntity> (shown in the RMIM by a solid line relationship) and scoped by a <LabeledDrug> (shown in the RMIM by a dotted line relationship). (See *3.2.1 Reference Information Model (RIM)* for an explanation of players and scopers.)

The 'classCode' of <InactiveIngredient> is IACT.

The data type of the 'InactiveIngredient.quantity' attribute is RTO<PQ,PQ>.

5.4.2.2.6 DrugWithGeneric

The <DrugWithGeneric> role is used to capture the nonproprietary (generic) name of the drug product.

The <DrugWithGeneric> role is played by a <LabeledDrug> (shown in the RMIM by a solid line relationship) and scoped by a <GenericDrug> (shown in the RMIM by a dotted line relationship). (See *3.2.1 Reference Information Model (RIM)* for an explanation of players and scopers.)

The 'classCode' of DrugWithGeneric is GRIC.

5.4.2.2.7 RegulatedProduct

The <RegulatedProduct> role is used to capture the drug product code (e.g., the National Drug Code [NDC] number in the U.S.) for a packaged drug product. This role is scoped by <Organization>, which is used to capture information about the organization that assigned the drug product code. (See *3.2.1 Reference Information Model (RIM)* for an explanation of players and scopers.)

The 'classCode' of <RegulatedProduct> is RGPR.

The 'code' is the drug product code (e.g., the NDC number in the U.S.).

5.4.2.2.8 containedLabeledDrug and containedPackage

These roles are used to capture information about drug package quantity.

- The <containedLabeledDrug> role captures information about the number of dosing units (e.g., tablets) in a package (e.g., bottle). The <containedLabeledDrug> role is played by a <LabeledDrug> and scoped by a <Package>. (See *3.2.1 Reference Information Model (RIM)* for an explanation of players and scopers.)
- The <containedPackage> role captures information about quantity when a drug product package is composed of more than one internal drug product package (e.g., a combination product consisting of two separate dosage forms). The <containedPackage> role is played by a <Package> in the combination product and scoped by the overall <Package>.

The 'classCode' of both <containedLabeledDrug> and <containedPackage> is CONT.

The data type of the 'quantity' attribute is RTO<PQ,PQ>.

5.4.2.3 Entity clones

According to the HL7 RIM, Roles are played by Entities. In the SPL document model, there are a number of Entity clones.

5.4.2.3.1 Person

<Person> is an Entity clone that provides details about a person who is a participant in a <Document> (<author>, <verifier>, <legalAuthenticator>) or <Section> (<author>). A <Person> plays the role of <AssignedEntity> in that participation.

<Person> contains a 'classCode' of PSN and a 'determinerCode' of INSTANCE.

<Person> contains a field for ‘name’, which is a free text field for the person’s name.

5.4.2.3.2 Organization

<Organization> is an Entity clone that provides details about an organization that is a participant in a <Document> (through the <author>, <verifier>, or <legalAuthenticator> role). An <Organization> scopes the role of <AssignedEntity> played by a <Person> in that participation. An <Organization> also scopes the role of <RegulatedProduct> that is used to capture the drug product code (e.g., NDC code). (See *3.2.1 Reference Information Model (RIM)* for an explanation of players and scopers.)

<Organization> contains a ‘classCode’ of ORG and a ‘determinerCode’ of INSTANCE.

<Organization> contains a field for ‘name’, which is a free text field for the organization’s name.

<Organization> also contains optional fields for capturing an identifier (‘id’), address (‘addr’), and contact information (‘telecom’) for the organization.

5.4.2.3.3 ActiveMoietyEntity

The <ActiveMoietyEntity> entity is used to capture information about the active moiety in a drug product.

The ‘classCode’ of <ActiveMoietyEntity> is MMAT (manufactured material) and it has a ‘determinerCode’ of KIND.

The optional ‘ActiveMoiety.code’ will be drawn from an external set of codes.

<ActiveMoiety> contains a field for ‘name’, which is a free text field for the name of the active moiety.

5.4.2.3.4 IngredientEntity

The <IngredientEntity> entity is used to capture information about ingredients in a drug product.

The ‘classCode’ of <IngredientEntity> is MMAT (manufactured material) and it has a ‘determinerCode’ of KIND.

‘IngredientEntity.code’ will be drawn from an external set of ingredient codes. Note that the ingredient codes for active ingredients and inactive ingredients are drawn from the same list – active and inactive ingredients are differentiated on the basis of Role.

<IngredientEntity> contains a field for ‘name’, which is a free text field for the “established name” of the ingredient.

5.4.2.3.5 LabeledDrug

The purpose of <LabeledDrug> is to capture the proprietary name and dosage form of a drug product. <LabeledDrug> is a specialization of the <Medication> entity that occurs in the Pharmacy domain information model.

<LabeledDrug> contains a ‘classCode’ of MMAT (manufactured material) and a ‘determinerCode’ of KIND.

The ‘LabeledDrug.code’ is drawn from the *EntityCode* vocabulary domain and has a value of DrugEntity (“a substance whose therapeutic effect is produced by chemical action within the body”).

<LabeledDrug> contains a field for ‘name’, which is a free text field for the proprietary name (also sometimes known as the brand name).

‘LabeledDrug.formCode’ is used to capture the dosage form of the drug. Values may be drawn from the *MaterialForm* HL7 vocabulary table or from other external code value sources.

5.4.2.3.6 Package

The purpose of <Package> is to capture the drug package type and quantity. <Package> is a specialization of the <Container> entity that occurs in the Pharmacy domain information model.

<Package> contains a ‘classCode’ of CONT (container) and a ‘determinerCode’ of KIND.

The ‘Package.code’ captures the package type and may be drawn from the *ContainerEntityType* sub-domain of the *EntityCode* vocabulary domain. ‘Package.code’ may also be drawn from a standard external vocabulary of package type codes.

The quantity in the package is captured by means of <containedLabeledDrug> and <containedPackage> roles.

5.4.2.3.7 GenericDrug

The purpose of <GenericDrug> is to capture the nonproprietary (generic) name of a <LabeledDrug>.

<GenericDrug> contains a ‘classCode’ of MMAT (manufactured material) and a ‘determinerCode’ of KIND.

The ‘GenericDrug.code’ is drawn from the *EntityCode* vocabulary domain and has a value of DrugEntity (“a substance whose therapeutic effect is produced by chemical action within the body”).

<GenericDrug> also contains a field for ‘name’, which is a free text field for the “established name”.

5.4.2.4 Arrow classes

The arrow classes are the classes that capture the relationships between Acts, Roles, and Entities. These classes are cloned from the ActRelationship class and the Participation class in the RIM.

Note that these relationship classes also become XML elements according to the HL7 XML ITS.

5.4.2.4.1 ActRelationship clones

5.4.2.4.1.1 relatedDocument

<relatedDocument> links a <Document> to a <relatedDocument>. The relationship is characterized by the ‘relatedDocument.typeCode’, the value of which is drawn from the *x_ActRelationshipDocument* vocabulary domain (the allowed values for which are replacement, addendum, and transformation).

5.4.2.4.1.2 component

<component> links <Document> to <NonXMLBody> or <StructuredBody>.

<component> also links <StructuredBody> to <Section>. The value for ‘component.typeCode’ is COMP (component).

5.4.2.4.1.3 component1

<component1> links <Observation> and <ObservationMedia> to <Section>. The value for ‘component1.typeCode’ is COMP (component).

5.4.2.4.1.4 component2

<component2> links a nested <Section> to the <Section> in which it is nested. The value for ‘component2.typeCode’ is COMP (component).

5.4.2.4.1.5 replacementOf

<replacementOf> links a <Section> to the <sectionReplaced> that it is replacing. The value for ‘replacementOf.typeCode’ is RPLC (replacement).

5.4.2.4.2 Participation clones

5.4.2.4.2.1 author

<author> links the <Document> to the <Person> and <Organization> involved in authoring the document (through the <AssignedEntity>). The value for ‘author.typeCode’, which is drawn from the *ParticipationType* HL7 vocabulary domain, is AUT.

5.4.2.4.2.2 verifier

<verifier> links the <Document> to the <Person> and <Organization> involved in reviewing the document (through the <AssignedEntity>). The value for ‘verifier.typeCode’, which is drawn from the *ParticipationType* HL7 vocabulary domain, is VRF.

5.4.2.4.2.3 legalAuthenticator

<legalAuthenticator> links the <Document> to the <Person> and <Organization> involved in legally authenticating the document (through the <AssignedEntity>). The value for ‘legalAuthenticator.typeCode’, which is drawn from the *ParticipationType* vocabulary domain, is LA.

5.4.2.4.2.4 subject

<subject> links <ManufacturedProduct> to <Section> or <Observation> (i.e., a manufactured product can be the subject of a document section or an observation). The value for ‘subject.typeCode’, which is drawn from the *ParticipationType* vocabulary domain, is SBJ (subject).

5.4.2.4.2.5 subjectOf

<subjectOf> links <ManufacturedProduct> to a <MonitoringProgramEvent> (i.e., a manufactured product can be the subject of a monitoring program event). This relationship is used to capture the controlled substance classification or schedule (e.g., DEA number in the U.S.).

5.4.2.4.2.6 consumedIn

<consumedIn> links <ManufacturedProduct> to <SubstanceAdmininstration> (i.e., a manufactured product is consumed in a substance administration). This relationship is used to capture the labeled route of administration of the manufactured product, which is in the 'routeCode' attribute of <SubstanceAdministration>.

5.4.3 How the classes fit together

The following table is included to help describe how the RIM-derived classes fit together to create the SPL model and capture the required markup of the product labeling document:

RMIM Class	RMIM Class	Relationship
Document	AssignedEntity	Connected by several Participations (author, verifier, legalAuthenticator) (e.g., an <AssignedEntity> participates in a <Document> in the role of an <author>)
	RelatedDocument	Connected by <relatedDocument> (an ActRelationship)
	documentBodyChoice	One of the two choices in documentBodyChoice (<NonXMLBody> and <StructuredBody>) is a <component> of <Document>
StructuredBody	Section	<Section> is a <component> of <StructuredBody>
Section	sectionReplaced	<Section> is a <replacementOf> <sectionReplaced>
	Section	<Section> can be a <component2> of <Section> (i.e., sections can nest)
	documentBodyEntry	<Observation> or <ObservationMedia> can be a <component1> of <Section>
	AssignedEntity	Connected by the <author> Participation (i.e., an <AssignedEntity> participates in a <Section> in the role of an <author>)
ManufacturedProduct	Section	<ManufacturedProduct> can be the <subject> of a <Section>
	Observation	<ManufacturedProduct> can be the <subject> of an <Observation>
	MonitoringProgramEvent	<ManufacturedProduct> can be the <subject> of a <MonitoringProgramEvent>
	SubstanceAdministration	<ManufacturedProduct> is <consumedIn> a <SubstanceAdministration>

5.5 SPL Hierarchical Description (HD)

The viewable SPL Hierarchical Description is a tabular representation (.xls file) of the sequence of elements (i.e., classes, attributes and associations) derived from the SPL RMIM and that define the SPL standard without reference to the XML Schema implementation (see *6.3.2 Reading a Hierarchical Description* for background information).

The HD is included as a separate file in the SPL ballot package (see PORR_HD050016.xls).

5.6 SPL Schema

The SPL Schema is an XML implementation derived from the SPL Hierarchical Description.

The SPL schema distribution package is included as a separate file in the SPL ballot package.

Technically, SPL is specified by four components:

- SPL Schema
- Schema for SPL narrative block (text)
- The HL7 Version 3 Data Types Schema
- HL7 Version 3 Vocabulary Schema

The schema distribution package contains a number of additional schemas, based on the HL7 decision to include all possible supporting schemas in the schema package for each message type.

For additional background information, see *6.3.3 Reading an XML Schema*.

See also *6.5.2 Mapping between SPL RMIM classes and XML Schema*.

6 Appendices

6.1 Glossary

Note: Terms may have multiple definitions, including:

- Standard dictionary definition
- HL7 definition
- Regulatory definition (U.S. or international)

Where more than one definition for a term is included in this table, each is identified by its source. However, it is understood that there may be other definitions that may apply in other realms in which SPL may be implemented.

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." (http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html)
21CFR201.57	Code of Federal Regulations, Title 21, Federal Food, Drug and Cosmetic Act, Part 201.57, "Specific Requirements on content and format of labeling for human prescription drugs." (http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html)
Act	In HL7, a RIM class that is defined as "a record of something that is being done, has been done, can be done, or is intended or requested to be done"
Active ingredient	1) An active ingredient in a product as described 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 moiety	1) The molecular structure responsible for the physiological or pharmacological action of the drug substance 2) The active moiety as described in regulations
ANSI	American National Standards Institute
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
Association	In HL7, an association defines a relationship between objects. The objects may be instances of two different classes or of the same class (reflexive association). Just as classes have instances, associations have instances too. An association instance is a connection between objects and is defined by an association that connects classes.
Attribute	1) In HL7, a RIM construct that further defines the concept being modeled in a RIM class. [Note that the HL7 ITS, in generating a schema from an RMIM, converts some RIM attributes to XML elements.] 2) In XML, a name-value pair included inside an XML element tag
CDA	Clinical Document Architecture
CDA document	A defined and complete information object that can exist outside of a messaging context and/or can be a payload within an HL7 message. Includes the CDA Header and CDA Body
CDA Level One DTD	The CDA Level One specification, expressed as an XML DTD
Character data	Text in a particular coding (e.g., ASCII) as distinguished from binary data)
Class	In HL7, an abstraction of things or concepts that are subjects of interest in a given application domain. All things or concepts subsumed under a class have the same properties and are subject to and conform to the same rules. Classes are the people, places, roles, things, and events about which information is kept. Classes have a name, description, and sets of attributes, relationships, and states.
Clinical document	A clinical document is a documentation of clinical observations and services, with the

	following characteristics: • Persistence – A clinical document continues to exist in an unaltered state, for a time period defined by local and regulatory requirements. • Stewardship – A clinical document is maintained by a person or organization entrusted with its care. • Potential for authentication – A clinical document is an assemblage of information that is intended to be legally authenticated. • 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. • Human readability – A clinical document is human readable.
Clinical Document Architecture	ANSI/HL7 CDA R1.0-2000. Specification for the structure and semantics of "clinical documents" for the purpose of exchange
Clone	Class cloning is the creation in a new HL7 model (e.g., RMIM) of one or more copies of a base class contained in the source model (RIM). The clone classes may have new extensions added to the base class name in order to assure that they have unique names within the derived model. In order to qualify as a valid clone of a source class, the clone must obey the following rules: • The clone may contain only attributes that are also part of the source class. • The clone may only participate in associations that are valid for the source class. • The cardinality and mandatory constraints for elements in the clone class must be at least as rigid as the constraints for the equivalent elements in the source class. • The vocabulary domains declared for any coded attributes in the clone must be identical to, or a subset of, the domain asserted in the source class, and if the coded attribute is "CNE" the cloned attribute must also be "CNE". • The clone need not include attributes or associations unless they are "Required" or "Mandatory" in the source model, regardless of their cardinality. • The clone may not include attributes or associations that are listed as "Not Permitted" in the source model.
CNE	Coded, No Extensions
Coded, No Extensions	If a vocabulary domain is "Coded, No Extensions" (CNE), the only allowable values for the CDA component are those in the vocabulary domain.
Coded, With Extensions	If a vocabulary domain is "Coded, With Extensions" (CWE), then local codes and other values not in the vocabulary domain can be used if necessary.
Combination product	(1) A product containing two or more individual products (2) Two or more separate products packaged together in a single package or as a unit (3) A product that is packaged separately but is used only with another product
Conformance	A valid document that complies with all of the HL7 rules and constraints
Content of labeling	All text, tables and figures in labeling as described in regulations for a specific product (e.g., 21CFR 201.56 and 201.57 for human prescription drugs, 201.66 for human over-the-counter drugs)
CWE	Coded, With Extensions
Data types	In HL7, data types define the structural format of the data carried in the attribute and influence the set of allowable values an attribute may assume
DEA drug schedule	Drug Enforcement Administration classification of drug substances according to abuse liability, as mandeated by the Controlled Substances Act 1970
Document root	The element in an XML document that contains all other elements; the first element in the document
Drug product	1) A dosage form (for example, tablet, capsule, solution, etc.) that contains an active drug ingredient or placebo 2) A finished dosage form as described in regulations
DTD	Document type definition
Element	A section of text in an XML document delimited by start and end tags; or, in the case of empty elements (elements with no content, only attributes), indicated by an empty tag
Entity	In HL7, a RIM class that is defined as "a physical thing, group of physical things or an

	organization capable of participating in Acts, while in a role”
Established name	1) The official name of a drug substance 2) In U.S 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, then 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 Pharmacopeia and in the Homoeopathic Pharmacopoeia under different official titles, the official title used in the United States Pharmacopeia shall apply unless it is labeled and offered for sale as a homoeopathic drug, in which case the official title used in the Homoeopathic Pharmacopoeia shall apply.
FD&C Act	Food, Drug and Cosmetic Act
FDA	U.S. 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 course grained and a data point would be fine grained.
Harmonization	The formal HL7 process by which changes are made to the RIM and supporting vocabulary domain tables
HD	Hierarchical Description
Health Level Seven	An ANSI-accredited Standards Developing Organization (SDO) operating in the healthcare arena. “Level Seven” refers to the highest level of the 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.
HMD	Hierarchical Message Description
Hierarchical Description	Serialization of subset of RIM objects, attributes, and associations with constraints on usage presented in table form. (Similar to the Hierarchical Message Description [HMD] defined in the 1999 HL7 Message Development Framework [MDF]).
HL7	Health Level Seven. 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 regulations
Ingredient	Any component of a drug product
ITS	Implementation Technology Specification
Label	Written material that is affixed to a container or package
Labeling	All labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article
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	A quantum set of specializations within the CDA
LOINC	Logical Observations, Identifiers, Names, and Codes (http://www.regenstrief.org/loinc/loinc.htm)
Markup	Computer-processable annotations within a multimedia document. In the context of this specification, markup syntax is according to the XML Recommendation
MDF	HL7 Message Development Framework
MIME	Multipurpose Internet Mail Extensions (MIME, RFC 2046)
Normative	Prescribing a norm or standard
Package	Container for holding a product, as described in regulations

Package quantity	The net quantity of contents of a product in package form
Participation	In the HL7 RIM, an association between an Act and a Role with an Entity playing that Role
Player	In HL7 Version 3, an Entity that is playing a Role
Prolog	An XML document structure. “Front matter” consisting of the XML Declaration and a Document Type Declaration
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
Reference Information Model (RIM)	An information model used as the ultimate defining reference for all HL7 standards.
Refined Message Information Model	A derivation of the RIM involving the creation of constrained clones of the base classes in the RIM
Regulated product	A drug product that is subject to regulatory requirements.
RIM	Reference Information Model
RMIM	Refined Message Information Model
Role	In FDA, a category of end use (i.e., reviewer, manager, executive or IT staff). In HL7, a RIM class that is defined as “a competency of the Entity playing the Role as identified, defined, guaranteed, or acknowledged by the Entity that scopes the Role” (i.e., the role that Entities play as they participate in health care Acts)
Scoper	In HL7 Version 3, each Role is "played" by one Entity, called the "player" and is "scoped" by another Entity, called the "scoper". Thus the Role of "patient" may be played by a person and scoped by the provider organization from which the patient will receive services. Similarly, the employer scopes an "employee" role.
Schema	A formal definition of the structure and content of a class of document. (See also W3C Schema)
Semantic	In the context of a technical specification, semantic refers to the meaning of an element as distinct from its syntax. Syntax can change without affecting semantics.
SGML	Standard Generalized Markup Language, ISO 8879:1986(E) as amended and corrected
Shadow	A copy of a previously defined clone in an RMIM that is being re-used in another place in the RMIM
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
Template	In the general sense, a structured collection of data/information that, in total, is of interest to one or more healthcare stakeholders. In HL7 V3, a constraint against a normative HL7 V3 specification (e.g., to restrict to specific value sets, to define test batteries, to specify required internal document documents)
URI	Uniform Resource Indicator
Valid document	A document which meets all of the validity constraints in the XML Specification
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 (http://www.w3.org)
W3C Schema	The three-part schema specification issued by the W3C **XML Schema Part 0: Primer** , W3C Recommendation, 2-May-2001, http://www.w3.org/TR/xmlschema-0/ **XML Schema Part 1: Structures**, W3C Recommendation, 2-May-2001, http://www.w3.org/TR/xmlschema-1/ **XML Schema Part 2: Datatypes**, W3C Recommendation, 2-May-2001,

	http://www.w3.org/TR/xmlschema-2/
Well-formed document	A document which meets all of the well-formedness constraints in the XML Specification
XHTML	XHTML 1.0. A Reformulation of HTML 4 in XML 1.0. W3C Recommendation 26-January-2000, revised 1 August 2002. (http://www.w3.org/TR/xhtml1/)
XML	Extensible Markup Language, specification of the W3C, a formal subset of SGML (http://www.w3.org/TR/REC-xml)
XML declaration	Markup stating that the document is an XML document and stating to which version of the XML specification the document is conformant
XML document	An XML document consists of a prolog, root document element, and other objects. A data object is an XML document if it is well-formed, as defined in the XML specification.
XML schema	See W3C Schema
XSL	Extensible Style Language, a specification of the W3C (www.w3.org/Style/XSL/) An XSL stylesheet specifies the presentation of a class of XML documents by describing how an instance of the class is transformed into an XML document that uses the formatting vocabulary.
XSLT	XSL transformation language, a specification of the W3C (http://www.w3.org/TR/xslt). A language for transforming XML documents into other XML documents.

6.2 Samples

6.2.1 Sample prescription drug labeling document

The following sample U.S. prescription drug labeling document has been used to illustrate the structure and data elements that are captured by means of this version of the SPL specification:

Xalatan®

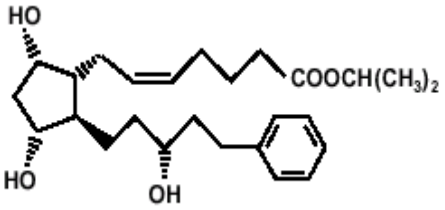
latanoprost ophthalmic solution

0.005% (50 µg/mL)

DESCRIPTION

Latanoprost is a prostaglandin F_{2a} analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is C_{26} H_{40} O_5 and its chemical structure is:

M.W. 432.58



Latanoprost is a colorless to slightly yellow oil that is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol and octanol. It is practically insoluble in water.

XALATAN Sterile Ophthalmic Solution (latanoprost ophthalmic solution) is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsmol/kg. Each mL of XALATAN contains 50 micrograms of latanoprost. Benzalkonium chloride, 0.02% is added as a preservative. The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous and water for injection. One drop contains approximately 1.5 µg of latanoprost.

CLINICAL PHARMACOLOGY

Mechanism of Action

Latanoprost is a prostanoid selective FP receptor agonist that is believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics/Pharmacodynamics

Absorption: Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to the acid form to become biologically active. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.

Distribution: The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost can be measured in aqueous humor during the first 4 hours, and in plasma only during the first hour after local administration.

Metabolism: Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Excretion: The elimination of the acid of latanoprost from human plasma is rapid ($t_{1/2}$ =17 min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose is recovered in the urine after topical and intravenous dosing, respectively.

Animal Studies
In monkeys, latanoprost has been shown to induce increased pigmentation of the iris. The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris, with no proliferative changes observed. The change in iris color may be permanent.

Ocular administration of latanoprost at a dose of 6 µg/eye/day (4 times the daily human dose) to cynomolgus monkeys has also been shown to induce increased palpebral fissure. This effect was reversible upon discontinuation of the drug.

INDICATIONS AND USAGE
XALATAN Sterile Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CLINICAL STUDIES
Patients with mean baseline intraocular pressure of 24 - 25 mmHg who were treated for 6 months in multi-center, randomized, controlled trials demonstrated 6 - 8 mmHg reductions in intraocular pressure. This IOP reduction with XALATAN Sterile Ophthalmic Solution 0.005% dosed once daily was equivalent to the effect of timolol 0.5% dosed twice daily.

A 3-year open-label, prospective safety study with a 2-year extension phase was conducted to evaluate the progression of increased iris pigmentation with continuous use of XALATAN once-daily as adjunctive therapy in 519 patients with open-angle glaucoma. The analysis was based on observed-cases population of the 380 patients who continued in the extension phase.

Results showed that the onset of noticeable increased iris pigmentation occurred within the first year of treatment for the majority of the patients who developed noticeable increased iris pigmentation. Patients continued to show signs of increasing iris pigmentation throughout the five years of the study. Observation of increased iris pigmentation did not affect the incidence, nature or severity of adverse events (other than increased iris pigmentation) recorded in the study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

CONTRAINDICATIONS
Known hypersensitivity to latanoprost, benzalkonium chloride or any other ingredients in this product.

WARNINGS
XALATAN Sterile Ophthalmic Solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes, and growth of eyelashes. Pigmentation is expected to increase as long as XALATAN is administered. After discontinuation of XALATAN, pigmentation of the iris is likely to be permanent while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The effects of increased pigmentation beyond 5 years are not known.

PRECAUTIONS
General: XALATAN Sterile Ophthalmic Solution may gradually increase the pigmentation of the iris. The eye color change is due to increased melanin content in the stromal melanocytes of the iris rather than to an increase in the number of melanocytes. This change may not be noticeable for several months to years (see **WARNINGS**). Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with XALATAN can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant color change may be permanent.

Eyelid skin darkening, which may be reversible, has been reported in association with the use of XALATAN (see **WARNINGS**).

XALATAN may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

XALATAN should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported during treatment with XALATAN. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. XALATAN should be used with caution in patients who do not have an intact posterior capsule or who have known risk factors for macular edema.

There is limited experience with XALATAN in the treatment of angle closure, inflammatory or neovascular glaucoma.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see **PRECAUTIONS,** *Information for Patients*).

Contact lenses should be removed prior to the administration of XALATAN, and may be reinserted 15 minutes after administration (see **PRECAUTIONS,** *Information for Patients*).

Information for Patients (see **WARNINGS** and **PRECAUTIONS**): Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XALATAN.

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XALATAN. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multiple-dose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

Patients should also be advised that XALATAN contains benzalkonium chloride, which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of XALATAN.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Drug Interactions: In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with XALATAN. If such drugs are used they should be administered at least five (5) minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Latanoprost was not mutagenic in bacteria, in mouse lymphoma or in mouse micronucleus tests.

Chromosome aberrations were observed *in vitro* with human lymphocytes.

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 µg/kg/day (approximately 2,800 times the recommended maximum human dose) for up to 20 and 24 months, respectively.

Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.

Pregnancy: Teratogenic Effects: Pregnancy Category C.
Reproduction studies have been performed in rats and rabbits. In rabbits an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XALATAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XALATAN is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Adverse events referred to in other sections of this insert:
Eyelash changes (increased length, thickness, pigmentation, and number of lashes); eyelid skin darkening; intraocular inflammation (iritis/uveitis); iris pigmentation changes; and macular edema, including cystoid macular edema (see **WARNINGS** and **PRECAUTIONS**).

Controlled Clinical Trials:
The ocular adverse events and ocular signs and symptoms reported in 5 to 15% of the patients on XALATAN Sterile Ophthalmic Solution in the three 6-month, multi-center, double-masked, active-controlled trials were blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, and punctate epithelial keratopathy.

Local conjunctival hyperemia was observed; however, less than 1% of the patients treated with XALATAN required discontinuation of therapy because of intolerance to conjunctival hyperemia.

In addition to the above listed ocular events/signs and symptoms, the following were reported in 1 to 4% of the patients: dry eye, excessive tearing, eye pain, lid crusting, lid discomfort/pain, lid edema, lid erythema, and photophobia.

The following events were reported in less than 1% of the patients: conjunctivitis, diplopia and discharge from the eye.

During clinical studies, there were extremely rare reports of the following: retinal artery embolus, retinal detachment, and vitreous hemorrhage from diabetic retinopathy.

The most common systemic adverse events seen with XALATAN were upper respiratory tract infection/cold/flu, which occurred at a rate of approximately 4%. Chest pain/angina pectoris, muscle/joint/back pain, and rash/allergic skin reaction each occurred at a rate of 1 to 2%.

Clinical Practice: The following events have been identified during postmarketing use of XALATAN in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to XALATAN, or a combination of these factors, include: asthma and exacerbation of asthma; corneal edema and erosions; dyspnea; eyelash and vellus hair changes (increased length, thickness, pigmentation, and number); eyelid skin darkening; herpes keratitis; intraocular inflammation (iritis/uveitis); keratitis; macular edema, including cystoid macular edema; misdirected eyelashes sometimes resulting in eye irritation; and toxic epidermal necrolysis.

OVERDOSAGE

Apart from ocular irritation and conjunctival or episcleral hyperemia, the ocular effects of latanoprost administered at high doses are not known. Intravenous administration of large doses of latanoprost in monkeys has been associated with transient bronchoconstriction; however, in 11 patients with bronchial asthma treated with latanoprost, bronchoconstriction was not induced. Intravenous infusion of up to 3 µg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous dosages of 5.5 to 10 µg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea and sweating.

If overdosage with XALATAN Sterile Ophthalmic Solution occurs, treatment should be symptomatic.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop (1.5 µg) in the affected eye(s) once daily in the evening.

The dosage of XALATAN Sterile Ophthalmic Solution should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 3 to 4 hours after administration and the maximum effect is reached after 8 to 12 hours.

XALATAN may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

XALATAN Sterile Ophthalmic Solution is a clear, isotonic, buffered, preserved colorless solution of latanoprost 0.005% (50 µg/mL). It is supplied as a 2.5 mL solution in a 5 mL clear low density polyethylene bottle with a clear low density polyethylene dropper tip, a turquoise high density polyethylene screw cap, and a tamper-evident clear low density polyethylene overcap.

NDC 0013-8303-04

2.5 mL fill, 0.005% (50 µg/mL)

Storage: Protect from light. Store unopened bottle under refrigeration at 2° to 8°C (36° to 46°F). Once opened the 2.5 mL container may be stored at room temperature up to 25°C (77°F) for 6 weeks.

Rx only

U.S. Patent Nos. 4,599,353; 5,296,504 and 5,422,368.

Manufactured for:
Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

By:
Automatic Liquid Packaging, Inc.
Woodstock, IL 60098, USA

Revised December 2002 818 057 204

6.2.2 Sample XML document – prescription drug labeling document

Below is an XML instance showing how the above sample prescription drug labeling document would be marked up to conform to the SPL schema. This XML instance document is also included as a separate file in the SPL Schema package (see SampleLabel.xml in the Files folder).

Note that the attributes that have fixed values in the schema (e.g., determinerCode, typeCode, contextControlCode, contextConductionInd) need not be included in the instance document. The exception is attributes that are Mandatory (e.g., classCode, moodCode), which must be included in the instance document.

```
<?xml version="1.0"?>
<Document xmlns="urn:hl7-org:v3" xmlns:voc="urn:hl7-org:v3/voc"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xsi:schemaLocation="urn:hl7-org:v3
PORR_MT050015.xsd">
   <!-- - - - - - - - - - - - - - - - - - - - - - - - -
  SPL Header
  - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
   <id root="2.16.840.1.113883.3.933.001"/>
   <code code="11488-4" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
   displayName="Human prescription drug label"/>
   <!--Note that there is no <title> element, so no title will be rendered-->
   <effectiveTime value="200212"/>
   <availabilityTime value="200212"/>
   <confidentialityCode code="N" codeSystem="2.16.840.1.113883.5.25"
   codeSystemName="Confidentiality"/>
   <author>
      <time value="20021201"/>
      <assignedEntity>
         <id root="2.16.840.1.113883.3.933.002"/>
         <representedOrganization>
            <name>
            Pharmacia &amp; Upjohn Company, A subsidiary of Pharmacia Corporation
            </name>
            <addr>Kalamazoo, MI 49001, USA</addr>
         </representedOrganization>
      </assignedEntity>
   </author>
   <legalAuthenticator>
      <time value="20021208"/>
      <signatureCode code="S"/>
      <assignedEntity>
         <id root="2.16.840.1.113883.3.933.003"/>
         <assignedPerson>
            <name>
               <given>Sam</given>
               <family>Signer</family>
            </name>
         </assignedPerson>
      </assignedEntity>
   </legalAuthenticator>
   <!-- - - - - - - - - - - - - - - - - - - - - - - - -
  SPL Body
  - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
   <component>
      <documentBodyChoice>
         <StructuredBody>
            <!-- - - - - - - - - - - - - - - - - - - - - - - - -
  Description section
  - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
            <component>
               <section>
                  <id root="2.16.840.1.113883.3.933.004"/>
                  <code code="34089-3" codeSystem="2.16.840.1.113883.6.1"
                  codeSystemName="LOINC" displayName="Description section"/>
                  <title>DESCRIPTION</title>
                  <text>
```

```
    <paragraph>Latanoprost is a prostaglandin F<sub>2a</sub> analogue.
    Its chemical name is isopropyl-(Z)-7[(5R,2R,3R,6S)3,5-dihydroxy-2-[(3R)-
    3-hydroxybutyl-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular
    formula is C<sub>40</sub>26H<sub>40</sub>O<sub>5</sub> and its
    chemical structure is: <renderMultiMedia referencedObject="MM1"/>
    </paragraph>
    <paragraph>>Latanoprost is a colorless to slightly yellow oil that is very
    soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl
    acetate, isopropanol, methanol and octanol. It is practically insoluble
    in water.
</paragraph>
    <paragraph>XALATAN Sterile Ophthalmic Solution (Latanoprost
    ophthalmic solution) is supplied as a sterile, isotonic, buffered aqueous
    solution of latanoprost with a pH of approximately 6.7 and an osmolality of
     approximately 267 mOsmol/kg. Each mL of XALATAN contains 50
     micrograms of latanoprost. Benzalkonium chloride, 0.02% is added as a
     preservative. The inactive ingredients are: sodium chloride, sodium
     dihydrogen phosphate monohydrate, disodium hydrogen phosphate
     anhydrous and water for injection. One drop contains approximately 1.5
     &#xB5;g of latanoprost.
</paragraph>
</text>
<subject>
    <manufacturedProduct>
       <manufacturedLabeledDrug>
          <name>Xalatan</name>
          <formCode code="TBD" displayName="ophthalmic solution"
          codeSystem="1.2.3.4" codeSystemName="FDA"/>
          <activeIngredient>
             <quantity>
                <numerator value="50" unit="micrograms"/>
                <denominator value="1" unit="mL"/>
             </quantity>
             <activeIngredientIngredientEntity>
                <code code="TBD" codeSystem="1.2.3.4"
                codeSystemName="FDA"/>
                <name>latanoprost</name>
                <activeMoiety>
                   <activeMoiety>
                      <code code="TBD" codeSystem="1.2.3.4"
                      codeSystemName="FDA"/>
                      <name>latanoprost</name>
                   </activeMoiety>
                </activeMoiety>
             </activeIngredientIngredientEntity>
          </activeIngredient>
          <playedDrugWithGeneric>
             <genericGenericDrug>
                <code code="TBD"
                codeSystem="2.16.840.1.113883.5.1060"
                codeSystemName="EntityCode"/>
                <name>latanoprost</name>
             </genericGenericDrug>
          </playedDrugWithGeneric>
          <inactiveIngredient>
             <inactiveIngredientIngredientEntity>
                <code code="TBD" codeSystem="1.2.3.4"
                codeSystemName="FDA"/>
                <name>benzalkonium chloride</name>
             </inactiveIngredientIngredientEntity>
          </inactiveIngredient>
          <inactiveIngredient>
             <inactiveIngredientIngredientEntity>
                <code code="TBD" codeSystem="1.2.3.4"
                codeSystemName="FDA"/>
                <name>sodium chloride</name>
             </inactiveIngredientIngredientEntity>
          </inactiveIngredient>
          <inactiveIngredient>
             <inactiveIngredientIngredientEntity>
                <code code="TBD" codeSystem="1.2.3.4"
```

```
                                codeSystemName="FDA"/>
                                <name>
                                sodium dihydrogen phosphate monohydrate
                                </name>
                             </inactiveIngredientIngredientEntity>
                          </inactiveIngredient>
                          <inactiveIngredient>
                             <inactiveIngredientIngredientEntity>
                                <code code="TBD" codeSystem="1.2.3.4"
                                codeSystemName="FDA"/>
                                <name>
                                disodium hydrogen phosphate anhydrous
                                </name>
                             </inactiveIngredientIngredientEntity>
                          </inactiveIngredient>
                          <inactiveIngredient>
                             <inactiveIngredientIngredientEntity>
                                <code code="TBD" codeSystem="1.2.3.4"
                                codeSystemName="FDA"/>
                                <name>water for injection</name>
                             </inactiveIngredientIngredientEntity>
                          </inactiveIngredient>
                       </manufacturedLabeledDrug>
                       <consumedIn>
                          <substanceAdministration>
                             <routeCode code="OPHTHALTA"
                             codeSystem="2.16.840.1.113883.5.112"
                             codeSystemName="RouteOfAdministration"
                             displayName="Ophthalmic"/>
                          </substanceAdministration>
                       </consumedIn>
                    </manufacturedProduct>
                 </subject>
                 <component1>
                    <documentBodyEntry>
                       <ObservationMedia MMID="MM1">
                          <value xsi:type="ED" mediaType="image/jpeg">
                             <reference value="latanoprost_molecular_structure.jpeg"/>
                          </value>
                       </ObservationMedia>
                    </documentBodyEntry>
                 </component1>
              </section>
           </component>
           <!-- - - - - - - - - - - - - - - - - - - - - - - - - - -
 Clinical Pharmacology section
 - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
           <component>
              <section>
                 <id root="2.16.840.1.113883.3.933.005"/>
                 <code code="34090-1" codeSystem="2.16.840.1.113883.6.1"
                 codeSystemName="LOINC" displayName="Clinical Pharmacology section"/>
                 <title>CLINICAL PHARMACOLOGY</title>
                 <component2>
                    <section>
                       <id root="2.16.840.1.113883.3.933.006"/>
                       <title>Mechanism of action</title>
                       <text>
                          <paragraph>Latanoprost is a prostanoid selective RT receptor
                          agaonist that is believed to reduce the intraocular . .
                       </paragraph>
                       </text>
                    </section>
                 </component2>
                 <component2>
                    <section>
                       <id root="2.16.840.1.113883.3.933.007"/>
                       <title>Absorption</title>
                       <text>
                          <paragraph>Latanoprost is absorbed through the cornea where
                          the isopropyl ester . .</paragraph>
```

```
                        </text>
                     </section>
                  </component2>
                  <component2>
                     <section>
                        <id root="2.16.840.1.113883.3.933.008"/>
                        <title>Distribution</title>
                        <text>
                           <paragraph>The distribution volume in humans . .
                        </paragraph>
                        </text>
                     </section>
                  </component2>
                  <component2>
                     <section>
                        <id root="2.16.840.1.113883.3.933.009"/>
                        <title>Metabolism</title>
                        <text>
                           <paragraph>Latanprost, an isopropyl ester prodrug, is
                           hydrolyzed by esterases . .</paragraph>
                        </text>
                     </section>
                  </component2>
                  <component2>
                     <section>
                        <id root="2.16.840.1.113883.3.933.010"/>
                        <title>Excretion</title>
                        <text>
                           <paragraph>The elimination of the acid of latanoprost from
                           human . .</paragraph>
                        </text>
                     </section>
                  </component2>
                  <component2>
                     <section>
                        <id root="2.16.840.1.113883.3.933.011"/>
                        <code code="TBD" codeSystem="2.16.840.1.113883.6.1"
                        codeSystemName="LOINC"
                        displayName="Animal Pharmacology and orToxicology section"/>
                        <title>Animal Studies</title>
                        <text>
                           <paragraph>In monkeys, latanoprost has been shown to
                            induce . .</paragraph>
                           <paragraph>Ocular administration of latanoprost at a dose of . .
                        </paragraph>
                        </text>
                     </section>
                  </component2>
               </section>
            </component>
            <!-- - - - - - - - - - - - - - - - - - - - - - - - - - -
  Indications and Usage section
  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
            <component>
               <section>
                  <id root="2.16.840.1.113883.3.933.012"/>
                  <code code="34067-9" codeSystem="2.16.840.1.113883.6.1"
                  codeSystemName="LOINC" displayName="Indications and Usage section"/>
                  <title>INDICATIONS AND USAGE</title>
                  <text>
                     <paragraph>XALATAN Sterile Ophthalmic Solution is indicated for the
                     reduction of elevated intraocular pressure in patients with open-angle
                     glaucoma or ocular hypertension.
                  </paragraph>
                  </text>
               </section>
            </component>
            <!-- - - - - - - - - - - - - - - - - - - - - - - - - - -
  Clinical Studies section
  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
            <component>
```

```
            <section>
               <id root="2.16.840.1.113883.3.933.013"/>
               <code code="34092-7" codeSystem="2.16.840.1.113883.6.1"
               codeSystemName="LOINC" displayName="Clinical Studies section"/>
               <title>CLINICAL STUDIES</title>
               <text>
                  <paragraph>Patients with mean baseline intraocular pressure of 24-25
                  mmHg . .
               </paragraph>
                  <paragraph>A 3-year open-label, prospective safety study with 2-year
                  extension . .
               </paragraph>
                  <paragraph>Results showed that the onset of noticeable iris
                  pigmentation . .
               </paragraph>
               </text>
            </section>
         </component>
         <!-- - - - - - - - - - - - - - - - - - - - - - - - - -
Contraindications section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
         <component>
            <section>
               <id root="2.16.840.1.113883.3.933.014"/>
               <code code="34070-3" codeSystem="2.16.840.1.113883.6.1"
               codeSystemName="LOINC" displayName="Contraindications section"/>
               <title>CONTRAINDICATIONS</title>
               <text>
                  <paragraph>Known hypersensitivity to latanprost, benzalkonium
                  chloride or any other ingredients in this product.
               </paragraph>
               </text>
            </section>
         </component>
         <!-- - - - - - - - - - - - - - - - - - - - - - - - - -
Warnings section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
         <component>
            <section>
               <id root="2.16.840.1.113883.3.933.015"/>
               <code code="34071-1" codeSystem="2.16.840.1.113883.6.1"
               codeSystemName="LOINC" displayName="Warnings section"/>
               <title>WARNINGS</title>
               <text>
                  <paragraph>XALATAN Sterile Ophthalmic Solution has been reported to
                  cause changes to pigmented tissues. The most frequently reported
                  changes have been . .
               </paragraph>
               </text>
            </section>
         </component>
         <!-- - - - - - - - - - - - - - - - - - - - - - - - - -
General Precautions section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
         <component>
            <section>
               <id root="2.16.840.1.113883.3.933.016"/>
               <code code="34072-9" codeSystem="2.16.840.1.113883.6.1"
               codeSystemName="LOINC" displayName="General Precautions section"/>
               <title>General</title>
               <text>
                  <paragraph>XALATAN Sterile Ophthalmic Solution may gradually
                  decrease the pigmentation of the iris . .
               </paragraph>
                  <paragraph>During clinical trials, the increase in brown iris pigment . .
               </paragraph>
                  <paragraph>Eyelid skin darkening, which may be irreversible, . .
               </paragraph>
                  <paragraph>XALATAN may gradually change eyelashes and vellus
                  hair . .
               </paragraph>
```

```
                    <paragraph>XALATAN should be used with caution in patients with  . .
                </paragraph>
                    <paragraph>Macular edema, including cystoid macular oedema, . .
                </paragraph>
                    <paragraph>There is limited experience with XALATAN. .
                </paragraph>
                    <paragraph>There have been reports of bacterial keratitis . .
                </paragraph>
                    <paragraph>Contact lenses should be removed prior to the
                    administration . .
                </paragraph>
                </text>
            </section>
        </component>
        <!-- - - - - - - - - - - - - - - - - - - - - - - - - - - -
Information for Patients section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
        <component>
            <section>
                <id root="2.16.840.1.113883.3.933.017"/>
                <code code="34076-0" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC" displayName="Information For Patients section"/>
                <title>Information for Patients</title>
                <text>
                    <paragraph>Patients should be advised about the potential for
                     increased brown . .
                </paragraph>
                    <paragraph>Patients should also be informed of the possibility of
                    eyelash . .
                </paragraph>
                    <paragraph>Patients should be instructed to avoid allowing the tip . .
                </paragraph>
                    <paragraph>Patients should also be advised that if they develop
                    an intercurrent . .
                </paragraph>
                    <paragraph>Patients should be advised that if they develop any ocular
                    reactions  . .
                </paragraph>
                    <paragraph>Patients should also be advised that XALATAN contains . .
                </paragraph>
                    <paragraph>If more than one topical ophthalmic drug is being used . .
                </paragraph>
                </text>
            </section>
        </component>
        <!-- - - - - - - - - - - - - - - - - - - - - - - - - - - -
Drug Interactions section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
        <component>
            <section>
                <id root="2.16.840.1.113883.3.933.018"/>
                <code code="34073-7" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC" displayName="Drug Interactions section"/>
                <title>Drug Interactions</title>
                <text>
                    <paragraph>In vitro studies have shown that precipitation occurs when
                    eye drops containing thimerosal are mixed with XALATAN. If such drugs
                    are used they should be administered at least five (5) minutes apart.
                </paragraph>
                </text>
            </section>
        </component>
        <!-- - - - - - - - - - - - - - - - - - - - - - - - - - - -
Carcinogenesis, Mutagenesis, Impairment of Fertility section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
        <component>
            <section>
                <id root="2.16.840.1.113883.3.933.019"/>
                <code code="34083-6" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC"
                displayName="Carcinogenesis and Mutagenesis and Impairment of
```



```
                Fertility section"/>
                <title>Carcinogenesis, Mutagenesis, Impairment of Fertility</title>
                <text>
                   <paragraph>Latanprost was not mutagenic in bacteria, in mouse
                   lymphoma or in mouse micronucleus tests.
                </paragraph>
                   <paragraph>Chromosome aberrations were observed in vitro with
                    human lymphocytes.
                </paragraph>
                   <paragraph>Latanoprost was not carcinogenic . .
                </paragraph>
                   <paragraph>Additional in vitro and in vivo studies on unscheduled
                   DNA synthesis . .
                </paragraph>
                </text>
             </section>
          </component>
          <!-- - - - - - - - - - - - - - - - - - - - - - - - - - -
Teratogenic Effects section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
          <component>
             <section>
                <id root="2.16.840.1.113883.3.933.020"/>
                <code code="34077-8" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC" displayName="Teratogenic Effects section"/>
                <title>Teratogenic Effects</title>
                <text>
                   <paragraph>Pregnancy Category C.
                </paragraph>
                   <paragraph>Reproduction studies have been performed in rats and
                   rabbits. In rabbits an incidence . .
                </paragraph>
                </text>
             </section>
          </component>
          <!-- - - - - - - - - - - - - - - - - - - - - - - - - - -
Nursing Mothers section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
          <component>
             <section>
                <id root="2.16.840.1.113883.3.933.021"/>
                <code code="34080-2" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC" displayName="Nursing Mothers section"/>
                <title>Nursing Mothers</title>
                <text>
                   <paragraph>It is not known whether this drug or its metabolites are
                   excreted in human milk. Because many drugs are excreted in human milk,
                   caution should be exercised when XALATAN is administered to a
                   nursing woman.
                </paragraph>
                </text>
             </section>
          </component>
          <!-- - - - - - - - - - - - - - - - - - - - - - - - - - -
Pediatric Use section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
          <component>
             <section>
                <id root="2.16.840.1.113883.3.933.022"/>
                <code code="34081-0" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC" displayName="Pediatric Use section"/>
                <title>Pediatric Use</title>
                <text>
                   <paragraph>Safety and effectiveness in pediatric patients have not
                   been established.
                </paragraph>
                </text>
             </section>
          </component>
          <!-- - - - - - - - - - - - - - - - - - - - - - - - - - -
Geriatric Use section
```

```xml
- - - - - - - - - - - - - - - - - - - - - - - - - - -->
          <component>
             <section>
                <id root="2.16.840.1.113883.3.933.023"/>
                <code code="34082-8" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC" displayName="Geriatric Use section"/>
                <title>Geriatric Use</title>
                <text>
                   <paragraph>No overall differences in safety or effectiveness have been
                    observed between elderly and younger patients.
                </paragraph>
                </text>
             </section>
          </component>
          <!-- - - - - - - - - - - - - - - - - - - - - - - - -
Adverse Reactions section
- - - - - - - - - - - - - - - - - - - - - - - - - - -->
          <component>
             <section>
                <id root="2.16.840.1.113883.3.933.024"/>
                <code code="34084-4" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC" displayName="Adverse Reactions section"/>
                <title>ADVERSE REACTIONS</title>
                <component2>
                   <section>
                      <id root="2.16.840.1.113883.3.933.025"/>
                      <title>Adverse events referred to in other sections of this insert
                      </title>
                      <text>
                         <paragraph>Eyelash changes (increased length, thickness,
                         pigmentation . .
                      </paragraph>
                      </text>
                   </section>
                </component2>
                <component2>
                   <section>
                      <id root="2.16.840.1.113883.3.933.026"/>
                      <title>Controlled Clinical Trials:</title>
                      <text>
                         <paragraph>The ocular adverse events and ocular signs and
                         symptoms reported in 5 to 15% of the patients . .
                      </paragraph>
                         <paragraph>Local conjunctival hyperemia was observed;
                         however, less than 1% . .
                      </paragraph>
                         <paragraph>In addition to the above listed ocular events/signs
                         and symptoms, the following were reported in 1 to 4% . .
                      </paragraph>
                         <paragraph>The following events were reported in less than 1%
                          of patients: conjunctivitis, diplopia and discharge from the eye.
                      </paragraph>
                         <paragraph>During clinical studies, there were extremely rare
                         reports . .
                      </paragraph>
                         <paragraph>The most common systemic adverse events
                         seen . .
                      </paragraph>
                      </text>
                   </section>
                </component2>
                <component2>
                   <section>
                      <id root="2.16.840.1.113883.3.933.027"/>
                      <title>Clinical Practice</title>
                      <text>
                         <paragraph>The following events have been identified during
                         postmarketing use . .
                      </paragraph>
                      </text>
                   </section>
```

```
                </component2>
             </section>
          </component>
          <!-- - - - - - - - - - - - - - - - - - - - - - - - - -
Controlled Substance section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
          <component>
             <section>
                <id root="2.16.840.1.113883.3.933.028"/>
                <code code="34085-1" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC" displayName="Controlled Substance section"/>
                <!--Note that there is no <title> element, so no title will be rendered-->
                <subject>
                   <manufacturedProduct>
                      <subjectOf>
                         <monitoringProgramEvent>
                            <code code="1" codeSystem="5.4.3.2"
                            codeSystemName="DEADrugSchedule"/>
                            <value/>
                         </monitoringProgramEvent>
                      </subjectOf>
                   </manufacturedProduct>
                </subject>
             </section>
          </component>
          <!-- - - - - - - - - - - - - - - - - - - - - - - - - -
Overdosage section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
          <component>
             <section>
                <id root="2.16.840.1.113883.3.933.029"/>
                <code code="34088-5" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC" displayName="Overdosage section"/>
                <title>OVERDOSAGE</title>
                <text>
                   <paragraph>Apart from ocular irritation and conjunctival or
                   episcleral . .
                </paragraph>
                   <paragraph>If overdosage with XALATAN Sterile Ophthalmic
                   Solution occurs, treatment should be symptomatic.
                </paragraph>
                </text>
             </section>
          </component>
          <!-- - - - - - - - - - - - - - - - - - - - - - - - - -
Dosage and Administration section
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
          <component>
             <section>
                <id root="2.16.840.1.113883.3.933.030"/>
                <code code="34068-7" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC"
                displayName="Dosage and Administration section"/>
                <title>DOSAGE AND ADMINISTRATION</title>
                <text>
                   <paragraph>The recommended dosage is one drop (1.5 &#xB5;g) in the
                   affected eye(s) once daily in the evening.
                </paragraph>
                   <paragraph>The dosage of XALATAN Sterile Ophthalmic Solution should
                   not exceed once daily since it has been shown that more frequent
                   administration may decrease the intraocular pressure lowering effect.
                </paragraph>
                   <paragraph>Reduction of the intraocular pressure starts approximately 3
                   to 4 hours after administration and the maximum effect is reached after 8
                   to 12 hours.
                </paragraph>
                   <paragraph>XALATAN may be used concomitantly with other topical
                   ophthalmic products to lower intraocular pressure. If more than one
                   topical ophthalmic drug is being used, the drugs should be administered at
                    least five (5) minutes apart.
                </paragraph>
```

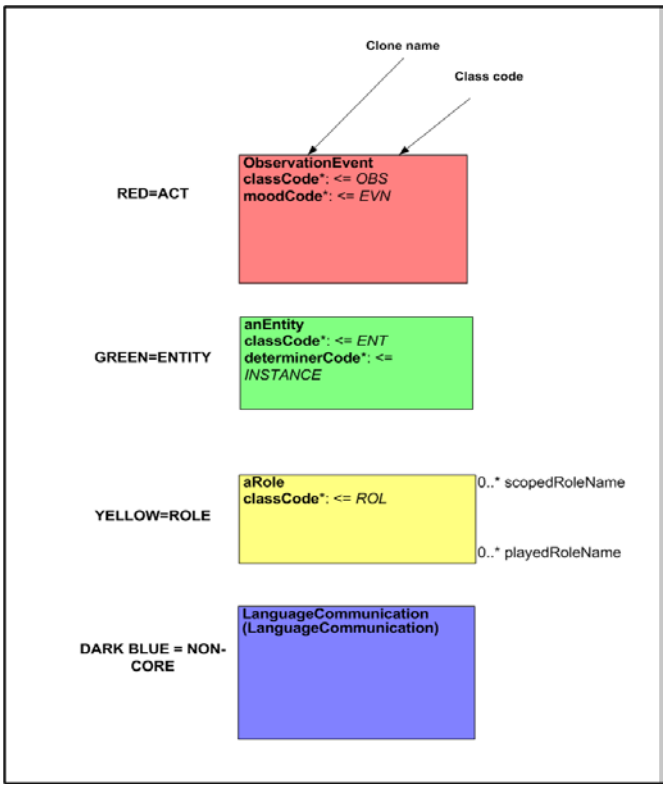
```
                </text>
             </section>
          </component>
          <!-- - - - - - - - - - - - - - - - - - - - - - - - - -
  How Supplied section
  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -->
          <component>
             <section>
                <id root="2.16.840.1.113883.3.933.031"/>
                <code code="34069-5" codeSystem="2.16.840.1.113883.6.1"
                codeSystemName="LOINC" displayName="How Supplied section"/>
                <title>HOW SUPPLIED</title>
                <text>
                   <paragraph>XALATAN Sterile Ophthalmic Solution is a clear, isotonic,
                   buffered, preserved colorless solution of latanoprost 0.005% (50
                   &#xB5;g/mL). It is supplied as a 2.5 mL solution in a 5 mL clear low
                   density polyethylene bottle with a clear low density polyethylene dropper
                   tip, a turquoise high density polyethylene screw cap, and a tamper-
                   evident clear low density polyethyelene overcap.
                </paragraph>
                   <paragraph>NDC 0013-8303-04
                </paragraph>
                   <paragraph>2.5 mL fill, 0.005% (50 &#xB5;g/mL).
                </paragraph>
                   <paragraph>Storage: Protect from light. Store unopened bottle under
                   refrigeration at 2&#xBA;to 8&#xBA;C (36&#xBA;to 46&#xBA;F). Once
                   opened the 2.5 mL container may be stored at room temperature up to 25
                   &#xBA;C (77F&#xBA;) for 6 weeks.
                </paragraph>
                </text>
                <subject>
                   <manufacturedProduct>
                      <manufacturedLabeledDrug>
                         <name>Xalatan</name>
                         <formCode code="TBD" codeSystem="1.2.3.4"
                         codeSystemName="DosageForm"
                         displayName="ophthalmic solution"/>
                         <playedcontainedLabeledDrug>
                            <quantity>
                               <numerator value="2.5" unit="mL"/>
                               <denominator value="1"/>
                            </quantity>
                            <containerPackage>
                               <code code="BOT" codeSystem="4.3.2.1"
                               codeSystemName="PackageType"
                               displayName="Bottle"/>
                               <regulator>
                                  <code code="0013-8303-04"
                                  codeSystem="2.16.840.1.113883.6.69"
                                  codeSystemName="NDC"/>
                               </regulator>
                            </containerPackage>
                         </playedcontainedLabeledDrug>
                      </manufacturedLabeledDrug>
                   </manufacturedProduct>
                </subject>
             </section>
          </component>
       </StructuredBody>
    </documentBodyChoice>
  </component>
</Document>
```

6.3 Introduction to HL7 V3 components used by SPL

For information about HL7 Version 3, go to http://www.hl7.org or contact Health Level Seven. The "HL7 Messaging Components" section of the Version 3 Guide contains detailed information about the makeup, appearance, and interpretation of the RMIM and HD (known as the Hierarchical Message Description [HD] in the ballot).

6.3.1 Reading an RMIM

The following diagram is included that helps to explain how to read a Visio RMIM diagram:



6.3.2 Reading a Hierarchical Description

The following table defines the columns of a Hierarchical Description.

Column	Description
No	Row number. Each row is sequentially numbered and identifies the order in which the data were serialized from the R-MIM.

Element Name	The name of the element as it appears in the R-MIM. This may or may not be the same as the value in Property. This value will be different when a class, association or role is cloned and renamed in the process of creating the R-MIM.
(row type)	Each row represents either a class, an association or an attribute from the R-MIM. Class rows have their name displayed in bold; associations have their name in italics; and attributes have their names in plain font.
Card	Cardinality. This specifies the minimum and maximum number of occurrences of the message element.
Mand	Mandatory. Valid values are M (Mandatory) or Blank. An M in the field requires that some data be sent for this element. If the data is not known, a value of unknown, not given, etc. must be sent. An M in this column (for Mandatory) differs from a 1 in the Cardinality column in that an M indicates that the message cannot be validly parsed without a value in this field or without defining a default. If no default is provided, you either do not send a message or must send a value. An M in this column also differs from an R in the Conformance column (explained below).
RIM Source	Identifies the class from which the attribute or association originates.
Of Message Element Type	This column identifies the data type of attributes or class name of associations.
SRC	Message Element Type Source. Valid values are D (data type), N (new, being defined starting at this row), U (use, meaning that an element, but not its value, from a previous row in the HMD is being reused), C (CMET), I (Instance, refers to the reuse of a particular element and its value as defined previously in the HMD), and R (recursive, into itself).
Domain	Vocabulary Domain Specification. Clicking on this link will take you to the Domain Specification for this element.
Dom is code	A Boolean indicating whether or not the Domain is a single code value
CS	Coding Strength. Valid values are CWE (coded with extensions, meaning that the code set can be expanded to meet local implementation needs) and CNE (coded no extensions, meaning that the code set cannot be expanded).
Conf	Conformance. Valid values are R (required), NP (not permitted), and Blank (not required). A value of R (required) means that the message elements must appear every time the message description is used for an Interaction. If the data is available, the element must carry the data. If the data is not available, a blank may be sent. NP (not permitted) means that the message element is never sent for this message type. Blank means that conformance for this element is to be negotiated on a site-specific basis.
Abstract	Is a boolean assigned to classes or associations in a gen-spec hierarchy, which becomes a choice in an HMD. If the value is true, then this type

	may not appear in message instances.
Nt	Note. If one is provided, this is simply a free text note provided by the committee.
C	Cue. This optional column, when used, provides a brief cue to implementers as to the intent of the field it is listed for.

6.3.3 Reading an XML Schema

The W3C XML Schema specification (http://www.w3.org/XML/Schema) defines the rules governing the creation of the SPL Schema. Because the SPL Schema is derived from the SPL Hierarchical Description, which is derived from the SPL RMIM, it is often helpful to compare the three artifacts to see, for instance, how the formal requirements specified in the hierarchical description manifest in the schema. The process by which an XML Schema is derived from a Hierarchical Description can also be found as part of the V3 guide.

The HL7 XML ITS defines the rules for creation of the SPL Schema from the SPL RMIM, including naming rules for elements and attributes. For information about the XML ITS, go to http://www.hl7.org or contact Health Level Seven. See also *6.5.2 Mapping between SPL RMIM classes and XML* Schema for a table that shows the translation between SPL RMIM class names and SPL Schema element names.

6.3.4 Understanding HL7 V3 Data Types

Detailed information about the data types used in the SPL specification can be obtained from "Data Types – Implementation Technology Specification for XML" (go to http://www.hl7.org or contact Health Level Seven).

An example of the information available in the Data Types ITS is:

Concept Descriptor (CD)

Definition: A concept descriptor represents any kind of concept usually by giving a code defined in a code system. A concept descriptor can contain the original text or phrase that served as the basis of the coding and one or more translations into different coding systems. A concept descriptor can also contain qualifiers to describe, e.g., the concept of a "left foot" as a postcoordinated term built from the primary code "FOOT" and the qualifier "LEFT". In exceptional cases, the concept descriptor need not contain a code but only the original text describing that concept.

Components of Concept Descriptor		
Name	**Type**	**Description**
code	st	The plain code symbol defined by the code system. For example, "784.0" is the code symbol of the ICD-9 code "784.0" for headache.
codeSystem	uid	Specifies the code system that defines the code.
codeSystemName	st	A common name of the coding system.
codeSystemVersion	st	If applicable, a version descriptor defined specifically for the given code system
displayName	st	A name or title for the code, under which the sending system shows the code value to its users.

originalText	ED	The text or phrase used as the basis for the coding.
translation	CD	A set of other concept descriptors that translate this concept descriptor into other code systems.
qualifier	LIST<CR>	Specifies additional codes that increase the specificity of the primary code.

Coded With Equivalents (CE)

Definition: Coded data that consists of a coded value (CV) and, optionally, coded value(s) from other coding systems that identify the same concept. Used when alternative codes may exist.

Property Summary of Coded With Equivalents

Name	Type	Description
code	ST	The plain code symbol defined by the code system. For example, "784.0" is the code symbol of the ICD-9 code "784.0" for headache.
codeSystem	UID	Specifies the code system that defines the code.
codeSystemName	ST	A common name of the coding system.
codeSystemVersion	ST	If applicable, a version descriptor defined specifically for the given code system
displayName	ST	A name or title for the code, under which the sending system shows the code value to its users.
originalText	ED	The text or phrase used as the basis for the coding.
translation	SET<CD>	A set of other concept descriptors that translate this concept descriptor into other code systems.

6.4 LOINC Document Codes and Document Section Codes

LOINC codes can be created for any number of document types or section names by following the standard submission process. These codes can be used in SPL documents as values for ‘Document.code’ or ‘Section.code’ – the code system name is LOINC and the code system identifier is 2.16.840.1.113883.6.1.

The LOINC committee is currently working on an ontology for defining formal names for document section names.

The following table shows the LOINC codes that have been created to date for drug labeling document types and section names:

Table 5. LOINC code values (CWE)

SPL Attribute	LOINC code	Name
Document.code	34391-3	HUMAN PRESCRIPTION DRUG LABEL
Document.code	34390-5	HUMAN OVER-THE-COUNTER DRUG LABEL
Section.code	34066-1	BOXED WARNING SECTION
Section.code	34067-9	INDICATIONS & USAGE SECTION
Section.code	34068-7	DOSAGE & ADMINISTRATION SECTION
Section.code	34069-5	HOW SUPPLIED SECTION
Section.code	34070-3	CONTRAINDICATIONS SECTION
Section.code	34071-1	WARNINGS SECTION
Section.code	34072-9	GENERAL PRECAUTIONS SECTION
Section.code	34073-7	DRUG INTERACTIONS SECTION
Section.code	34074-5	DRUG &OR LABORATORY TEST INTERACTIONS SECTION
Section.code	34075-2	LABORATORY TESTS SECTION
Section.code	34076-0	INFORMATION FOR PATIENTS SECTION
Section.code	34077-8	TERATOGENIC EFFECTS SECTION
Section.code	34078-6	NONTERATOGENIC EFFECTS SECTION
Section.code	34079-4	LABOR & DELIVERY SECTION
Section.code	34080-2	NURSING MOTHERS SECTION
Section.code	34081-0	PEDIATRIC USE SECTION
Section.code	34082-8	GERIATRIC USE SECTION
Section.code	34083-6	CARCINOGENESIS & MUTAGENESIS & IMPAIRMENT OF FERTILITY SECTION
Section.code	34084-4	ADVERSE REACTIONS SECTION
Section.code	34085-1	CONTROLLED SUBSTANCE SECTION
Section.code	34086-9	ABUSE SECTION
Section.code	34087-7	DEPENDENCE SECTION
Section.code	34088-5	OVERDOSAGE SECTION
Section.code	34089-3	DESCRIPTION SECTION
Section.code	34090-1	CLINICAL PHARMACOLOGY SECTION
Section.code	34091-9	ANIMAL PHARMACOLOGY &OR TOXICOLOGY SECTION
Section.code	34092-7	CLINICAL STUDIES SECTION
Section.code	34093-5	REFERENCES SECTION

6.5 Implementation Notes

The following contains background information and explanatory material that can help those implementing the SPL specification.

6.5.1 Mapping between SPL data elements and RMIM

The table below shows how HL7 V3 constructs were incorporated into the RMIM to capture some data element requirements for drug product labeling (see *4.1 Product Labeling Requirements*).

SPL DATA ELEMENTS FOR DRUGS	MAPPING TO SPL RMIM
[Imprint information for solid dosage form]	
Imprint code	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDAIMPRINTCD (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The code included as a free text description is in the 'text' field
Size	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDASIZE (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
Shape	In <Observation>class (an observation about a <ManufacturedProduct>) Code = FDASHAPE (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
Color	In <Observation>class (an observation about a <ManufacturedProduct>) Code = FDACOLOR (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
Coating	In <Observation>class (an observation about a <ManufacturedProduct>) Code = FDACOATING (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
Scoring	In <Observation>class (an observation about a <ManufacturedProduct>) Code = FDASCORING (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
Logo	In <Observation>class (an observation about a <ManufacturedProduct>) Code = FDALOGO (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
[Package(s)]	
NDC	'code' in <RegulatedProduct> (code = the code value; codeSystem = NDC)
Package type	'code' in <Package> class (In the *EntityCode* HL7 vocabulary domain, there is a potential set of values in the *ContainerEntityType* subset)
Package quantity	'quantity' attribute in <containedLabeledDrug> or <containedPackage>
Controlled substance classification or schedule (e.g., DEA number in U.S.)	Free text 'value' in <MonitoringProgramEvent> The 'code' in <MonitoringProgramEvent> is CTLSUB – that may be further constrained to identify a particular controlled substance classification or schedule (e.g., there is a nested value under CTLSUB for DEADrugSchedule)
Proprietary name	'name' in <LabeledDrug>
Active ingredient name(s)	'name' in <IngredientEntity> (playing the role of <ActiveIngredient>)
Active ingredient code(s)	'code in <IngredientEntity> (playing the role of <ActiveIngredient>)
Active moiety code(s)	'code' in <ActiveMoietyEntity>
Strength of active ingredient	'quantity' in <ActiveIngredient>
Dosage form	'formCode' in <LabeledDrug>
Labeled route of administration	'routeCode' in <SubstanceAdministration>
Inactive ingredient name(s)	'name' in <IngredientEntity> (playing the role of <InactiveIngredient>)
Inactive ingredient code(s)	'code in <IngredientEntity> (playing the role of <InactiveIngredient>)
Strength of inactive ingredient	'quantity' in <InactiveIngredient>

6.5.2 Mapping between SPL RMIM classes and XML Schema

The table below shows how SPL RMIM class names are converted to XML element names in the SPL Schema according to the HL7 XML ITS.

RMIM CLASS	XML ELEMENT
Document	Document
author	author
AssignedEntity	assignedEntity
Person	assignedPerson
Organization	representedOrganization
verifier	verifier
legalAuthenticator	legalAuthenticator
relatedDocument (ActRelationship clone)	relatedDocument
RelatedDocument (Act clone)	relatedDocument
component	component
documentBodyChoice	documentBodyChoice
NonXMLBody	NonXMLBody
StructuredBody	StructuredBody
component	component
Section	section
replacementOf	replacementOf
sectionReplaced	priorSectionReplaced
component2	component2
subject	subject
ManufacturedProduct	manufacturedProduct
LabeledDrug	manufacturedLabeledDrug
ActiveIngredient	activeIngredient
IngredientEntity	activeIngredientIngredientEntity or inactiveIngredientIngredientEntity
ActiveMoietyEntity	activeMoiety
DrugWithGeneric	playedDrugWithGeneric
GenericDrug	genericGenericDrug
InactiveIngredient	inactiveIngredient
containedLabeledDrug	playedcontainedLabeledDrug
Package	containerPackage
RegulatedProduct	regulator
Organization	regulatorOrganization
containedPackage	containedPackage and scopedcontainedPackage
subjectOf	subjectOf
MonitoringProgramEvent	monitoringProgramEvent
consumedIn	consumedIn
SubstanceAdministration	substanceAdministration
component1	component1
documentBodyEntry	documentBodyEntry
Observation	Observation
ObservationMedia	ObservationMedia

6.5.3 Validation against the SPL specification

Currently, validation of approved drug product labeling documents typically involves only a manual check of the content of the labeling for completeness and accuracy.

In terms of the standard, a product labeling document is a "valid" XML document if it complies with the constraints expressed in the SPL Schema. (This definition of validity is taken from the W3C XML Recommendation). However validity of an SPL document against SPL Schema does not mean that all HL7 rules and constraints have been met. It is not possible to represent all the constraints of a Hierarchical Description explicitly in an XML schema such that a validating XML processor can determine whether or not they were adhered to. A product labeling document is in "conformance" if it is valid and if it complies with all HL7 rules and constraints. It is expected that additional application logic, above and beyond that found in a validating XML processor, will be required to determine whether or not a product labeling document is in complete conformance with the SPL specification.

Validation of the markup of the document against the SPL specification remains to be developed.

The mechanism for validation of the content of the document by means of the Schema is outside the scope of this specification and will be managed by the regulatory agency reviewing the document.

6.5.4 Validation and conformance to the CDA standard

The SPL specification is not a CDA specification, although it was based on CDA. Therefore, no validation or conformance checking of product labeling documents as CDA documents is possible or necessary.

6.5.5 Transformation Issues

An SPL document may be original markup (meaning that the immediate output of an XML document authoring application is an SPL document), although the SPL Schema is not intended to be an authoring schema. Normally, an SPL document is the result of a mapping or transformation from original markup (where the immediate output of a document authoring application is not an SPL document). Because many organizations have or are actively developing their own internal document markup or metadata, there may be a need to transform documents built against local specifications into documents that conform to the SPL specification for purposes of exchange. No transformation issues have been identified at this time.

The source of the transformation can be represented with the <RelatedDocument>, where the value of the relatedDocument.typeCode is XFRM.

A proper transformation must ensure that the human readable content of the document is not impacted. Local business rules determine whether or not a transformed document replaces the source. If it does, an additional relationship of type "RPLC" is to be used. The "XFRM" relationship can also be used when translating a document in a local format into SPL for the purpose of exchange. In this case, the target of the "XFRM" relationship is the local document identifier.

6.5.6 Content and presentation requirements

The SPL model includes a flat (non-hierarchical) set of optional and extensible document section codes. This was done deliberately because the actual section names, and the relationship between sections, can vary from one document instance to another.

For example, some of the sections within a prescription drug product labeling document and an over-the-counter drug label may be the same but order and nesting of the sections may differ. Approved prescription drug labeling documents tend to have very specific requirements for content and presentation of content, as do over-the-counter

labeling documents. Although fulfillment of these requirements is out of scope for this specification, a number of elements in the specification may facilitate design of potential solutions (including stylesheets or HL7 Templates).

It is possible that the Templates standard currently under development within HL7 will be useful as a mechanism for constraining the content and format of SPL documents. However, no specific requirements or implementation guidelines have been developed at this time. The current specification consists of a single SPL XML Schema; in future, application of one or more of a hierarchical set of HL7 Templates may serve to constrain the richness and flexibility of SPL.

NOTE:

For example, the SPL specification permits the use of document codes and section codes. Thus, it is possible to differentiate a "U.S. Prescription Drug Label" from a "U.S. OTC Drug Label" (or, by the same token, differentiate a “U.S. Prescription Drug Label” from a “UK Prescription Drug Summary of Characteristics”) because the two will have distinct document codes in the document instance. An HL7 Template provides a formal mechanism to say that a particular type of labeling document must contain certain sections, or that a certain section must contain certain observations or other data elements; each type of document may have a template.

HL7 Templates are in a draft state at the time of this writing, therefore no definitive statements can be made regarding the mechanism by which SPL and HL7 Templates will interoperate. There are however, several ways by which SPL can be constrained today - by an approved HL7 mechanism (such as the creation of a derived static model) and/or by the creation of a local implementation guide (which may define constraints using a combination of narrative, constraining vocabulary tables, formal constraint rules, etc).

There is no requirement that SPL must be constrained in order to be used.

6.6 Sample MIME Encapsulation of an SPL Document in an HL7 Version 2.x and Version 3 Message

If there is a desire to send an SPL document in an HL7 Version 2.x or 3 message, it is expected that the mechanism defined for CDA documents (described below) would apply.

CDA recommends that Internet standard RFC 2557 "MIME Encapsulation of Aggregate Documents, such as HTML (MHTML)" (http://www.ietf.org/rfc/rfc2557.txt) be used for sending CDA documents in HL7 V2.x and V3 messages. SPL follows the CDA recommendation.

The following figures show a sample MIME encapsulation of a CDA document in a V2.x message and a V3 message – SPL documents could be treated in the same way:

Figure 3. Example of a CDA document in an MDM message.

```
MSH|...
EVN|...
PID|...
PV1|...
TXA|...
OBX|1|ED|11492-6^History and Physical^LN||
   ^multipart^related^A^
   MIME-Version: 1.0
   Content-Type: multipart/related; boundary="HL7-CDA-boundary";
   type="text/xml"; start="10.12.45567.43"
   Content-Transfer-Encoding: BASE64

   --HL7-CDA-boundary
   Content-Type: text/xml; charset="US-ASCII"
   Content-ID: <10.12.45567.43>

   ... Base 64 of base CDA document, which contains
     ...
     <ObservationMedia>
       <id root="10.23.4567.345"/>
       <value mediaType="image/jpeg>
         <reference value="canned_left_hand_image.jpeg"/>
       </value>
     </ObservationMedia>
     ...

   --HL7-CDA-boundary
   Content-ID: <10.23.4567.345>
   Content-Location: canned_left_hand_image.jpeg
   Content-Type: image/JPEG

   ... Base64 image ...

   --HL7-CDA-boundary--

|...
```

Figure 4. Example of a CDA document in a Version 3 message.

```
<someMessage>
  <Act.Code code="11488-4"
    codeSystem="2.16.840.1.113883.6.1" displayName="Consultation note"/>
  <Act.text type="multipart/related">
MIME-Version: 1.0
Content-Type: multipart/related; boundary="HL7-CDA-boundary";
type="text/xml"; start="10.12.45567.43"
Content-Transfer-Encoding: BASE64

--HL7-CDA-boundary
Content-Type: text/xml; charset="US-ASCII"
Content-ID: &lt;10.12.45567.43>

... Base 64 of of base CDA document, which contains
  ...
  <ObservationMedia>
    <id root="10.23.4567.345"/>
    <value mediaType="image/jpeg>
      <reference value="canned_left_hand_image.jpeg"/>
    </value>
  </ObservationMedia>
  ...

--HL7-CDA-boundary
Content-ID: &lt;10.23.4567.345>
Content-Location: canned_left_hand_image.jpeg
Content-Type: image/JPEG

... Base64 image ...

--HL7-CDA-boundary--

  </Act.text>
</someMessage>
```

6.7 Regulatory Requirements

There are numerous U.S. and international regulations and guidance documents that mandate not only the structure but also the content (including vocabulary and presentation), of product labeling. All organizations involved in the manufacture and distribution of drugs must conform to labeling requirements published in regulations issued by

their relevant governing body. Guidance documents are supporting documents that are written to clarify regulations and suggest approaches, in more specific detail.

Vocabulary used in regulatory documents may be described in regulations and/or guidance. Regulations and guidance are subject to change for many reasons. These may include updating requirements, enhancing harmonization efforts and recommending changes in formats. Additionally, terms may have different definitions in regulation and guidance depending upon the context in which they may be used. As a result, when referring to regulatory vocabularies it is important to consider these requirements. The inclusion of specific definitions for structure, vocabulary or presentation in the SPL specification is problematic when considering the need to use the appropriate regulatory terms for the specific situation. Pointing to a specific vocabulary source (such as the regulations that mandate the names of sections in a drug labeling document) is less than optimal because every change in those regulations would require re-balloting of the standard. Instead, this standard indicates that the relevant regulatory sources for standard vocabulary or codes should be used.

This specification is intended to be a first step in a project for which the ultimate goal is to do detailed modeling of the entire content of product labeling and in future to include a messaging component. The initial goals (to be able to review, store, and disseminate up-to-date drug product labeling) will be met by means of identification of major sections in the label along with specific data elements deemed necessary to support the U.S. FDA labeling data warehouse, all of which have been accomplished with this version of the specification. It is intended that requirements based on regulations in other countries can also be met in future by following the same process of analysis and modeling.

6.7.1 FDA requirements

The U.S. Food and Drug Administration, which initiated and has sponsored development of this standard, has a number of unique requirements for specific document sections and data elements related to regulatory issues and constraints for prescription drug product labeling. In fact, while specific requirements may differ, it is likely that similar issues will be associated with use of this standard in other regulatory environments as well.

The overall statute providing authority to the FDA to ensure the safety and effectiveness of drugs is provided in the Food, Drug, and Cosmetic Act. Regulations are used to enforce the statutory authority conferred by Congress. Regulations are explicit in describing requirements for drug labeling and are codified in the “Code of Federal Regulations, Title 21, Federal Food, Drug and Cosmetic Act” or 21CFR201.56 and 21CFR201.57.

6.7.2 Mapping between FDA requirements and SPL RMIM

The FDA requirements articulated to date will be met by the following constructs in the SPL model:

FDA REQUIREMENTS FOR DRUG PRODUCT LABELING	MAPPING TO SPL RMIM
Boxed warning	‘Section.code’
Indications and usage	‘Section.code’
Dosage and administration	‘Section.code’
How supplied	‘Section.code’
[Imprint information for solid dosage form]	
Imprint code	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDAIMPRINTCD (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The code is included as free text in the ‘text’ field
Size	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDASIZE (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the ‘text’ field
Shape	In <Observation> class (an observation about a <ManufacturedProduct>)

	Code = FDASHAPE (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
Color	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDACOLOR (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
Coating	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDACOATING (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
Scoring	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDASCORING (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
Logo	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDALOGO (In *ActCode* vocabulary domain – in *FDALabelData* subset of *ObservationType*) The description is included as free text in the 'text' field
[Package(s)]	
NDC	'code' in <RegulatedProduct> (code = code value; codeSystem = NDC)
Package type	'code' in <Package> class (In the *EntityCode* HL7 vocabulary domain, there is a set of potential values in the *ContainerEntityType* subset)
Package quantity	'quantity' attribute in <containedLabeledDrug> or <containedPackage>
Contraindications	'Section.code'
Warnings	'Section.code'
General precautions	'Section.code'
Drug interactions	'Section.code'
Drug/laboratory test interactions	'Section.code'
Laboratory tests	'Section.code'
Information for patients	'Section.code'
Teratogenic effects	'Section.code'
Nonteratogenic effects	'Section.code'
Labor and delivery	'Section.code'
Nursing mothers	'Section.code'
Pediatric use	'Section.code'
Geriatric use	'Section.code'
Carcinogenesis, mutagenesis, impairment of fertility	'Section.code'
Adverse reactions	'Section.code'
Controlled substance classification or schedule (e.g., DEA number in U.S.)	Free text 'value' in <MonitoringProgramEvent> The 'code' in <MonitoringProgramEvent> is CTLSUB – that may be further constrained to identify a particular controlled substance classification or schedule (e.g., there is a nested value under CTLSUB for DEADrugSchedule)
Abuse	'Section.code'
Dependence	'Section.code'
Overdosage	'Section.code'
Description	'Section.code'
Proprietary name	'name' in <LabeledDrug>
Active ingredient name(s)	'name' in <IngredientEntity> (playing the role of <ActiveIngredient>)
Active ingredient code(s)	'code in <IngredientEntity> (playing the role of <ActiveIngredient>)
Active moiety code(s)	'code' in <ActiveMoietyEntity>
Strength of active ingredient	'quantity' in <ActiveIngredient>
Dosage form	'formCode' in <LabeledDrug>
Labeled route of administration	'routeCode' in <SubstanceAdministration>
Inactive ingredient name(s)	'name' in <IngredientEntity> (playing the role of <InactiveIngredient>)
Inactive ingredient code(s)	'code in <IngredientEntity> (playing the role of <InactiveIngredient>)
Clinical pharmacology	'Section.code'
Animal pharmacology/toxicology	'Section.code'
Clinical studies	'Section.code'
References	'Section.code'

6.8 References

Clinical Document Architecture (CDA) References

- Alschuler L, Beebe C, Boyer S, Dolin RH (eds.). HL7 Clinical Document Architecture Framework, Release 1.0. ANSI-approved HL7 Standard, Nov 2000. Ann Arbor, Mich.: Health Level Seven, Inc., 2000.
- Dolin RH, Alschuler L, Beebe C, Biron PV, Boyer S, Essin D, Kimber E, Lincoln T, Mattison JE. The HL7 Clinical Document Architecture. J Am Med Inform Assoc. 2001; 8:552-569.

Health Level 7 References [www.hl7.org]

- HL7 Reference Information Model, Version 2.02
- HL7 Messaging Standard, Version 2.4
- HL7 Version 3 Message Development Framework, 1999.
- HL7 Version 3 Standard; Data Type Specification, Schema
- XML Implementation Technology Specification (ITS)

Other data standards references

- Unified Medical Language System, National Library of Medicine. (http://www.nlm.nih.gov/research/umls/umlsmain.html)
- College of American Pathologists Standards for Laboratory Accreditation (http://www.cap.org/apps/docs/laboratory_accreditation/standards/accstandards.html)
- Logical Observations, Identifiers, Names, and Codes (LOINC) (http://www.regenstrief.org/loinc/loinc.htm)

World Wide Web Consortium References [www.w3.org]

- XML Schema Part 1: Structures. W3C Working Draft 6-May-1999 www.w3.org/1999/05/06-xmlschema-1/
- XML Schema Part 2: Datatypes. World Wide Web Consortium Working Draft 06-May-1999. www.w3.org/1999/05/06-xmlschema-2/
- XML Linking Language (XLink). World Wide Web Consortium Working Draft 3-March-1998. www.w3.org/TR/1998/WD-xlink-19980303
- Extensible Markup Language (XML) 1.0. W3C Recommendation 10-February-1998. www.w3.org/TR/1998/REC-xml-19980210.html
- Extensible Stylesheet Language (XSL) www.w3.org/Style/XSL/
- XHTML 1.0. A Reformulation of HTML 4 in XML 1.0. W3C Recommendation 26-January-2000. www.w3.org/TR/xhtml1/

Food and Drug Administration References

- Code of Federal Regulations, Title 21, Federal Food, Drug and Cosmetic Act, Section 201.56, "General Requirements on content and format of labeling for human prescription drugs." (http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html)
- Code of Federal Regulations, Title 21, Federal Food, Drug and Cosmetic Act, Section 201.57, "Specific Requirements on content and format of labeling for human prescription drugs." (http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html)
- Code of Federal Regulations, Title 21, Federal Food, Drug and Cosmetic Act, Section 201.66, "Format and content requirements for over-the-counter (OTC) drug product labeling." (http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html)
- Code of Federal Regulations, Title 21, Federal Food, Drug and Cosmetic Act, Section 610.60 (G), "General Biological Products Standards – Labeling Standards." (http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfrv7_01.html)
- FIPS PUB 186, Digital Signature Standard (DSS), May 19, 1994. (http://www.itl.nist.gov/fipspubs/fip186.htm)

6.9 Acknowledgements

In addition to those listed at the top of this document, the following people and committees have contributed to the development of the Structured Product Labeling (SPL) specification, as well as the Clinical Document Architecture (CDA) on which this specification was based:

We would like to thank U.S. Food and Drug Administration's Center for Drug Evaluation and Research (CDER), Office of Information Management, and Office of Women's Health for the vision and support that made this standard possible.

We would also like to acknowledge the other co-editors of the Clinical Document Architecture – Liora Alschuler, Calvin Beebe, and Fred Behlen – who continue to bring so much dedication and hard work to development of the CDA standard. In addition, the development of the Clinical Document Architecture would not have been possible without the hard work and support of Health Level Seven, volunteers, officers and staff, in particular, the members of the Structured Documents Technical Committee. We would also like to point out the need for a close working relationship between various committees in ensuring the harmony of the various work products generated by HL7. In particular, we gratefully acknowledge the contributions and domain expertise of the Regulatory Clinical Research Information Management (RCRIM) Technical Committee, Medical Records/Information Management Technical Committee, Orders & Observation Technical Committee, Vocabulary Technical Committee, and Medications Special Interest Group.

We thank Pharmacia & Upjohn Company for making the sample label used in this specification available. We would also like to thank the members of the PhRMA SPL Working Group for sharing their insights and experiences in applying the SPL to instances of labeling.