

HL7 Structured Product Labeling

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Editors:

Gunther Schadow
Regenstrief Institute, Indiana University School of Informatics and IU School of Medicine
gschadow@regenstrief.org

Steven Gitterman
Center for Drug Evaluation and Research, U.S. Food and Drug Administration
steven.gitterman@fda.hhs.gov

Release 1 Editors:

Sandy Boyer
Consultant
slboyer@attglobal.net

Robert H. Dolin, M.D.
Kaiser Permanente
Robert.H.Dolin@kp.org

HL7 Steward:

Regulatory Clinical Research Information Management (RCRIM) Technical Committee

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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), 7 and 8 (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 3.10 *Product Labeling Requirements*
- Description of the model (general concepts, components) – see 4
- *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*
- Clinical Product Information Module (Section 6). This is the part of the specification that deals with indications, dosage, contraindications, interactions and other issues regarding the clinical use of the product. This part of the specification is in a separate module at this time because it was added to the SPL specification in release 2.

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).

NOTE: Since SPL is part of the HL7 version 3 suite of specifications it is planned that the SPL specification will be turned into the same publication format in which all other HL7 version 3 specifications exist. Also, there is a significant overlap between the SPL specification and the Clinical Document Architecture (CDA) specification. It is planned to reorganize the material in SPL and CDA such that shared features would have to be specified only once rather than redundantly for SPL and CDA. These reorganizations are planned for the future release 3 of both SPL and CDA.

1.2 Editorial conventions

This specification uses the following notation conventions:

- XML element names are surrounded by angle brackets, use camelCase, with lower case initial (e.g., <effectiveTime>).
- HL7 information model class names (see 5.4.1 *RMIM diagram*) use CamelCase with capital initial and are presently also surrounded by angle brackets. (e.g., <ManufacturedProduct>).
- The names of XML elements are determined by the names of the RMIM attributes and associations, not just from the RMIM class names (although often these are similar.) Therefore the use of angle brackets

¹Although 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.

around information model class names is rather unusual and will be phased out in the future. It is not used in (Section 6), and retained in the other sections only for historic reasons.

- RMIM class names form a component of the names of the XML Schema types but are not visible in the XML document instance.
- When referring to HL7 information model attributes it is done by concatenation of the class name and the attribute name (e.g., 'Act.code'). The RIM attribute names are also often surrounded by single quotation marks (e.g., 'code' or 'Act.code'). (Note that 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 7.1 *Glossary*) are cited in double quotes on first mention within this document. Acronyms are not quoted but are expanded in the glossary.

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*). 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. Limited support for the presentation of content is provided in CDA and has been adopted by SPL (see *4.1.2.2.4 SPL Section Narrative Block*).

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

- Incorporation of revised sections 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.
 4. While SPL is not considered a U.S. specific standard, the pending U.S. FDA Physicians' Labeling Rule (PLR) has been addressed mainly through the additions of the excerpt elements, which can be mounted by a stylesheet into the Highlights section required by the PLR.

3 GENERAL CONCEPTS

3.1 Characteristics of SPL Documents

3.1.1 Relationship of the SPL Specification to the 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 *4.1.1 SPL Header*) and a body (see *4.1.2 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 structured markup (i.e., <nonXMLBody> or <structuredBody> respectively; see *4.1.2.1 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 *4.1.2.2.4 SPL Section Narrative Block*), and any number of data elements (see *4.1.2.3 SPL Body Structures*).

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

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 3.6 “Human Readability” and Rendering SPL Documents and 3.4 SPL Conformance for the principles governing representation of the narrative block, the conformance requirements on the part of senders when populating the block, and requirements for 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 4.1.2.3 SPL Body Structures). The data elements can reference specific text in the narrative block (see 4.1.2.6 Relationship between SPL Narrative Block and SPL Body Structures).

Figure 1. Major components of an SPL document

```
<document>
  <!-- SPL Header -->
  <structuredBody>
    <component>
      <section>
        <text> ... </text>
        <component>
          <observation> ... </observation>
        </component>
      </section>
    </component>
  </structuredBody>
</document>
```

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*.)

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Final Standard.

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 – this is described further below in this section.)
- **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 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 visually determined.

The RMIM classes become XML Schema types. The associations (connections) and attributes of these classes 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 Substance) 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 Medicine. In the HL7 V3 model, this relationship is expressed by saying that the <Medicine> Entity (the product) is the scoper of the role (either <ActiveIngredient> or <InactiveIngredient>) that is played by the <Substance> (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*).

Comment [G1]: These changes reflect the use of new (i.e., changed) names in the RMIM schema. These changes reflect both the omission of confusing terms and name changes to be consistent with the Pharmacy sig medication model.

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 7.3.3 *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 method by which a SPL instance is packaged and exchanged is outside the scope of this standard. We refer to the discussion of requirements and possible solutions in the *Clinical Document Architecture* specification.

For examples, see 7.6 *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 V3 Messaging ITS where possible and where it deviates, will provide a documented rationale.
- **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 be rendered per the rules defined in 4.1.2.2.4 *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 4.1.2.2.4 *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

SPL documents can be revised, either in their entirety or section-by-section. 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 *4.1.2.2.4 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, and should be addressed with commercially available tools 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 used 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. In order to support local extensibility requirements, it is permitted to include additional XML elements and attributes that are not included in the SPL schema. These extensions should not change the meaning of any of the standard data items, and receivers must be able to safely ignore these elements. Document recipients must be able to faithfully render the SPL document while ignoring extensions.

3.8.1 Foreign Namespace extensions

Extensions may be included in the instance in a namespace other than the HL7v3 namespace, but must not be included within an ED datatype (since the contents of an ED datatype within the conformant message may be in a different namespace). Since all conformant content (outside of elements of type ED) is in the HL7 namespace, the

sender can put any extension content into a foreign namespace (any namespace other than the HL7 namespace). Receiving systems must not report an error if such extensions are present.

3.8.2 Extensions in the HL7 namespace

Where there is a requirement to extend a message definition with attributes or associations that could be derived from a valid HL7 refinement of the RIM but which have been excluded from the SPL Schema, the content should be included in the HL7 namespace, but with an "HL7extension" attribute used to indicate that it is an extension. The XML attribute "HL7extension" with non-empty content must be included in any element representing an HL7 class, association, or attribute that is not included in the CDA Schema.

When these extension mechanisms mark up content of general relevance, HL7 encourages users to get their requirements formalized in a subsequent version 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 1. 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 2. 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.

Comment [G2]: Relocated from section 4 .1

3.10 Product Labeling Requirements

3.10.1 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)
- Document-set id (an identifier that remains constant across different revisions of the document.)
- 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.

3.10.2 Section requirements

HL7 structured documents contain sections. Product labeling documents tend to be organized into commonly understood sections (e.g., indications, precautions). 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 also contain images (e.g., the chemical structure of a drug).

3.10.3 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 ingredients (name, code, strength)
- Active moiety (code)
- Inactive ingredients (name, code, strength)
- Labeled route of administration
- Proprietary name (sometimes known as brand name)
- Nonproprietary (generic) name

4 SPL OVERVIEW

4.1 SPL Model

Comment [G3]: Previous section 4.1 moved into section 3

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 *7.5.1 Mapping between SPL data elements and RMIM* for a detailed description of how each of the required drug product data elements has been captured (see *3.10.3 Data element requirements*).

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

4.1.1 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.

4.1.1.1 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.

4.1.1.1.1 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.

4.1.1.1.2 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 globally-unique 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 7.4 *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.

4.1.1.1.3 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 4.1.1.3 *SPL Header Participants* and 4.1.2.2.3 *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>.

4.1.1.1.4 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 overridden. 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.

4.1.1.1.5 Document language

The 'languageCode' specifies the human language of character data in the product labeling document (whether 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*).

4.1.1.2 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.

4.1.1.3 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 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 indication³.

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.

4.1.1.3.1 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>.
- <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.

4.1.1.3.2 Author's Organization

The SPL Header can specify the organization from which the document originates and that is in charge of maintaining the document (e.g., the owner of the marketing authority or a contractor in charge of the labeling), 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.

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.)

4.1.1.3.3 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).

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).

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.

4.1.1.3.4 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.

4.1.2 SPL Body

4.1.2.1 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 SPL XML (e.g., a PDF document.)

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

4.1.2.2 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 <Section> class is a container used to wrap other containers. A <section> element 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.

4.1.2.2.1 SPL Section Attributes

4.1.2.2.1.1 Section classification

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

4.1.2.2.1.2 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 7.4 *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

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.

4.1.2.2.1.3 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.

4.1.2.2.1.4 Section confidentiality

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

4.1.2.2.1.5 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*).

4.1.2.2.2 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.

4.1.2.2.3 SPL Section Participants

4.1.2.2.3.1 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..

4.1.2.2.4 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.

The <section> element derived from the <Section> class contains an optional local identifier (represented as an XML ID attribute) that can serve as the target of a reference.

Comment [G4]: An ID attribute was added to the <section> element explicitly for this purpose.

4.1.2.2.4.1 Content

The SPL <content> element is used to wrap a fragment of the 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 4.1.2.6.2 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 'styleCode' attribute that can be used to indicate the text decoration or emphasis present in the source document. styleCode 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.

Comment [G5]: Note: the <content> element no longer carries the emphasis attribute.

NOTE: The styleCode attribute exists for most elements in SPL Narrative blocks (see Figure 2. Content Model of 'Section.text').

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.

4.1.2.2.4.2 linkHtml

The <linkHtml> element is a generic referencing mechanism. 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 <linkHtml>. 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 4.1.2.2.4.5 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.

4.1.2.2.4.3 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.

4.1.2.2.4.4 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.

4.1.2.2.4.5 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.

Comment [G6]: The <link><linkHtml> construct has been simplified to <link> alone. <linkHtml> also now includes the styleCode attribute.

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 <linkHtml> (see 4.1.2.2.4.2 *linkHtml*).

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 4.1.2.2.4.9 *Caption*) which can also be rendered at the point of reference.

4.1.2.2.4.6 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 (as a <caption> child; see 4.1.2.2.4.9 *Caption*) and an optional styleCode attribute.

4.1.2.2.4.7 List

A <list> is similar to the HTML list. A <list> has an optional caption (see 4.1.2.2.4.9 *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). <list> also carries the optional styleCode attribute. 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 is present must come first before any other character data, and an optional styleCode attribute.

4.1.2.2.4.8 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 3. Changes to the strict XHTML table model in SPL*) by removing formatting tags other than the *styleCode* attribute and by setting the content model of cells to be similar to the contents of other elements in the SPL Narrative Block.

Table 3. Changes to the strict XHTML table model in SPL

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

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

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

change this:
<!ELEMENT th %Flow;>
to this:
<!ELEMENT th (#PCDATA | content | linkHtml | sub | sup | br | footnote | footnoteRef |
localCaptionCode | renderMultiMedia)*>

A complete list of SPL table model elements is listed below in *Figure 2. Content Model of 'Section.text'*.

4.1.2.2.4.9 Caption

The <caption> is a label for a paragraph, list, list item, table, or table cell. It can also be a label for an <observationMedia>; the <renderMultiMedia> element indicates where the multimedia object should be rendered.

A <caption> contains plain text (which may include subscripts, superscripts, <footnote>, and <footnoteref>), and may contain links (see 4.1.2.2.4.2 link). The only rendered text is the plain text within the <caption>, although the optional *styleCode* attribute may be used..

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.

Comment [G7]: The <localCaptionCode> element has been eliminated; see appendix 6/10.

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"  
  styleCode NMTOKENS #IMPLIED>
```



```

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

<!ELEMENT content (#PCDATA | content | link linkHtml | sub | sup | br | footnote |
footnoteRef | renderMultiMedia)*>
<!ATTLIST content
  %textAtts;
  revised (insert | delete) #IMPLIED>

<!ELEMENT linkHtml (#PCDATA | footnote | footnoteRef)* >

<!ATTLIST linkHtml
  name CDATA #IMPLIED [DEPRECATE]
  href CDATA #IMPLIED
  rel CDATA #IMPLIED
  rev CDATA #IMPLIED
  title CDATA #IMPLIED
  %textAtts;>

<!ELEMENT sub (#PCDATA)>

<!ELEMENT sup (#PCDATA)>

<!ELEMENT br EMPTY>

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

<!ELEMENT footnoteRef EMPTY>
<!ATTLIST footnoteRef %textAtts;
  IDREF IDREF #REQUIRED>

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

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

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

<!ELEMENT item (#PCDATA | caption | content | linkHtml | sub | sup | br | footnote |
footnoteRef | 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+>
<!ELEMENT caption (#PCDATA | linkHtml | sub | sup |
footnote | footnoteRef)*>
<!ELEMENT thead (tr)+>
<!ELEMENT tfoot (tr)+>
<!ELEMENT tbody (tr)+>
<!ELEMENT colgroup (col)*>
<!ELEMENT col EMPTY>
<!ELEMENT tr (th | td)+>
<!ELEMENT th (#PCDATA | content | linkHtml | sub | sup | br | footnote |
footnoteRef | renderMultiMedia)*>
<!ELEMENT td (#PCDATA | content | linkHtml | sub | sup | br | footnote |
footnoteRef | renderMultiMedia | paragraph | list)*>

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

<!ATTLIST caption %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;

```

4.1.2.3 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 *3.10 Product Labeling 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.

4.1.2.3.1 Observation

The <Observation> class inserts codes and other observations into SPL documents.

Comment [G8]: Note: <documentBodyEntry> has been eliminated.

The 'classCode' for <Observation> is OBS.

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

At present this class is deprecated in SPL and is maintained for backward compatibility. Use Characteristic instead, which better relates the characteristics with the thing so characterized.

4.1.2.3.2 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 <linkHtml> (see 4.1.2.2.4.2 *linkHtml*). 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 which contains the media data either inline or by reference.

The XML ID attribute on the <observationMedia> element is used by the <renderMultiMedia> element to identify the media to be rendered (see 4.1.2.2.4.5 *renderMultiMedia*).

4.1.2.3.3 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 of the <PackagedMedicine> class. In the SPL schema, <code> is a child of the <containerPackagedMedicine> element, a child of the <medicine><container> elements..

Comment [G9]: Scoping by organization for what was previously the RegulatedProduct doesn't exist in release 2.

Comment [G10]: Note: this is a change from the earlier Release 1 model: the package model, including NDC code, has been altered. See appendix 6.10 for more details.

4.1.2.3.4 Package type

The package type is captured by means of the 'formCode' attribute of the <PackagedMedicine> class; in the SPL schema, the <formCode> element is also a child of the <containerPackagedMedicine> element.

4.1.2.3.5 Package quantity

The package quantity is captured by means of the 'quantity' attribute on the <Content> class. In the SPL schema, the <quantity> element is a child of <container>, itself a child of <medicine>. (For a <part> element, i.e., a component of a multiple component product [e.g., a contraceptive product with estrogens and progestins], quantity is either a child of <part> [if not in a separate subpackage] or a child of container [for a product such as a 'kit' where the components of the kit are in separate packaging within the main package].

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

The controlled substance classification or schedule is captured by means of the 'code' attribute of the <Policy> class where <Policy> is the <subjectOf> a <Medicine>. In the SPL schema, the <policy> element is a child of the <manufacturedProduct><subjectOf> elements. 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.

4.1.2.3.7 Active ingredient

The established name of an active ingredient is captured by means of the 'name' attribute on the <Substance> class in the SPL model when <Substance> is playing the role of <ActiveIngredient>. In the SPL schema,

<activeIngredient> is composed of <quantity> and <substance> children; the <name> element is a child of <substance>.

The code for the active ingredient is captured by means of the 'code' attribute of the <code> child element of the <substance> element.

The strength of the active ingredient is captured by means of the 'quantity' attribute of the <ActiveIngredient> class; in the SPL schema, <quantity> is a child element of the <activeIngredient> element.

4.1.2.3.8 Active moiety

The name of the active moiety of the active ingredient is captured by means of the 'name' attribute on the <ActiveMoietyEntity> class in the SPL model. In the SPL schema, this is represented as the <name> element child of <activeIngredientSubstance><activeMoiety><activeMoiety>. The active moiety code is captured by means of the <code> child element of the same.

4.1.2.3.9 Inactive ingredient

The established name of an inactive ingredient is captured by means of the 'name' attribute on the <Substance> class in the SPL model when the <Substance> is playing the role of <InactiveIngredient>. In the SPL schema, <inactiveIngredient> is composed of <quantity> and <inactiveIngredientSubstance> children; the <name> element is a child of <inactiveIngredientSubstance>.

The code for the inactive ingredient is captured by means of the 'code' attribute of the <code> child element of the <inactiveIngredientSubstance> element.

The strength of the inactive ingredient is captured by means of the 'quantity' attribute of the <InactiveIngredient> class; in the SPL schema, <quantity> is a child element of the <inactiveIngredient> element.

4.1.2.3.10 Labeled route of administration

The 'routeCode' attribute on the <SubstanceAdministration> class is used to capture the labeled route of administration of a drug product; in the SPL schema, 'code' is an attribute of the <routeCode> element, a child of the <manufacturedProduct><consumedIn><substanceAdministration> elements.

4.1.2.3.11 Proprietary name

The proprietary or brand name is captured by means of the 'name' attribute of the <Medicine> class; in the SPL schema, the <name> element is a child of the <manufacturedMedicine> element.

4.1.2.3.12 Generic name

The nonproprietary (generic) name is captured by means of the 'name' attribute on the <GenericDrug> class; in the SPL schema, the generic name is captured as the <name> child of the <manufacturedMedicine><asEntityWithGeneric><genericMedicine> elements.

4.1.2.3.13 PharmaceuticalClass and SpecializedKind

"Generalization" elements to specify a classification to the Medicine, Substance and ActiveMoiety. This is used to specify any or all of (a) cellular/molecular action (e.g., Ca-channel blocker); (b) physiologic action (e.g., vasodilator); and (c) molecular/chemical class (e.g. aminopenicillin).

4.1.2.3.14 Multicomponent Products

Multicomponent products are captured by use of the <Medicine> entities playing the Role of <MedicinePart>. There may be many <MedicineParts> for each <Medicine>; quantity is an optional attribute of <MedicinePart>. The schema for <part> (the element for the <MedicinePart> class) is similar to <manufacturedProduct> with the addition

of the <quantity> child. Multicomponent products such as contraceptives (e.g., separate estrogens and progestins in a single container), can be represented where each drug would be a <part> of the parent contraceptive medicine, and the quantity of each represented in the <quantity> child of <part>. (The quantity of the parent <medicine> would be '1' for a single wheel containing both medications in this example.) For a 'kit' where the multicomponent product is composed of separate containers bundled together (e.g., a box with multiple separate containers, each of which has quantities of a <medicine>), <quantity> of each <part> would represent the number of packages of each <part> and the <container> child of the <medicine> element would contain the quantity of each drug in the separate bundled packages. Appropriate nesting will permit SPL to model the large variety of multicomponent products available.

4.1.2.3.15 Controlled Substance Schedule (DEA Schedule)

Controlled Substance Schedule (e.g., DEA Schedule in the U.S.) is captured as the code attribute of the <Policy> class. In the SPL schema this is represented as a <manufacturedProduct><subjectOf><policy><code>.

4.1.2.3.16 Characteristics (such as imprints, etc.)

For the current version of the SPL specification, the <Characteristic> class is utilized to capture a code-value pair to give any product specification data elements of interest (e.g., imprint information for solid oral dosage form). <Characteristic> is derived from the RIM <Observation> class, hence the 'classCode' for <Characteristic> is OBS. The 'code' has a data type of CE and the 'value' has a data type of ANY, which allows codes or numeric values to be specified. There is also a 'text' field that allows entry of free text describing the characteristics (e.g., a description of the size, shape, color, etc. of a solid oral dosage form).

The vocabulary domain for 'Characteristic.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

In the SPL schema <characteristics> are the <subjectOf> a <manufacturedProduct>, i.e., <manufacturedProduct><subjectOf><characteristic>.

4.1.2.4 Approval Information

A record of the approval of a Medicine (product) or Substance, signifying that a substance or product is approved for the use specified in the SPL data. An Approval can have the following data:

- Approval.id: approval number (which in the U.S. is the New Drug Application (NDA) number)
- Author: the author of the Approval signifies the Territory (country or state) for which approval was granted, with optionally some detail about the approving Agency.
- The date when Approval was granted is specified in the author.time.
- Approval.statusCode, tells whether approval was granted (complete) or whether the approval is presently in progress (active). Thus, a substance or product that is not approved yet but about which an approval is in process and approval number is known can also have the Approval structure but must indicate a status of "active" in the Approval.statusCode. Likewise, a substance or product whose approval has been withdrawn would have a statusCode of "obsolete".

4.1.2.5 Comments

Editorial comments can be added to a section using the <Comment> class. E.g.

<section><subjectOf><comment><text> would contain the free text of the comment. The comment can reference a precise location in the section text using the TextFragmentReference. The following is an example:

```
<section>
...
<text>Pramoxicol SM is <content ID="cmt123">the cure for hair
loss</content>.</text>
...
<subjectOf>
  <comment>
    <text>This is a unfounded hype, you need to strike this</text>
    <statusCode code="active"/>
    <effectiveTime .../>
    <subject>
      <textFragmentReference>
        <text>
          <reference url="#cmt123"/>
        </text>
      </textFragmentReference>
    </subject>
  </comment>
</subjectOf>
...
</section>
```

A comment should be attributed to an <author> but this author is separate from the document author. Even if no specific author is assigned to a Comment, such Comment is not automatically attributed to the document or section author. A Comment is not even considered part of the Section; it only references the Section and can be sent along with a Section but might be stripped from the Section without such stripping being considered an alteration of the Section.

4.1.2.6 Relationship between SPL Narrative Block and SPL Body Structures

4.1.2.6.1 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 7.3.3 *Understanding HL7 V3 Data Types*).

4.1.2.6.2 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 4.1.2.2.4.1 *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 round,<content ID="a1">white</content>, scored tablet.
</paragraph>
</text>
...
<component>
  <section>
    <subject>
      <manufacturedProduct>
        <subjectOf>
          <characteristic classCode="OBS">
            <id root="78AF9883-92D3-4028-8AFB-B00BC8220117"/>
            <code code="FDACOLOR" .../>
            <value xsi:type="CE" code="..." codeSystem="...">
              <originalText>
                <reference value="#a1"/>
              </originalText>
            </value>
          </characteristic>
        </subjectOf>
      </manufacturedProduct>
    </subject>
  </section>
</component>
.....
```

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 exactly inside the section text.

The <renderMultiMedia> element (see 4.1.2.2.4.5 *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.

The ID attribute of <observationMedia> is the target of the <renderMultimedia> referencedObject attribute.

Comment [G11]: The MMID attribute of observationMedia has been replaced by the ID attribute. <observationMedia> has also been altered to the camelCase convention.

Figure 4. Referencing out of the SPL Narrative Block

```
<section>
  <paragraph>Latanoprost is a prostaglandin F<sub>2α</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>H<sub>40</sub>O<sub>5</sub> and its
  chemical structure is:
  <renderMultiMedia referencedObject="MM1"/>
</paragraph>
</section>
<component>
  <observationMedia ID="MM1">
    <id root="4B86F343-92D3-4028-8AFB-B00BC8220117"/>
    <value xsi:type="ED" mediaType="image/jpeg">
      <reference value="latanoprost_molecular_structure.jpeg"/>
    </value>
  </observationMedia>
</component>
</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 documents⁴. 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.

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_MT050024).

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

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”.

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 is preserved, and a hierarchy is created (the Hierarchical Description [HD]).

Using the HL7 XML Implementation Technology Specification (ITS), the HMD is converted to an XML schema. (The HL7 XML ITS is the specification of the common rules for converting any HL7 HMD to XML.) Some additional hand-crafting of the SPL Schema is also necessary.

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 the appendix 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 2.02⁵
- XML Implementation Technology Specification (ITS), HL7 V3, version 1.11
- Visio R-MIM Stencils, version 2.98
- RoseTree, version 2.9.37

Comment [G12]: Need to validate that these values are correct.

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 type⁵. Values of XML attributes of type "IDREF" or "IDREFS" must match the value of an ID attribute on some element within the document.

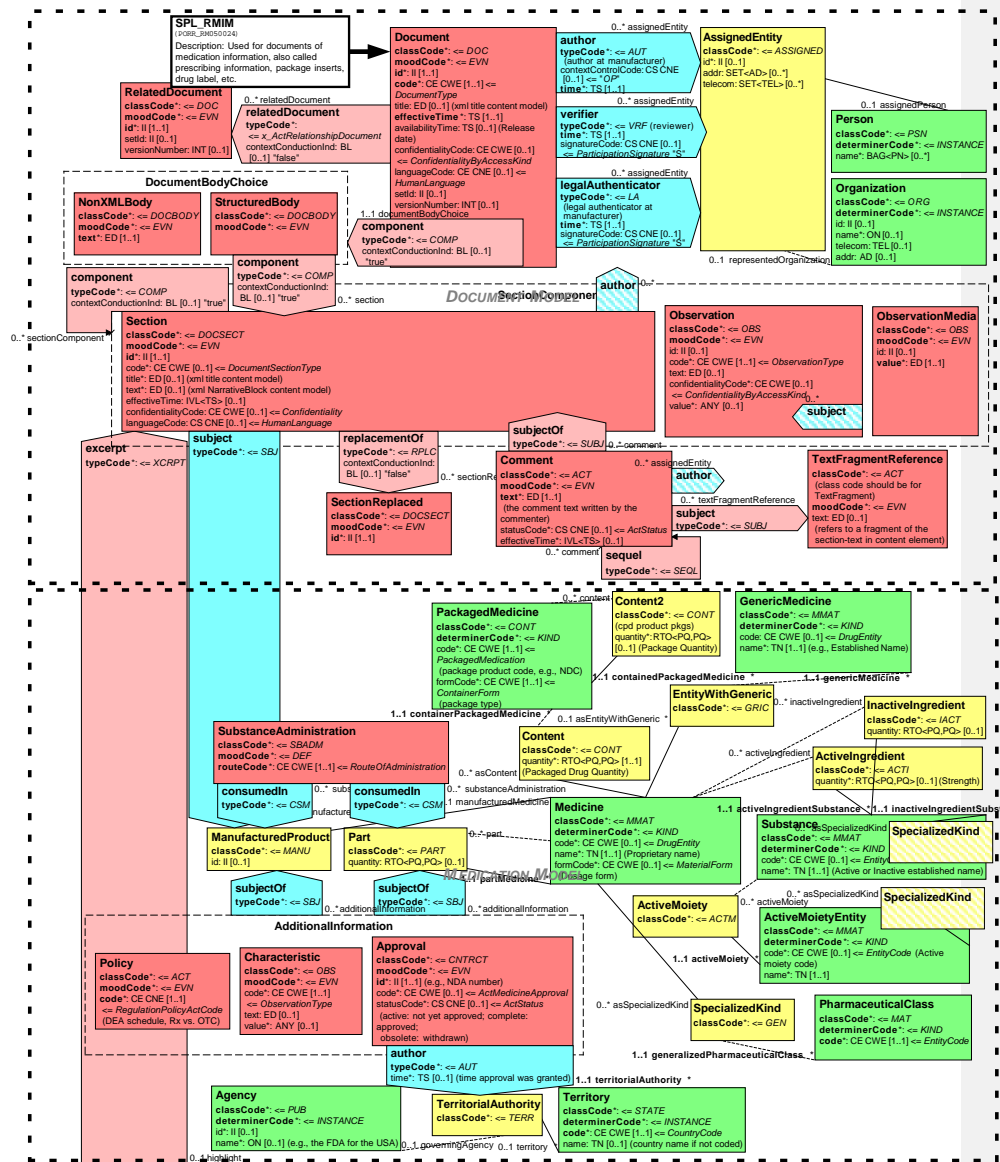
⁵ This document discusses both XML data types and HL7 Version 3 Data Types, Release 1. Unless otherwise qualified, the term "data type" refers to HL7 Version 3 Data Types.

5.4 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_RM050024.gif` and `PORR_RM050024.vsd`).



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 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; however, naming conventions may alter the name to conform to camelCase convention..
- 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> class 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.

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, <Observations>, or <ObservationMedia>.

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 a <component> relationship (an ActRelationship clone). The 'typeCode' for <component> 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> may be a <component> of a <StructuredBody> or a <component> of a section, i.e., contained within a <Section> via a <component> relationship.

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).

<Observation> is included for backward compatibility and is currently deprecated. Use Characteristic instead, which better relates the characteristics with the thing so characterized.

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> may be a <component> of a <StructuredBody> or a <component> of a section, i.e., contained within a <Section> through the <component> relationship.

5.4.2.1.9 Policy

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

Comment [G13]: Replaces monitoringProgramEvent

<Policy> contains a 'classCode' of ACT (from the *ActClass* HL7 vocabulary domain) and a 'moodCode' of EVN (event). The default 'Policy.code' is CTLSUB (from the *ActCode* HL7 vocabulary domain) and 'Policy.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.

5.4.2.1.11 Characteristic

<Characteristics> is designed to capture physical imprinting information of the drug product as the <subjectOf> relationship to a ManufacturedProduct role. Release 1 of SPL captures <characteristics> as <observations>, with the latter now deprecated.

5.4.2.1.12 Comment and TextFragmentReference

The Comment is used to attach editorial comments to a section. The Comment is attributed to a specific author and not attributed to the author of the section. Often the comment authors will be different from the section author. The comment contains the free text, and it can reference a specific fragment in the section text through the TextFragmentReference. The Comment.statusCode can be used to distinguish comments that are open issues (active) from those that had been resolved (complete).

Comments can further be linked (sequel) such that one commenter can respond to another comment. When linking comments, the response to a comment is nested as a <sequel><comment> inside the <comment> element to which it responds.

5.4.2.1.13 Approval

The Approval class is used to specify a record of the Approval of the labeled drug including

- a) Approval.id: approval number (which in the U.S. is the New Drug Application (NDA) number)
- b) Author: the author of the Approval signifies the Territory (country or state) for which approval was granted, with optionally some detail about the approving Agency.
- c) The date when Approval was granted is specified in the author.time.
- d) Approval.statusCode, tells whether approval was granted (complete) or whether the approval is presently in progress (active). Thus, a substance or product that is not approved yet but about which an approval is in process and approval number is known can also have the Approval structure but must indicate a status of "active" in the Approval.statusCode. Likewise, a substance or product whose approval has been withdrawn would have a statusCode of "obsolete".

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.

- 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> 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 <Policy>. <Policy> 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 a <Substance> (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 a <Substance> (shown in the RMIM by a solid line relationship) and scoped by a <Medicine> (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 a <Substance> (shown in the RMIM by a solid line relationship) and scoped by a <Medicine> (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 EntityWithGeneric

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

The <EntityWithGeneric> role is played by a <Medicine> (shown in the RMIM by a solid line relationship) and scoped by a <GenericMedicine> (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 EntityWithGeneric is GRIC.

5.4.2.2.7 SpecializedKind

The <SpecializedKind> role is used to specify a pharmaceutical class of the entity to which they are attached. This can be the class of an ingredient substance or moiety. The so annotated substance or moiety is then considered a "specialization" or "specialized kind" of the generalized pharmaceutical class.

The 'classCode' of SpecializedKind is GEN.

5.4.2.2.8 Content and Content2

These roles are used to capture information about the drug container, drug package quantity, and NDC codes.

- The <Content> role captures information about the number of dosing units (e.g., tablets) in a package (e.g., bottle) and the package (container). The <Content> role is played by a <Medicine> and scoped by a <PackagedMedicine>. (See 3.2.1 *Reference Information Model (RIM)* for an explanation of players and scopers.)
- The <Content2> role is retained for backwards compatibility as it was present in SPL release 1. This would allow specifying sub-containers of a larger container. However, using this method there would be no way to specify the content of those sub-containers. The use case for this has now been addressed with the Part role which is used to show parts of the overall product where each part can have its own packaging.

The 'classCode' of both <Content> and <SubContent> is CONT.

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

5.4.2.2.9 Part

The <Part> role is involved in the capture of information about a component of a multicomponent product. It provides a link between a parent <Medicine> and the detailed information regarding a component of a multicomponent product.

The <Part> role has a participation relationship to a two Act clones :

- A <Part> is consumed in a <SubstanceAdministration>. <SubstanceAdministration> is used to capture the labeled route of administration of a drug product. This is to specify the labeled route specifically for that part.
- A <Part> may be the subject of a specific <Policy>. <Policy> is used to capture the controlled substance classification or schedule of a drug (e.g., DEA number in the U.S.).

The 'classCode' for <Part> is PART.

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> contains 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.

<ActiveMoietyEntity> contains a field for 'name', which is a free text field for the name of the active moiety.

5.4.2.3.4 Substance

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

The 'classCode' of <Substance> is MMAT (manufactured material) and it has a 'determinerCode' of KIND.

'Substance.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.

<Substance> contains a field for 'name', which is a free text field for the “established name” of the ingredient.

5.4.2.3.5 Medicine

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

<Medicine> contains a 'classCode' of MMAT (manufactured material) and a 'determinerCode' of KIND.

The 'Medicine.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”).

<Medicine> contains a field for 'name', which is a free text field for the proprietary name (also sometimes known as the trade name).

'Medicine.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 PackagedMedicine

The purpose of <PackagedMedicine> is to capture the drug as a packaged product, together with the package form (e.g., bottle, box, vial, blisterpack), quantity, and packaged product code (e.g., NDC code in the U.S.). <PackagedMedicine>.

<PackagedMedicine> contains a 'classCode' of CONT (container) and a 'determinerCode' of KIND.

The 'PackagedMedicine.formCode' captures the package type and may be drawn from the *MaterialForm* sub-domain of the *EntityCode* vocabulary domain. 'PackagedMedicine.formCode' may also be drawn from a standard external vocabulary of package type codes.

PackagedMedicine.code captures a code that specifies the medicine at a particular quantity in its package. In the U.S. this is the NDC.

The quantity in the package is numerically represented in the <Content> role.

5.4.2.3.7 GenericDrug

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

<GenericMedicine> contains a 'classCode' of MMAT (manufactured material) and a 'determinerCode' of KIND.

The 'GenericMedicine.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").

<GenericMedicine> also contains a field for 'name', which is a free text field for the "established name".

5.4.2.3.8 PharmaceuticalClass

The purpose of <PharmaceuticalClass> is to capture classifications of the medicine, these can be chemical classifications or classifications by mechanism of action.

The 'classCode' of is MAT (material) and a 'determinerCode' of KIND.

The 'PharmaceuticalClass.code' is drawn from the *EntityCode* vocabulary domain and would be populated with an external vocabulary for such pharmaceutical classes.

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>, <Observation>, and <ObservationMedia>. The value for 'component.typeCode' is COMP (component).

Comment [G14]: Note: <component1> and <component2> are removed in SPL release 2.

5.4.2.4.1.3 replacementOf

<replacementOf> links a <Section> to the <sectionReplaced> that it is replacing. The value for 'replacementOf.typeCode' is REPLC (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 <Policy> (i.e., a manufactured product can be the subject of a policy) and/or <Characteristics>. This relationship is used to capture the controlled substance classification or schedule (e.g., DEA number in the U.S.) and the imprinting characteristics (e.g., color) of a solid dosage form.

5.4.2.4.2.6 consumedIn

<consumedIn> links <ManufacturedProduct> to <SubstanceAdministration> (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>.

5.5 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 *7.3.1 Reading a Hierarchical Description* for background information).

The HD is included as a separate file in the SPL ballot package (see PORR_HD050024.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 *7.3.2 Reading an XML Schema*.

6 CLINICAL PRODUCT INFORMATION MODULE

6.1 Introduction

This section specifies extensions to SPL that add structured product information that is relevant for safe and effective use of a drug. These clinical product information extensions will be labeled SPL “level 2” whereas the previously defined information model will be referred to as SPL “level 1”. Level 2 is designed as an extension to Level 1 that adds new features at very few connection-points.

6.1.1 Scope

The scope of further SPL development at this time is set by the U.S. Food and Drug Administration (FDA) in its mission to support existing and future drug labeling and drug listing regulations in the U.S. The most important scope-setter for major current SPL development is the so called “Physicians’ Labeling Rule,” that was announced as NPRM in 2000 and for which the release of the final rule is now imminent.

This scope is outlined by the following list of data requirements that are being addressed.

- 1) Drug Interaction
 - a) highlight text
 - b) other drug or class interacting
 - c) consequence
 - d) special population
- 2) Food Interaction
 - a) highlight text
 - b) food or meal interacting
 - c) consequence
 - d) special population
- 3) Laboratory Test Interaction
 - a) highlight text
 - b) laboratory test interacting
 - c) consequence
 - d) special population
- 4) Adverse Event
 - a) highlight text
 - b) (*does not apply*)
 - c) consequence
 - d) special population
- 5) Indication
 - a) indication name
 - b) limitations
 - c) pharmacologic class (e.g. antihypertensive)
- 6) Dosing
 - a) initiation dose
 - b) usual daily dose
 - c) do not exceed dose
- 7) Monitoring

- a) which tests to run, how frequent
- b) criteria for test results

8) Mechanism of Action

- cellular/molecular action (e.g., Ca-channel blocker)
- physiologic action (e.g., vasodilator)
- molecular/chemical class (e.g. aminopenicillin)

10) Miscellaneous

- Adverse Event contact Phone Number
- Initial approval date of the molecular compound
- Approval number and country of approval for the product

These data items have been initiated by the FDA but have since their inception been discussed and refined during meetings of the International Committee for Harmonization (ICH) of medicinal product regulations. This specification is not intentionally limited to U.S. FDA needs but has considered the input from the all international interested parties as they had been brought forward through the steward committee of HL7, through other HL7 committees (e.g., Pharmacy SIG in the Orders & Observations TC), or through any other channel available.

NOTE: These data elements do not intend to completely represent the entire content of the label. The data elements do not encode all detail and nuances of the label. They only represent the highlights in such a way as to allow computers to index, refer to, and link information between different labels and between labels and patient medical record data. This is done to make the label information more accessible to the physician. If any information of the text is not encoded, this does not imply that this information could be ignored, it simply means that it would not be indexed in the same manner.

6.2 Specification

The technical specification focuses on the information model from which the XML representations are derived. The XML Schema that includes all level 1 and level 2 material is distributed separately as the file "PORR_MT050024.xsd". According to general HL7 practice, while the XML format intended by the schema is normative, the detail of *how* the schema achieves these intentions and therefore the schema itself is not normative.

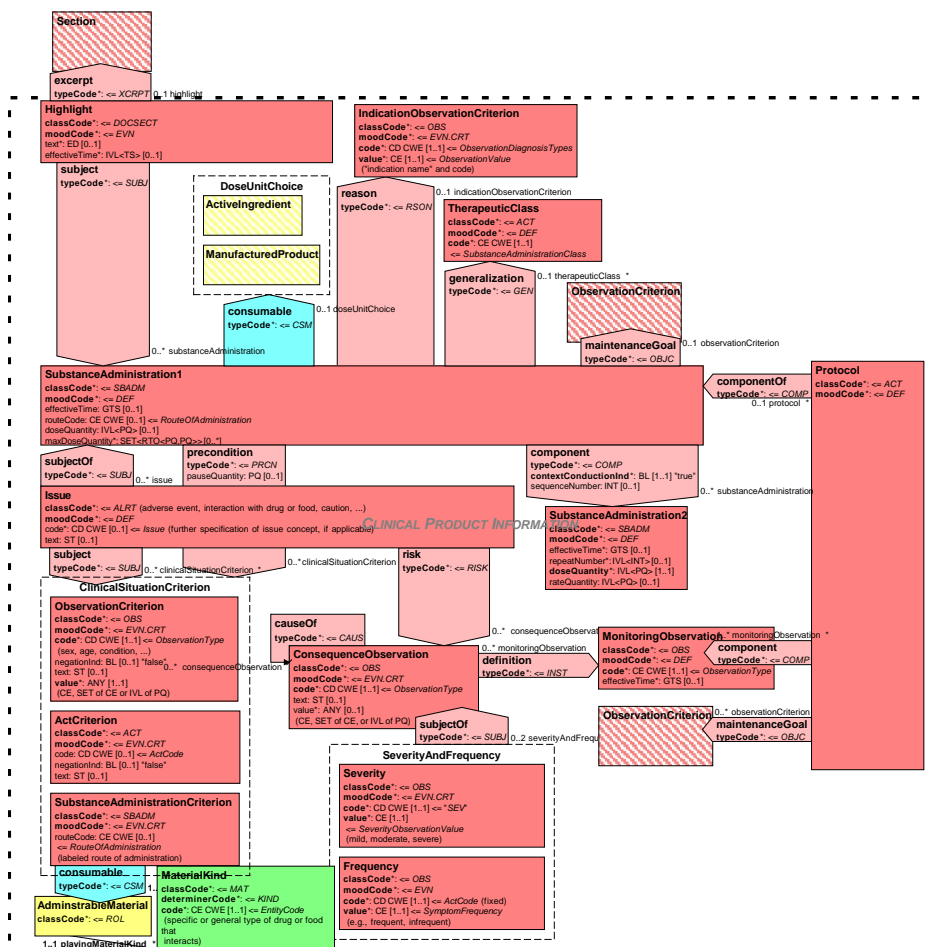
For conformance, producers of SPL documents must produce documents that are valid against this schema, and consumers of these documents only need to expect documents that conform to this schema, however, neither party is required to use this schema while operating on SPL documents.

6.2.1 Refined Information Model (RMIM)

The following release 2 data elements have been built into the model and schema specified in the previous sections. These are the Mechanism of Action and the Approval data.

This section defines the clinical product information. This clinical product information is added through the medium of "Highlights". A Highlight is an abstract or excerpt of a single topic discussed in a single section or subsection. This abstract is presented in the form of a short text fragment as well as with structured information.

The following RMIM diagram is a continuation of the RMIM diagram shown in the previous section. It connects with the excerpt act relationship to the Section class leading into the Highlight class.



6.2.1.1 Highlight

A Highlight is an abstract or excerpt of a single topic discussed in a single section or sub-section. This abstract is presented in the form of a short text fragment as well as with structured information. The highlights are targeted at prescribers and judiciously chosen to present the most important information the prescriber needs to know in order to prescribe a medicine safely and effectively.

The Highlights can be assembled to form a short abstract of the comprehensive prescribing information as a “quick reference” to the prescriber.

All structured information to specify the clinical use of the drug is connected through the highlights element. This is done mostly because the highlights provide a good criterion to focus on the important detail when preparing the structured information. It also facilitates review of the structured information for correctness.

The following information model shows an overview of all defined information structures connected through the Highlights. It covers the following general topics:

- Indications
- Dosage and Administration
- Monitoring
- Adverse Events, Indications, Contraindications and other Cautions or Warnings.

In short anything that describes the proper usage of the drug. Since this module is all about appropriate and safe use of the drug, the use of the drug, i.e., the central SubstanceAdministration is the entry of all structured data of the highlights. This SubstanceAdministration is a **definition** and defines the key data of a proper use of the medicine.

Rather than describing all attributes and classes in topologic order, the specification is organized into thematic areas. The following is an overview of the topics and how this information model addresses these topics:

6.2.1.2 Indication

6.2.1.2.1 IndicationObservationCriterion

An observation criterion that is specified as the “reason” (ActRelationship) of the SubstanceAdministration. The observation criterion consists of a code to indicate that the observation is a diagnoses, symptoms, conditions, etc. and a value-code to represent the specific indication, e.g. hypertension, etc.

The classCode of the reason ActRelationship can be further refined to indicate different motivations, such as “mitigating therapy”, “palliative therapy” or “adjunct therapy”. Also it can specify whether this is a first or second line therapy.

6.2.1.2.2 Precondition and ClinicalSituationCriterion

The ClinicalSituationCriterion is a choice of either ObservationCriterion, SubstanceAdministrationCriterion or general ActCriterion. This is used to describe certain clinical situations as either preconditions or as situations that would be of concern when using the drugs (see Issue below.) When used as a precondition, the ClinicalSituationCriteria further limit the indication to a specific population or other clinical situation.

The ObservationCriterion is similar to the IndicationObservationCriterion with a code and a value, but the value can express both coded and quantitative data types for clinical conditions as well as, for instance, age ranges. The clinical situation criteria can be stated positively as requirements (e.g. patient over 12 years of age) or negatively as limitations or exclusion criteria (e.g., **not** for patient under 12 years of age.)

The SubstanceAdministrationCriterion is used if the indication is for adjunctive treatment for use with patients who undergo another treatment specified in the SubstanceAdministrationCriterion.

The ActCriterion is a general criterion to give a procedure code or a code of any other clinical service that would be used to limit either positively or negatively the indication of the drug.

The “precondition” act relationship links ClinicalSituationCriteria are linked with the main SubstanceAdministration. That way multiple preconditions can be specified. When multiple criteria are specified, they are logically conjoined (AND), i.e., they must all hold true.

The precondition has a pauseQuantity attribute which is used to specify a certain time constraint between the clinical situation and the use of the drug. I.e., use “15 minutes before exercise” or “X should be given at least 8 hours after Y”.

6.2.1.2.3 TreatmentClass

The treatment class allows to give a code that classifies the intent of the treatment, i.e., “antihypertensive”. These classifications are sometimes considered properties of the substance and in that case are specified as the classifying

codes (generalization) of the substance or product. However, some substances have multiple purposes, and it is that purpose that eventually determines the proper dosage. This is sometimes known as indication “grouping”.

Note: Two mechanisms are specified to represent grouping or classifications of the drug substances on the one hand and their use on the other hand. Pharmacologic class (e.g., aminopenicillin, aminoglycosides, etc.) or mechanism of action (e.g., MAO inhibitor, ACE inhibitor, Ca-channel blocker, beta-2-blocker, etc.) is a classification of drug substances, either of drug products, their active ingredients or active moiety, and all represented by generalization Roles to a PharmaceuticalClass. Classification of treatment intent (e.g., antihypertensive, antiphlogistic, antiinfective, etc.) are classifications of the SubstanceAdministration act, and represented as a generalization of the treatment act through the “generalization” ActRelationship to TreatmentClass.

6.2.1.2.4 MaintenanceGoal and ObservationCriterion

The indication can be further specified to express an objective as to what the treatment should be. For instance, if the goal of the treatment is absence of acute asthma attacks, the maintenance goal can describe this. This is used to allow the treatment effect to be coded and still keep the indication a simple code that is comparable with actual patient problem list data. For instance, the indication would be “asthma” and the maintenance goal would be “no bronchospasm” to indicate “prevention of bronchospasm in patients with asthma”.

6.2.1.3 Dosing

Dosage amount is specified in the SubstanceAdministration.doseQuantity attribute. A “do not exceed” dose is specified as the SubstanceAdministration.maxDoseQuantity attribute (maximum amount per any time interval, e.g., 4 g in any 24-hour period).

If dosage regimens should vary, this can be specified by component SubstanceAdministrations. In that case, the main SubstanceAdministration **must not** have a doseQuantity of itself, and instead the subordinate component SubstanceAdministration would carry the doseQuantity for each different dose. This is used for example, to specify a loading dose, or a tapering dose.

A regimen with a loading dose is specified using two components, the first representing the initial dose, with repeatNumber = 1 (meaning “once”) or any other limitation in number or time. That first component would be followed by a second component that can repeat for the rest of the duration of the therapy.

For tapering doses, the first component would represent the duration of the therapy and the second (or following) components specify the tapering-off scheme.

Timing patterns (e.g., twice a day, every 8 hours, etc.) and timing boundaries (e.g., for 10 days) can be specified for the main SubstanceAdministration and its component SubstanceAdministration.

In addition, SubstanceAdministration.effectiveTime can give general timing constraints, such as, “give 1 hour before meal”. However, more specific clinical situations in which to give the medicine (e.g., 15 minutes before exercise or before sexual intercourse, etc.) must be specified using preconditions to a ClinicalSituationCriterion.

6.2.1.4 Monitoring

Monitoring is understood as observations (tests) required to embed the SubstanceAdministration in a Protocol of safe and effective treatment. This Protocol contains MonitoringObservation steps and maintenance goals as MonitoringObservationCriteria.

MonitoringObservation steps prescribe the tests that should be performed and in what frequency.

MonitoringObservation.code detailing the tests that should be performed (e.g. thrombocytes count, liver enzymes, etc.) The MonitoringObservation.effectiveTime is used to specify the recommended frequency of these tests in the same way as the frequency of SubstanceAdministration is specified.

MonitoringObservationCriteria specify the boundaries within which certain test results should remain, such as blood levels of the drug or its metabolites should remain to ensure efficacy and avoid toxicity. **MonitoringObservation.code** specifies the observations that would be performed (e.g. digoxin level, gentamicin level, etc.) and the **MonitoringObservation.value** specifies a result-value interval with single bounds (e.g. maximal limits) or two bounds (range) that should be maintained throughout the treatment

6.2.1.5 Adverse Events, Contraindications, Interactions and other Issues

Adverse events, interactions, contraindications and other issues of special caution are represented in one uniform structure. The Pharmacy SIG has established a special kind of Act, called Issue for this purpose. An Issue has one or more other Acts as subjects and indicate that there is a certain problem requiring special caution with its subject Acts. In the case of SPL, the subject is the SubstanceAdministration described in the label. One or more additional subjects can be used to specify additional ClinicalSituationCriteria such as ObservationCriteria or SubstanceAdministrationCriteria. The latter is used to represent interactions which is an Issue involving the administration of two substances.

An Issue should specify a risk, as a coded ConsequenceObservation criterion with information about severity and frequency of the undesired outcome. The description of the risk can nest to refine to a level of specificity that makes the adverse event actually recognizable. For example, a risk may be specified as a "hypersensitivity syndrome" but then specific manifestations may be given including "rash," or "Guillain-Barré Syndrome", or even quantitative measures as "leukopenia with WBC below 1000/mm³."

MonitoringObservations can be linked with Issues by the fact that the MonitoringObservation is the same as one of the ConsequenceObservation. For example, if the risk is Leukopenia with WBC below 1000/mm³, then the MonitoringObservation of WBC will thus be linked to the Leukopenia adverse event.

7 APPENDICES

7.1 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

	<p>following characteristics:</p> <ul style="list-style-type: none"> • 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	<p>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.</p> <p>In order to qualify as a valid clone of a source class, the clone must obey the following rules:</p> <ul style="list-style-type: none"> • 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	<p>(1) A product containing two or more individual products</p> <p>(2) Two or more separate products packaged together in a single package or as a unit</p> <p>(3) A product that is packaged separately but is used only with another product</p>
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 mandated 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	<p>1) A dosage form (for example, tablet, capsule, solution, etc.) that contains an active drug ingredient or placebo</p> <p>2) A finished dosage form as described in regulations</p>
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.

7.2 Samples

7.2.1 Sample prescription drug labeling document

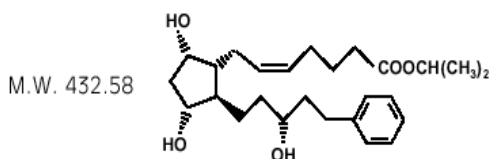
The following sample U.S. prescription drug labeling document has been used to illustrate the structure and data elements that are captured by means of this version of the SPL specification:

Xalatan[®]
latanoprost ophthalmic solution

0.005% (50 µg/mL)

DESCRIPTION

Latanoprost is a prostaglandin F_{2α} 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 C₂₆H₄₀O₅ and its chemical structure is:



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 μ g/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

HL7 Structured Product Labeling, Release 2
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Final Standard.

7.2.2 Sample SPL Level 1 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 xalatan.xml in the Files folder).

```
<?xml version="1.0" encoding="ASCII"?>
<?xml-stylesheet href="spl.xml" type="text/xml"?>
<document xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xmlns:splx="urn:hl7-org:splx" xmlns:voc="urn:hl7-
org:v3/voc" xmlns="urn:hl7-org:v3">
  <id root="6e5f7f24-421c-11d9-885e-359253aa2240"/>
  <code code="34391-3" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC" displayName="Human
prescription drug label"/>
  <title>Xalatan
latanoprost ophthalmic solution
```

```
EXAMPLE DOCUMENT -...</title>
  <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="6e641305-421c-11d9-885e-359253aa2240"/>
      <representedOrganization>
        <name>
          Pharmacia & Upjohn Company, A subsidiary of Pharmacia...</name>
        <addr>Kalamazoo, MI 49001,...</addr>
      </representedOrganization>
    </assignedEntity>
  </author>
  <legalAuthenticator>
    <time value="20021208"/>
    <signatureCode code="S"/>
    <assignedEntity>
      <id root="6e6599a6-421c-11d9-885e-359253aa2240"/>
      <assignedPerson>
        <name>
          <given>Sam...</given>
          <family>Signer...</family>
        </name>
      </assignedPerson>
    </assignedEntity>
  </legalAuthenticator>
  <component>
    <structuredBody>
      <component>
        <section>
          <id root="6e6599a7-421c-11d9-885e-359253aa2240"/>
          <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...<sub>2a...</sub> analogue.
            Its chemical name is...<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...</paragraph>
          <paragraph>XALATAN Sterile Ophthalmic Solution (Latanoprost...</paragraph>
        </text>
        <subject>
          <manufacturedProduct>
            <manufacturedMedicine>
```

```

<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>
  <activeIngredientSubstance>
    <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>
  </activeIngredientSubstance>
</activeIngredient>
<asEntityWithGeneric>
  <genericMedicine>
    <code code="TBD" codeSystem="2.16.840.1.113883.5.1060"
codeSystemName="EntityCode"/>
    <name>latanoprost...</name>
  </genericMedicine>
</asEntityWithGeneric>
<inactiveIngredient>
  <inactiveIngredientSubstance>
    <code code="TBD" codeSystem="1.2.3.4" codeSystemName="FDA"/>
    <name>benzalkonium...</name>
  </inactiveIngredientSubstance>
</inactiveIngredient>
<inactiveIngredient>
  <inactiveIngredientSubstance>
    <code code="TBD" codeSystem="1.2.3.4" codeSystemName="FDA"/>
    <name>sodium...</name>
  </inactiveIngredientSubstance>
</inactiveIngredient>
<inactiveIngredient>
  <inactiveIngredientSubstance>
    <code code="TBD" codeSystem="1.2.3.4" codeSystemName="FDA"/>
    <name>sodium dihydrogen phosphate...</name>
  </inactiveIngredientSubstance>
</inactiveIngredient>
<inactiveIngredient>
  <inactiveIngredientSubstance>
    <code code="TBD" codeSystem="1.2.3.4" codeSystemName="FDA"/>
    <name>disodium hydrogen phosphate...</name>
  </inactiveIngredientSubstance>
</inactiveIngredient>
<inactiveIngredient>
  <inactiveIngredientSubstance>
    <code code="TBD" codeSystem="1.2.3.4" codeSystemName="FDA"/>
    <name>water for...</name>
  </inactiveIngredientSubstance>
</inactiveIngredient>
<asContent>
  <quantity>
    <numerator value="2.5" unit="mL"/>
    <denominator value="1"/>
  </quantity>
  <containerPackagedMedicine>
    <code code="0013-8303-04" codeSystem="2.16.840.1.113883.6.69"
codeSystemName="NDC"/>

```

```

        <formCode code="BOT" codeSystem="4.3.2.1" codeSystemName="PackageType"
displayName="Bottle"/>
        </containerPackagedMedicine>
      </asContent>
    </manufacturedMedicine>
    <consumedIn>
      <substanceAdministration>
        <routeCode code="OPHTHALTA" codeSystem="2.16.840.1.113883.5.112"
codeSystemName="RouteOfAdministration" displayName="Ophthalmic"/>
      </substanceAdministration>
    </consumedIn>
  </manufacturedProduct>
</subject>
<component>
  <observationMedia ID="MM1">
    <value xsi:type="ED" mediaType="image/jpeg">
      <reference value="xalatan-01.jpg"/>
    </value>
  </observationMedia>
</component>
</section>
</component>
<component>
  <section>
    <id root="6e6bb428-421c-11d9-885e-359253aa2240"/>
    <code code="34090-1" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Clinical Pharmacology section"/>
    <title>CLINICAL...</title>
    <component>
      <section>
        <id root="6e6bb429-421c-11d9-885e-359253aa2240"/>
        <title>Mechanism of...</title>
        <text>
          <paragraph>Latanoprost is a prostanoid selective RT receptor...</paragraph>
        </text>
      </section>
    </component>
    <component>
      <section>
        <id root="6e6d3aca-421c-11d9-885e-359253aa2240"/>
        <title>Absorption...</title>
        <text>
          <paragraph>Latanoprost is absorbed through the cornea where...</paragraph>
        </text>
      </section>
    </component>
    <component>
      <section>
        <id root="6e6ec16b-421c-11d9-885e-359253aa2240"/>
        <title>Distribution...</title>
        <text>
          <paragraph>The distribution volume in humans ....</paragraph>
        </text>
      </section>
    </component>
    <component>
      <section>
        <id root="6e6ec16c-421c-11d9-885e-359253aa2240"/>
        <title>Metabolism...</title>
        <text>
          <paragraph>Latanprost, an isopropyl ester prodrug, is...</paragraph>
        </text>
      </section>
    </component>
  </component>
</section>

```



```

<id root="6e70480d-421c-11d9-885e-359253aa2240"/>
<title>Excretion...</title>
<text>
  <paragraph>The elimination of the acid of latanoprost from...</paragraph>
</text>
</section>
</component>
<component>
  <section>
    <id root="6e71ceae-421c-11d9-885e-359253aa2240"/>
    <code code="TBD" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Animal Pharmacology and or Toxicology section"/>
    <title>Animal...</title>
    <text>
      <paragraph>In monkeys, latanoprost has been shown to
        induce...</paragraph>
      <paragraph>Ocular administration of latanoprost at a dose of ....</paragraph>
    </text>
  </section>
</component>
</section>
</component>
<component>
  <section>
    <id root="6e71ceaf-421c-11d9-885e-359253aa2240"/>
    <code code="34067-9" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Indications and Usage section"/>
    <title>INDICATIONS AND...</title>
    <text>
      <paragraph>XALATAN Sterile Ophthalmic Solution is indicated for the...</paragraph>
    </text>
  </section>
</component>
<component>
  <section>
    <id root="6e735550-421c-11d9-885e-359253aa2240"/>
    <code code="34092-7" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Clinical Studies section"/>
    <title>CLINICAL...</title>
    <text>
      <paragraph>Patients with mean baseline intraocular pressure of 24-25...</paragraph>
      <paragraph>A 3-year open-label, prospective safety study with 2-year...</paragraph>
      <paragraph>Results showed that the onset of noticeable iris...</paragraph>
    </text>
  </section>
</component>
<component>
  <section>
    <id root="6e74dbf1-421c-11d9-885e-359253aa2240"/>
    <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 latanoprost, benzalkonium...</paragraph>
    </text>
  </section>
</component>
<component>
  <section>
    <id root="6e766292-421c-11d9-885e-359253aa2240"/>
    <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...</paragraph>
    </text>
  </section>

```

```

</section>
</component>
<component>
  <section>
    <id root="6e796fd3-421c-11d9-885e-359253aa2240"/>
    <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...</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...</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...</paragraph>
    </text>
  </section>
</component>
<component>
  <section>
    <id root="6e7af674-421c-11d9-885e-359253aa2240"/>
    <code code="34076-0" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Information For Patients section"/>
    <title>Information for...</title>
    <text>
      <paragraph>Patients should be advised about the potential for
      ...</paragraph>
      <paragraph>Patients should also be informed of the possibility of...</paragraph>
      <paragraph>Patients should be instructed to avoid allowing the tip ....</paragraph>
      <paragraph>Patients should also be advised that if they develop...</paragraph>
      <paragraph>Patients should be advised that if they develop any ocular...</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>
<component>
  <section>
    <id root="6e7c7d15-421c-11d9-885e-359253aa2240"/>
    <code code="34073-7" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Drug Interactions section"/>
    <title>Drug...</title>
    <text>
      <paragraph>In vitro studies have shown that precipitation occurs when...</paragraph>
    </text>
  </section>
</component>
<component>
  <section>
    <id root="6e7e03b6-421c-11d9-885e-359253aa2240"/>
    <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...</title>
    <text>
      <paragraph>Latanprost was not mutagenic in bacteria, in mouse...</paragraph>
      <paragraph>Chromosome aberrations were observed in vitro with
      ...</paragraph>
      <paragraph>Latanoprost was not carcinogenic ....</paragraph>
      <paragraph>Additional in vitro and in vivo studies on unscheduled...</paragraph>
    </text>
  </section>
</component>
</component>

```

```

<section>
  <id root="6e7f8a57-421c-11d9-885e-359253aa2240"/>
  <code code="34077-8" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Teratogenic Effects section"/>
  <title>Teratogenic...</title>
  <text>
    <paragraph>Pregnancy Category...</paragraph>
    <paragraph>Reproduction studies have been performed in rats and...</paragraph>
  </text>
</section>
</component>
<component>
  <section>
    <id root="6e8110f8-421c-11d9-885e-359253aa2240"/>
    <code code="34080-2" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Nursing Mothers section"/>
    <title>Nursing...</title>
    <text>
      <paragraph>It is not known whether this drug or its metabolites are...</paragraph>
    </text>
  </section>
</component>
<component>
  <section>
    <id root="6e829799-421c-11d9-885e-359253aa2240"/>
    <code code="34081-0" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Pediatric Use section"/>
    <title>Pediatric...</title>
    <text>
      <paragraph>Safety and effectiveness in pediatric patients have not...</paragraph>
    </text>
  </section>
</component>
<component>
  <section>
    <id root="6e841e3a-421c-11d9-885e-359253aa2240"/>
    <code code="34082-8" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Geriatric Use section"/>
    <title>Geriatric...</title>
    <text>
      <paragraph>No overall differences in safety or effectiveness have...</paragraph>
    </text>
  </section>
</component>
<component>
  <section>
    <id root="6e85a4db-421c-11d9-885e-359253aa2240"/>
    <code code="34084-4" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Adverse Reactions section"/>
    <title>ADVERSE...</title>
    <component>
      <section>
        <id root="6e85a4dc-421c-11d9-885e-359253aa2240"/>
        <title>Adverse events referred to in other sections of this...</title>
        <text>
          <paragraph>Eyelash changes (increased length, thickness,...</paragraph>
        </text>
      </section>
    </component>
  </section>
</component>
  <section>
    <id root="6e88b21d-421c-11d9-885e-359253aa2240"/>
    <title>Controlled Clinical...</title>
    <text>
      <paragraph>The ocular adverse events and ocular signs and...</paragraph>
      <paragraph>Local conjunctival hyperemia was observed;...</paragraph>
    </text>
  </section>
</component>

```

```

        <paragraph>In addition to the above listed ocular events/signs...</paragraph>
        <paragraph>The following events were reported in less than...</paragraph>
        <paragraph>During clinical studies, there were extremely rare...</paragraph>
        <paragraph>The most common systemic adverse events
        seen ....</paragraph>
    </text>
</section>
</component>
<component>
    <section>
        <id root="6e88b21e-421c-11d9-885e-359253aa2240"/>
        <title>Clinical...</title>
        <text>
            <paragraph>The following events have been identified during...</paragraph>
        </text>
    </section>
</component>
</section>
</component>
<component>
    <section>
        <id root="6e8a38bf-421c-11d9-885e-359253aa2240"/>
        <code code="34085-1" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Controlled Substance section"/>
        <subject>
            <manufacturedProduct>
                <subjectOf>
                    <policy>
                        <code code="1" codeSystem="5.4.3.2" codeSystemName="DEADrugSchedule"/>
                    </policy>
                </subjectOf>
            </manufacturedProduct>
        </subject>
    </section>
</component>
<component>
    <section>
        <id root="6e8d4600-421c-11d9-885e-359253aa2240"/>
        <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...</paragraph>
            <paragraph>If overdosage with XALATAN Sterile Ophthalmic...</paragraph>
        </text>
    </section>
</component>
<component>
    <section>
        <id root="6e8d4601-421c-11d9-885e-359253aa2240"/>
        <code code="34068-7" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="Dosage and Administration section"/>
        <title>DOSAGE AND...</title>
        <text>
            <paragraph>The recommended dosage is one drop (1.5 &#181;g) in the...</paragraph>
            <paragraph>The dosage of XALATAN Sterile Ophthalmic Solution should...</paragraph>
            <paragraph>Reduction of the intraocular pressure starts approximately...</paragraph>
            <paragraph>XALATAN may be used concomitantly with other topical...</paragraph>
        </text>
    </section>
</component>
<component>
    <section>
        <id root="6e905342-421c-11d9-885e-359253aa2240"/>
        <code code="34069-5" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"
displayName="How Supplied section"/>

```

```

<title>HOW...</title>
<text>
  <paragraph>XALATAN Sterile Ophthalmic Solution is a clear, isotonic,...</paragraph>
  <paragraph>NDC...</paragraph>
  <paragraph>2.5 mL fill, 0.005% (50...</paragraph>
  <paragraph>Storage: Protect from light. Store unopened bottle under...</paragraph>
</text>
</section>
</component>
</structuredBody>
</component>
</document>

```

7.2.3 Sample SPL Level 2 Document

Below is an XML instance showing how another prescription drug labeling document would be marked up to conform to the SPL schema at level 2 with highlights and all highlight information structured. This XML instance document is also included as a separate file in the SPL Schema package (see capoten.xml in the Files folder).

```

<?xml version="1.0" encoding="ASCII"?>
<?xml-stylesheet type="text/xsl" href="spl2.xsl"?>
<document xmlns="urn:hl7-org:v3" xmlns:voc="urn:hl7-org:v3/voc" xmlns:xsi="http://www.w3.org/2001/XMLSchema-
instance" xmlns:splx="urn:hl7-org:splx">
  <id root="f21ee15d-f5e7-11d8-9eec-01a868e9b85b"/>
  <code code="34391-3" codeSystem="2.16.840.1.113883.6.1" displayName="Human prescription drug label"/>
  <title>CAPOTEN&#174;...<br/>(captopril...</title>
  <effectiveTime value="200405"/>
  <availabilityTime value="200405"/>
  <confidentialityCode code="N" codeSystem="2.16.840.1.113883.5.25" codeSystemName="Confidentiality"/>
  <author>
    <time value="20040505"/>
    <assignedEntity>
      <id root="f221ee9e-f5e7-11d8-9eec-01a868e9b85b"/>
      <representedOrganization>
        <name>Bristol-Myers Squibb...</name>
        <addr>NJ 08543,...</addr>
      </representedOrganization>
    </assignedEntity>
  </author>
  <component>
    <structuredBody>
      <component>
        <section ID="WARNING-USE-IN-PREGNANCY">
          <id root="f223753f-f5e7-11d8-9eec-01a868e9b85b"/>
          <code code="34066-1" codeSystem="2.16.840.1.113883.6.1" displayName="boxed warning"/>
          <title>WARNING: USE IN...</title>
          <text>
            <paragraph>When used in pregnancy during the second and third...<linkHtml
styleCode="MainTitleSubTitleNumber" href="#Fetal-Neonatal-Morbidity-and-Mortality"/>...</paragraph>
          </text>
        </section>
      </component>
      <component>
        <section ID="INDICATIONS-AND-USAGE">
          <id root="f224fbe0-f5e7-11d8-9eec-01a868e9b85b"/>
          <code code="34067-9" codeSystem="2.16.840.1.113883.6.1" displayName="Indications and Usage
section"/>
          <title>INDICATIONS AND...</title>
          <component>
            <section ID="Indication-Hypertension">
              <id root="f2268281-f5e7-11d8-9eec-01a868e9b85b"/>
              <code code="XSS1" codeSystem="2.16.840.1.113883.6.1" displayName="Indication item
subsection"/>
              <title>Hypertension...</title>

```

```

<text>
  <paragraph>CAPOTEN is indicated for the treatment of...</paragraph>
  <paragraph>In using CAPOTEN, consideration should be given to the risk...<linkHtml
styleCode="MainTitle" href="#Neutropenia-Agranulocytosis"/>...</paragraph>
  <paragraph>CAPOTEN (captopril) may be used as initial therapy for...</paragraph>
  <paragraph>CAPOTEN is effective alone and in combination with other...</paragraph>
</text>
<excerpt>
  <highlight>
    <text>
      <paragraph styleCode="Bullet">
        <caption>Hypertension...</caption> (caution in renally-impaired patients), alone
or in...</paragraph>
      </text>
    </subject>
    <substanceAdministration>
      <reason>
        <indicationObservationCriterion>
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          </value>
        </indicationObservationCriterion>
      </reason>
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    <observationCriterion>
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codeSystem="TBD">
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    </observationCriterion>
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  </issue>
</subjectOf>
</substanceAdministration>
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  <code code="XSS1" codeSystem="2.16.840.1.113883.6.1" displayName="Indication item
subsection"/>
  <title>Heart...</title>
  <text>
    <paragraph>CAPOTEN is indicated in the treatment of congestive heart...</paragraph>
  </text>
  <excerpt>
    <highlight>
      <text>
        <paragraph styleCode="Bullet">
          <caption>Congestive Heart...</caption> usually in combination with diuretics
and...</paragraph>
        </text>
      </subject>
      <substanceAdministration>
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    </reason>
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    <code code="XSS1" codeSystem="2.16.840.1.113883.6.1" displayName="Indication item"
subsection"/>
    <title>Left Ventricular Dysfunction After Myocardial...</title>
    <text>
      <paragraph>CAPOTEN is indicated to improve survival following...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">
            <caption>Left Ventricular (LV) Dysfunction after Myocardial...</caption> to
improve survival and reduce morbidity in clinically...</paragraph>
          </text>
        </subject>
        <substanceAdministration>
          <reason>
            <indicationObservationCriterion>
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Myocardial...</originalText>
              </value>
            </indicationObservationCriterion>
          </reason>
        </substanceAdministration>
      </subject>
    </highlight>
  </excerpt>
</section>
</component>
<component>
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    <code code="XSS1" codeSystem="2.16.840.1.113883.6.1" displayName="Indication item"
subsection"/>
    <title>Diabetic...</title>
    <text>
      <paragraph>CAPOTEN is indicated for the treatment of diabetic...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">
            <caption>Diabetic...</caption> (Type I IDD with proteinuria &gt; 500 mg/day
and...</paragraph>
          </text>
        </subject>
        <substanceAdministration>
          <reason>
            <indicationObservationCriterion>
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    <code code="34068-7" codeSystem="2.16.840.1.113883.6.1" displayName="Dosage and
Administration section"/>
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    <component>
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        <code code="XSS2" codeSystem="2.16.840.1.113883.6.1" displayName="Dosage and
administration item subsection"/>
        <title>General...</title>
        <text>
          <paragraph>CAPOTEN (captopril) should be taken one hour before meals....</paragraph>
        </text>
        <excerpt>
          <highlight>
            <text>
              <paragraph>
                <caption>General:...</caption> Take 1 hour before meals.
Individualize...</paragraph>
            </text>
          </highlight>
        </excerpt>
        <table>
          <col align="left"/>
          <col align="left"/>
          <col align="left"/>
          <col align="center"/>
          <thead>
            <tr>
              <th scope="col">Indication...</th>
              <th scope="col">Initiation of...</th>
              <th scope="col">Usual Daily...</th>
              <th scope="col">Do Not...</th>
            </tr>
          </thead>
          <tbody styleCode="continued" ID="ct-1">
            <tr styleCode="phantom">
              <td/>
              <td/>
              <td/>
              <td/>
            </tr>
          </tbody>
        </table>
      </table>
    </text>
  </subject>
  <substanceAdministration>
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      <offset>
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      </offset>
    </effectiveTime>
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</subject>

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        </highlight>
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      <code code="XSS2" codeSystem="2.16.840.1.113883.6.1" displayName="Dosage and
administration item subsection"/>
      <title>Hypertension...</title>
      <text>
        <paragraph>Initiation of therapy requires consideration of recent...</paragraph>
        <paragraph>The initial dose of CAPOTEN is 25 mg bid or tid. If...</paragraph>
        <paragraph>The dose of CAPOTEN in hypertension usually does not
exceed...</paragraph>
        <paragraph>If CAPOTEN is being started in a patient already receiving...<linkHtml
styleCode="MainTitleNumber" href="#Hypotension-Patients-on-Diuretic-Therapy"/>, with dosage and titration of CAPOTEN
as noted...</paragraph>
        <paragraph>If further blood pressure reduction is required, the dose...</paragraph>
        <paragraph>For patients with severe hypertension (e.g., accelerated or...</paragraph>
        <paragraph>When necessitated by the patient's clinical condition, the...</paragraph>
        <paragraph>Beta blockers may also be used in conjunction with CAPOTEN...<linkHtml
styleCode="MainTitleNumber" href="#Agents-Affecting-Sympathetic-Activity"/>, but the effects of the two drugs are less
than...</paragraph>
      </text>
      <excerpt>
        <highlight>
          <text>
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                  <td>Hypertension...</td>
                  <td>25 mg bid or...</td>
                  <td>25-150 mg bid or...<footnote>Usual daily dosing does not exceed
50 mg BID or TID. ...<linkHtml href="#Hypertension"/></footnote>
                  </td>
                  <td>450...</td>
                </tr>
              </tbody>
            </table>
          </text>
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              <reason>
                <indicationObservationCriterion>
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</component>
<component>
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    <code code="XSS2" codeSystem="2.16.840.1.113883.6.1" displayName="Dosage and
administration item subsection"/>
    <title>Heart...</title>
    <text>
      <paragraph>Initiation of therapy requires consideration of recent...<linkHtml
styleCode="MainTitleSubTitleNumber" href="#Hypotension"/>; for these patients, titration to the usual daily
dosage...</paragraph>
      <paragraph>For most patients the usual initial daily dosage is 25 mg...</paragraph>
      <paragraph>CAPOTEN should generally be used in conjunction with a...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <table styleCode="continuation">
            <tbody styleCode="continuation" ID="ct-1.2">
              <tr>
                <td>Heart...</td>
                <td>25 mg...</td>
                <td>50-100 mg...</td>
                <td>450...</td>
              </tr>
            </tbody>
          </table>
        </text>
      </highlight>
    </excerpt>
  </component>
  <substanceAdministration>
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      <numerator value="450" unit="mg"/>
      <denominator value="1" unit="d"/>
    </maxDoseQuantity>
    <reason>
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      </value>
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  </reason>
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  </component>
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        <high value="100" unit="mg"/>
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  </component>
</substanceAdministration>
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</component>
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    <code code="XSS2" codeSystem="2.16.840.1.113883.6.1" displayName="Dosage and
administration item subsection"/>
    <title>Left Ventricular Dysfunction After Myocardial...</title>
    <text>
      <paragraph>The recommended dose for long term use in patients...</paragraph>
      <paragraph>Therapy may be initiated as early as three days following a...<linkHtml
styleCode="MainTitleNumber" href="#Pharmacodynamics"/>...</paragraph>
      <paragraph>CAPOTEN may be used in patients treated with other post...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <table styleCode="continuation">
            <tbody styleCode="continuation" ID="ct-1.3">
              <tr>
                <td>LV Dysfunction after...</td>
                <td>12.5 mg...<footnote>A single dose of 6.25 mg should precede
initiation of 12.5...<linkHtml href="#Dosage-Left-Ventricular-Dysfunction-After-Myocardial-Infarction"/>
                </footnote>
                </td>
              </tr>
            </tbody>
          </table>
        </text>
      </highlight>
    </excerpt>
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        <reason>
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  </component>
</substanceAdministration>
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    <code code="XSS2" codeSystem="2.16.840.1.113883.6.1" displayName="Dosage and
administration item subsection"/>
    <title>Diabetic...</title>
    <text>
      <paragraph>The recommended dose of CAPOTEN for long term use to treat...</paragraph>
      <paragraph>Other antihypertensives such as diuretics, beta blockers,...</paragraph>
    </text>
    <excerpt>
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        <text>
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                <td>Diabetic...</td>
                <td>25 mg...</td>
              </tr>
            </tbody>
          </table>
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    </excerpt>
    <subject>
      <substanceAdministration>
        <reason>
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            </value>
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        </reason>
        <component>
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              <period value="8" unit="h"/>
            </effectiveTime>
            <doseQuantity value="25" unit="mg"/>
          </substanceAdministration>
        </component>
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    </subject>
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</component>

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        </substanceAdministration>
      </component>
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  <code code="XSS2" codeSystem="2.16.840.1.113883.6.1" displayName="Dosage and
administration item subsection"/>
  <title>Dosage Adjustment in Renal...</title>
  <text>
    <paragraph>Because CAPOTEN is excreted primarily by the kidneys,...</paragraph>
    <paragraph>Accordingly, for patients with significant renal...<linkHtml
styleCode="MainTitleSubTitleNumber" href="#Hemodialysis"/>...</paragraph>
  </text>
  <excerpt>
    <highlight>
      <text>
        <paragraph>
          <content styleCode="emphasis">Adjust dose in renal...</content>
        </paragraph>
        <linkHtml href="#Impaired-Renal-Function"/>
      </text>
    </subject>
    <substanceAdministration>
      <subjectOf>
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        <observationCriterion>
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  <id root="f23bdf4c-f5e7-11d8-9eec-01a868e9b85b"/>
  <code code="34069-5" codeSystem="2.16.840.1.113883.6.1" displayName="How Supplied section"/>
  <title>HOW...</title>
  <text>
    <paragraph>12.5 mg tablets in bottles of 100 and 1000, 25 mg tablets...</paragraph>
    <paragraph>Unimatic unit dose packs containing 100 tablets are also...</paragraph>
    <paragraph>The 12.5 mg tablet is a biconvex oval with a partial bisect...</paragraph>
    <paragraph>All captopril tablets are white and may exhibit a slight...</paragraph>
    <paragraph>Storage: Do not store above 86 &#176;F. Keep bottles tightly...</paragraph>
  </text>
  <subject>
    <manufacturedProduct>

```

```

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  <name>Capoten...</name>
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      <numerator value="12.5" unit="mg"/>
      <denominator value="1"/>
    </quantity>
    <activeIngredientSubstance>
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      <name>captopril...</name>
    </activeIngredientSubstance>
  </activeIngredient>
  <asEntityWithGeneric>
    <genericMedicine>
      <name>captopril...</name>
    </genericMedicine>
  </asEntityWithGeneric>
</manufacturedMedicine>
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  <characteristic>
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    <value xsi:type="INT" value="2"/>
  </characteristic>
</subjectOf>
<consumedIn>
  <substanceAdministration>
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      </activeIngredient>
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      </asEntityWithGeneric>
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    </subjectOf>
    <consumedIn>
      <substanceAdministration>
        <routeCode code="(p.o.)" codeSystem="TBD" displayName="oral"/>
      </substanceAdministration>
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</subject>

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    <manufacturedMedicine>
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          <denominator value="1"/>
        </quantity>
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        </activeIngredientSubstance>
      </activeIngredient>
      <asEntityWithGeneric>
        <genericMedicine>
          <name>captopril...</name>
        </genericMedicine>
      </asEntityWithGeneric>
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    <subjectOf>
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      </substanceAdministration>
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</subject>

```

```

        </manufacturedProduct>
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      <text>
        <paragraph>Tablets: 12.5, 25, 50, 100 mg:...</paragraph>
      </text>
    </highlight>
  </excerpt>
</section>
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section"/>
    <title>CONTRAINDICATIONS...</title>
    <text>
      <paragraph>CAPOTEN (captopril) is contraindicated in patients who are...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph>Known hypersensitivity (e.g., angioedema) to any ACE...</paragraph>
        </text>
        <subject>
          <substanceAdministration>
            <subjectOf>
              <issue classCode="CONTRAINDICATION">
                <subject>
                  <observationCriterion>
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ACE...</originalText>
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            </subjectOf>
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    <code code="34071-1" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings section"/>
    <title>WARNINGS/PRECAUTIONS...</title>
    <text>
      <paragraph>To report SUSPECTED SERIOUS ADRs, call (manufacturer) at...</paragraph>
    </text>
    <component>
      <section ID="Angioedema">
        <id root="f23eec8f-f5e7-11d8-9eec-01a868e9b85b"/>
        <code code="XSS5" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings sub-
section"/>
        <title>Angioedema...</title>
        <text>
          <paragraph>Angioedema involving the extremities, face, lips, mucous...</paragraph>
          <paragraph>Swelling confined to the face, mucous membranes of the...<linkHtml
styleCode="MainTitleNumber" href="#PATIENT-COUNSELING-INFORMATION"/> and...<linkHtml
styleCode="MainTitleNumber" href="#ADVERSE-REACTIONS"/>...</paragraph>
        </text>
      </section>
    </component>
  </section>

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</text>
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codeSystem="TBD">
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myeloid...</originalText>
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            <causeOf>
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codeSystem="2.16.840.1.113883.6.1"/>
                <value xsi:type="IVL_PQ">
                  <high value="1000" unit="/mm3"/>
                </value>
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            </causeOf>
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          <consequenceObservation>
            <code code="(dx)"
codeSystem="2.16.840.1.113883.6.1"/>
            <value xsi:type="CE" code="(myeloid-hypoplasia)"
codeSystem="TBD">
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            </value>
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        </causeOf>
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</substanceAdministration>
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    <code code="XSS5" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings sub-
section"/>
    <title>Proteinuria...</title>
    <text>
      <paragraph>Total urinary proteins greater than 1 g per day were seen...</paragraph>
    </text>
  </section>
</component>
<component>
  <section ID="Hypotension">
    <id root="f241f9d2-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="XSS5" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings sub-
section"/>
    <title>Hypotension...</title>
    <text>
      <paragraph>Excessive hypotension was rarely seen in hypertensive...<linkHtml
styleCode="MainTitleNumber" href="#Hypotension-Patients-on-Diuretic-Therapy"/>...</paragraph>
      <paragraph>In heart failure, where the blood pressure was either...</paragraph>
      <paragraph>BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN
THESE...</paragraph>
      <paragraph>Hypotension is not per se a reason to discontinue...</paragraph>

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</text>
<excerpt>
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    <text>
      <paragraph styleCode="Bullet">Excessive...</paragraph>
    </text>
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codeSystem="TBD">
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                </value>
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            </risk>
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    <code code="XSS5" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings sub-
section"/>
    <title>Fetal/Neonatal Morbidity and...</title>
    <text>
      <paragraph>ACE inhibitors can cause fetal and neonatal morbidity and...</paragraph>
      <paragraph>The use of ACE inhibitors during the second and third...</paragraph>
      <paragraph>These adverse effects do not appear to have resulted from...</paragraph>
      <paragraph>Rarely (probably less often than once in every thousand...</paragraph>
      <paragraph>If oligohydramnios is observed, captopril should be...</paragraph>
      <paragraph>Infants with histories of in utero exposure to ACE...</paragraph>
      <paragraph>When captopril was given to rabbits at doses about 0.8 to...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">Fetal/Neonatal Morbidity and...</paragraph>
        </text>
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          <substanceAdministration>
            <subjectOf>
              <issue classCode="WARNING">
                <risk>
                  <consequenceObservation>
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mortality)" codeSystem="TBD">
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                    </value>
                  </consequenceObservation>
                </risk>
              </issue>
            </subjectOf>
          </substanceAdministration>
        </subject>
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section"/>
    <title>Hepatic...</title>
    <text>
      <paragraph>Rarely, ACE inhibitors have been associated with a syndrome...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">Hepatic...</paragraph>
        </text>
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            <subjectOf>
              <issue classCode="WARNING">
                <risk>
                  <consequenceObservation>
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codeSystem="TBD"/>
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                  </value>
                </consequenceObservation>
              </risk>
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          </subjectOf>
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    </highlight>
  </excerpt>
</section>
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  <section ID="Impaired-Renal-Function">
    <id root="f2468db5-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="XSS5" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings sub-
section"/>
    <title>Impaired Renal...</title>
    <text>
      <paragraph>Hypertension--Some patients with renal disease,...</paragraph>
      <paragraph>Heart Failure--About 20 percent of patients develop stable...</paragraph>
      <paragraph>See...<linkHtml styleCode="MainTitleNumber" href="#CLINICAL-
PHARMACOLOGY"/>, DOSAGE AND ADMINISTRATION (2.6), ADVERSE REACTIONS:...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">Use with caution in renal...</paragraph>
        </text>
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          <substanceAdministration>
            <subjectOf>
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                <subject>
                  <observationCriterion>
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codeSystem="TBD"/>
                    <originalText>renal...</originalText>
                  </value>
                </observationCriterion>
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            </issue>
          </subjectOf>
        </substanceAdministration>
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</subject>
</issue>
</subjectOf>
</substanceAdministration>
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    <code code="XSS5" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings sub-
section"/>
    <title>Hyperkalemia...</title>
    <text>
      <paragraph>Elevations in serum potassium have been observed in some...<linkHtml
styleCode="MainTitleNumber" href="#PATIENT-COUNSELING-INFORMATION"/>...<linkHtml
styleCode="MainTitleNumber" href="#DRUG-INTERACTIONS"/>; ADVERSE REACTIONS: Altered Laboratory
Findings...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">Hyperkalemia...</paragraph>
        </text>
        <subject>
          <substanceAdministration>
            <subjectOf>
              <issue classCode="WARNING">
                <risk>
                  <consequenceObservation>
                    <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
                    <value xsi:type="CE" code="(hyperkalemia)"
codeSystem="TBD">
                      <originalText>Hyperkalemia...</originalText>
                    </value>
                  </consequenceObservation>
                </risk>
              </issue>
            </subjectOf>
          </substanceAdministration>
        </subject>
      </highlight>
    </excerpt>
  </section>
</component>
<component>
  <section ID="Cough">
    <id root="f2499af7-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="XSS5" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings sub-
section"/>
    <title>Cough...</title>
    <text>
      <paragraph>Cough has been reported with the use of ACE inhibitors....</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">Cough...</paragraph>
        </text>
        <subject>
          <substanceAdministration>
            <subjectOf>
              <issue classCode="WARNING">
                <risk>

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<consequenceObservation>
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</consequenceObservation>
</risk>
</issue>
</subjectOf>
</substanceAdministration>
</subject>
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</excerpt>
</section>
</component>
<component>
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    <id root="f24b2198-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="XSS5" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings sub-
section"/>
    <title>Valvular...</title>
    <text>
      <paragraph>There is concern, on theoretical grounds, that patients...</paragraph>
    </text>
  </section>
</component>
<component>
  <section ID="Surgery-Anesthesia">
    <id root="f24ca839-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="XSS5" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings sub-
section"/>
    <title>Surgery/Anesthesia...</title>
    <text>
      <paragraph>In patients undergoing major surgery or during anesthesia...</paragraph>
    </text>
  </section>
</component>
<component>
  <section ID="Hemodialysis">
    <id root="f24ca83a-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="XSS5" codeSystem="2.16.840.1.113883.6.1" displayName="Warnings sub-
section"/>
    <title>Hemodialysis...</title>
    <text>
      <paragraph>Recent clinical observations have shown an association of...</paragraph>
    </text>
  </section>
</component>
</section>
</component>
<component>
  <section ID="DRUG-INTERACTIONS">
    <id root="f24e2edb-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="34073-7" codeSystem="2.16.840.1.113883.6.1" displayName="DRUG INTERACTIONS"/>
    <title>DRUG...</title>
    <component>
      <section ID="Hypotension-Patients-on-Diuretic-Therapy">
        <id root="f24fb57c-f5e7-11d8-9eec-01a868e9b85b"/>
        <code code="9999999-9" codeSystem="2.16.840.1.113883.6.1" displayName="INTERACTION
ITEM SUBSECTION"/>
        <title>Hypotension--Patients on Diuretic...</title>
        <text>
          <paragraph>Patients on diuretics and especially those in whom...</paragraph>
          <paragraph>The possibility of hypotensive effects with captopril can...</paragraph>
        </text>
      </section>
    </component>
  </section>
</component>

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    <highlight>
    <text>
    <paragraph styleCode="Bullet">Diuretics...</paragraph>
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    <issue classCode="INTERACTION">
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    <substanceAdministrationCriterion>
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    <code code="(Diureticum)" codeSystem="TBD">
    <originalText>Diuretics...</originalText>
    </code>
    </playingMaterialKind>
    </administrableMaterial>
    </consumable>
    </substanceAdministrationCriterion>
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    </issue>
    </subjectOf>
    </substanceAdministration>
    </subject>
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  </excerpt>
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</component>
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    <code code="XSS6" codeSystem="2.16.840.1.113883.6.1" displayName="Interaction item"
    subsection"/>
    <title>Agents Having Vasodilator...</title>
    <text>
    <paragraph>Data on the effect of concomitant use of other vasodilators...</paragraph>
    </text>
    <excerpt>
    <highlight>
    <text>
    <paragraph styleCode="Bullet">Other...</paragraph>
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    <substanceAdministration>
    <subjectOf>
    <issue classCode="INTERACTION">
    <subject>
    <substanceAdministrationCriterion>
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    <administrableMaterial>
    <playingMaterialKind>
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    </code>
    </playingMaterialKind>
    </administrableMaterial>
    </consumable>
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    </section>
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      <code code="XSS6" codeSystem="2.16.840.1.113883.6.1" displayName="Interaction item
subsection"/>

      <title>Agents Causing Renin...</title>
      <text>
        <paragraph>Captopril's effect will be augmented by antihypertensive...</paragraph>
      </text>
      <excerpt>
        <highlight>
          <text>
            <paragraph styleCode="Bullet">Agents Causing Renin...</paragraph>
          </text>
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            <substanceAdministration>
              <subjectOf>
                <issue classCode="INTERACTION">
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                    <substanceAdministrationCriterion>
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                        <administrableMaterial>
                          <playingMaterialKind>
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codeSystem="TBD">
                            </originalText>Agents Causing
Renin...</originalText>
                            </code>
                          </playingMaterialKind>
                        </administrableMaterial>
                      </consumable>
                    </substanceAdministrationCriterion>
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                </issue>
              </subjectOf>
            </substanceAdministration>
          </subject>
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  <component>
    <section ID="Agents-Affecting-Sympathetic-Activity">
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      <code code="XSS6" codeSystem="2.16.840.1.113883.6.1" displayName="Interaction item
subsection"/>

      <title>Agents Affecting Sympathetic...</title>
      <text>
        <paragraph>The sympathetic nervous system may be especially important...</paragraph>
      </text>
      <excerpt>
        <highlight>
          <text>
            <paragraph styleCode="Bullet">Beta-Blockers...</paragraph>
          </text>
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              <subjectOf>
                <issue classCode="INTERACTION">
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                        <administrableMaterial>
                          <playingMaterialKind>

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<code code="(BetaBlocker)" codeSystem="TBD">
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</administrableMaterial>
</consumable>
</substanceAdministrationCriterion>
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</issue>
</subjectOf>
</substanceAdministration>
</subject>
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</excerpt>
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</component>
<component>
  <section ID="Agents-Increasing-Serum-Potassium">
    <id root="f2544960-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="XSS6" codeSystem="2.16.840.1.113883.6.1" displayName="Interaction item"
subsection"/>
    <title>Agents Increasing Serum...</title>
    <text>
      <paragraph>Since captopril decreases aldosterone production, elevation...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">Agents Increasing Serum...</paragraph>
        </text>
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          <substanceAdministration>
            <subjectOf>
              <issue classCode="INTERACTION">
                <subject>
                  <substanceAdministrationCriterion>
                    <consumable>
                      <administrableMaterial>
                        <playingMaterialKind>
                          <code code="(AgentIncreasingSerumPotassium)"
codeSystem="TBD">
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Serum...</originalText>
                          </code>
                        </playingMaterialKind>
                      </administrableMaterial>
                    </consumable>
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              </issue>
            </subjectOf>
          </substanceAdministration>
        </subject>
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    <code code="XSS6" codeSystem="2.16.840.1.113883.6.1" displayName="Interaction item"
subsection"/>
    <title>Inhibitors Of Endogenous Prostaglandin...</title>
    <text>
      <paragraph>It has been reported that indomethacin may reduce the...</paragraph>
    </text>

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</section>
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  <section ID="Lithium">
    <id root="f25756a2-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="XSS6" codeSystem="2.16.840.1.113883.6.1" displayName="Interaction item
subsection"/>
    <title>Lithium...</title>
    <text>
      <paragraph>Increased serum lithium levels and symptoms of lithium...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">Lithium...</paragraph>
        </text>
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          <substanceAdministration>
            <subjectOf>
              <issue classCode="INTERACTION">
                <subject>
                  <substanceAdministrationCriterion>
                    <consumable>
                      <administrableMaterial>
                        <playingMaterialKind>
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                          </code>
                        </playingMaterialKind>
                      </administrableMaterial>
                    </consumable>
                  </substanceAdministrationCriterion>
                </subject>
              </issue>
            </subjectOf>
          </substanceAdministration>
        </subject>
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  </section>
</component>
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  <section ID="Drug-Laboratory-Test-Interactions">
    <id root="f25756a3-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="34074-5" codeSystem="2.16.840.1.113883.6.1" displayName="Drug/laboratory
test interactions"/>
    <title>Drug/Laboratory Test...</title>
    <text>
      <paragraph>Captopril may cause a false positive urine test for...</paragraph>
    </text>
  </section>
</component>
</section>
</component>
<component>
  <section ID="USE-IN-SPECIFIC-POPULATIONS">
    <id root="f258dd44-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="XMS7" codeSystem="2.16.840.1.113883.6.1" displayName="USE IN SPECIFIC
POPULATIONS"/>
    <title>USE IN SPECIFIC...</title>
    <component>
      <section>
        <id root="f25a63e5-f5e7-11d8-9eec-01a868e9b85b"/>
        <code code="XSS7.1" codeSystem="2.16.840.1.113883.6.1" displayName="Special Population
subsection - Pregnancy"/>
        <text>

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<paragraph>
  <content styleCode="bold">Categories C (first trimester) and D (second and
third...<linkHtml styleCode="MainTitleSubTitleNumber" href="#Fetal-Neonatal-Morbidity-and-Mortality"/>....</content>
</paragraph>
</text>
<excerpt>
  <highlight>
    <text>
      <paragraph styleCode="Bullet">Pregnancy: Fetal/Neonatal Morbidity
and...</paragraph>
    </text>
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      <substanceAdministration>
        <subjectOf>
          <issue classCode="WARNING">
            <subject>
              <observationCriterion>
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                </value>
              </observationCriterion>
            </subject>
          </risk>
          <consequenceObservation>
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            <value xsi:type="CE" code="(fetal-neonatal-morbidity-and-
mortality)" codeSystem="TBD">
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            </value>
          </consequenceObservation>
        </risk>
      </issue>
    </subjectOf>
  </substanceAdministration>
</subject>
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</excerpt>
</section>
</component>
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  <section ID="Lactating-Women">
    <id root="f25a63e6-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="34080-2" codeSystem="2.16.840.1.113883.6.1" displayName="Special
Populations subsection - Lactating Women"/>
    <title>Lactating...</title>
    <text>
      <paragraph>Concentrations of captopril in human milk are approximately...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">Lactating Women: Potential for serious adverse
reactions in...</paragraph>
        </text>
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          <substanceAdministration>
            <subjectOf>
              <issue classCode="WARNING">
                <subject>
                  <observationCriterion>
                    <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
                    <value xsi:type="CE" code="(LactatingWoman)"
codeSystem="TBD">
                      <originalText>Lactating...</originalText>
                    </value>
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            </subjectOf>
          </substanceAdministration>
        </subject>
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  </section>
</component>

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        </observationCriterion>
      </subject>
    </risk>
    <consequenceObservation>
      <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
      <value xsi:type="CE" code="(serious-adverse-reaction)"
codeSystem="TBD">
        <originalText>serious adverse reactions in
nursing...</originalText>
      </value>
    </consequenceObservation>
  </risk>
</issue>
</subjectOf>
</substanceAdministration>
</subject>
</highlight>
</excerpt>
</section>
</component>
<component>
  <section ID="Pediatric-Use">
    <id root="f25bea87-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="34081-0" codeSystem="2.16.840.1.113883.6.1" displayName="Special Population
subsection - Pediatric Use"/>
    <title>Pediatric...</title>
    <text>
      <paragraph>Safety and effectiveness in children have not been...</paragraph>
      <paragraph>Infants, especially newborns, may be more susceptible to...</paragraph>
      <paragraph>CAPOTEN (captopril) should be used in children only if...</paragraph>
    </text>
    <excerpt>
      <highlight>
        <text>
          <paragraph styleCode="Bullet">Pediatric Use: Safety and effectiveness not
established. ...</paragraph>
        </text>
        <subject>
          <substanceAdministration>
            <subjectOf>
              <issue classCode="WARNING">
                <text>Safety and effectiveness not established. Use only if
other...</text>
              </subject>
              <observationCriterion>
                <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
                <value xsi:type="CE" code="(PediatricAge)"
codeSystem="TBD">
                  <originalText>Pediatric...</originalText>
                </value>
              </observationCriterion>
            </subject>
          </issue>
        </subjectOf>
        </substanceAdministration>
      </subject>
      </highlight>
    </excerpt>
  </section>
</component>
</section>
</component>
<component>
  <section ID="ADVERSE-REACTIONS">
    <id root="f25d7128-f5e7-11d8-9eec-01a868e9b85b"/>

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section"/>
<code code="34084-4" codeSystem="2.16.840.1.113883.6.1" displayName="Adverse Reactions
<title>ADVERSE...</title>
<text>
<paragraph>Reported incidences are based on clinical trials involving...</paragraph>
<paragraph>
<caption>Renal:...</caption> About one of 100 patients developed proteinuria (see...<linkHtml
styleCode="MainTitleNumber" href="#Proteinuria"/>)...</paragraph>
<paragraph>Each of the following has been reported in approximately 1...</paragraph>
<paragraph>
<caption>Hematologic:...</caption> Neutropenia/agranulocytosis has occurred (see...<linkHtml
styleCode="MainTitleNumber" href="#Neutropenia-Agranulocytosis"/>). Cases of anemia, thrombocytopenia, and
pancytopenia have...</paragraph>
<paragraph>
<caption>Dermatologic:...</caption> Rash, often with pruritus, and sometimes with
fever,...</paragraph>
<paragraph>Flushing or pallor has been reported in 2 to 5 of 1000...</paragraph>
<paragraph>
<caption>Cardiovascular:...</caption> Hypotension may occur; see...<linkHtml
styleCode="MainTitleNumber" href="#Hypotension-Patients-on-Diuretic-Therapy"/> for discussion of hypotension with
captopril...</paragraph>
<paragraph>Tachycardia, chest pain, and palpitations have each been...</paragraph>
<paragraph>Angina pectoris, myocardial infarction, Raynaud's syndrome,...</paragraph>
<paragraph>
<caption>Dysgeusia:...</caption> Approximately 2 to 4 (depending on renal status and
dose)...</paragraph>
<paragraph>
<caption>Angioedema:...</caption> Angioedema involving the extremities, face, lips,
mucous...<linkHtml styleCode="MainTitleNumber" href="#PATIENT-COUNSELING-INFORMATION"/>)...</paragraph>
<paragraph>
<caption>Cough:...</caption> Cough has been reported in 0.5 % of patients treated
with...<linkHtml styleCode="MainTitleSubTitleNumber" href="#Cough"/>)...</paragraph>
<paragraph>The following have been reported in about 0.5 to 2 percent...</paragraph>
<paragraph>Other clinical adverse effects reported since the drug was...</paragraph>
<paragraph>
<caption>Body as a...</caption> Anaphylactoid reactions (see...<linkHtml
styleCode="MainTitleSubTitleNumber" href="#Hemodialysis"/>)...</paragraph>
<paragraph>
<caption>General:...</caption> Asthenia,...</paragraph>
<paragraph>
<caption>Cardiovascular:...</caption> Cardiac arrest, cerebrovascular
accident/insufficiency,...</paragraph>
<paragraph>
<caption>Dermatologic:...</caption> Bullous pemphigus, erythema multiforme
(including...</paragraph>
<paragraph>
<caption>Gastrointestinal:...</caption> Pancreatitis, glossitis,...</paragraph>
<paragraph>
<caption>Hematologic:...</caption> Anemia, including aplastic and...</paragraph>
<paragraph>
<caption>Hepatobiliary:...</caption> Jaundice, hepatitis, including rare cases of
necrosis,...</paragraph>
<paragraph>
<caption>Metabolic:...</caption> Symptomatic...</paragraph>
<paragraph>
<caption>Musculoskeletal:...</caption> Myalgia,...</paragraph>
<paragraph>
<caption>Nervous/Psychiatric:...</caption> Ataxia, confusion. depression,
nervousness,...</paragraph>
<paragraph>
<caption>Respiratory:...</caption> Bronchospasm, eosinophilic pneumonitis,...</paragraph>
<paragraph>
<caption>Special...</caption> Blurred...</paragraph>
<paragraph>
<caption>Urogenital:...</caption>...</paragraph>
<paragraph>As with other ACE inhibitors, a syndrome has been reported...</paragraph>

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<paragraph>
  <caption>Fetal/Neonatal Morbidity and...</caption>
  See...<linkHtml styleCode="MainTitleSubTitleNumber" href="#Fetal-Neonatal-Morbidity-and-
Mortality"/>....</paragraph>
</text>
<excerpt>
  <highlight>
    <text>
      <paragraph>
        <caption>Most Common Adverse Reactions (&#8805;...</caption>
      </paragraph>
      <paragraph styleCode="Bullet">rash (sometimes with arthralgia and eosinophilia),
taste...</paragraph>
      <paragraph styleCode="CenterBold">To report SUSPECTED SERIOUS ADRs, call
(manufacturer) at...</paragraph>
    </text>
    <subject>
      <substanceAdministration>
        <subjectOf>
          <issue classCode="ADR">
            <risk>
              <consequenceObservation>
                <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
                <value xsi:type="CE" code="(rash)" codeSystem="TBD">
                  <originalText>Rash...</originalText>
                </value>
              </consequenceObservation>
            </risk>
            <risk>
              <consequenceObservation>
                <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
                <value xsi:type="CE" code="(arthralgia)" codeSystem="TBD">
                  <originalText>arthralgia...</originalText>
                </value>
              </consequenceObservation>
            </risk>
            <risk>
              <consequenceObservation>
                <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
                <value xsi:type="CE" code="(eosinophilia)" codeSystem="TBD">
                  <originalText>eosinophilia...</originalText>
                </value>
              </consequenceObservation>
            </risk>
            <risk>
              <consequenceObservation>
                <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
                <value xsi:type="CE" code="(taste-impairment)" codeSystem="TBD">
                  <originalText>taste...</originalText>
                </value>
              </consequenceObservation>
            </risk>
            <risk>
              <consequenceObservation>
                <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
                <value xsi:type="CE" code="(cough)" codeSystem="TBD">
                  <originalText>cough...</originalText>
                </value>
              </consequenceObservation>
            </risk>
            <risk>
              <consequenceObservation>
                <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
                <value xsi:type="CE" code="(pruritus)" codeSystem="TBD">
                  <originalText>pruritus...</originalText>
                </value>
              </consequenceObservation>
            </risk>
          </subjectOf>
        </substanceAdministration>
      </subject>
    </excerpt>
  </text>
</paragraph>

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        </consequenceObservation>
      </risk>
    </risk>
    <consequenceObservation>
      <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
      <value xsi:type="CE" code="(chest-pain)" codeSystem="TBD">
        <originalText>chest...</originalText>
      </value>
    </consequenceObservation>
  </risk>
  <risk>
    <consequenceObservation>
      <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
      <value xsi:type="CE" code="(palpitations)" codeSystem="TBD">
        <originalText>palpitations...</originalText>
      </value>
    </consequenceObservation>
  </risk>
  <risk>
    <consequenceObservation>
      <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
      <value xsi:type="CE" code="(tachycardia)" codeSystem="TBD">
        <originalText>tachycardia...</originalText>
      </value>
    </consequenceObservation>
  </risk>
  <risk>
    <consequenceObservation>
      <code code="(dx)" codeSystem="2.16.840.1.113883.6.1"/>
      <value xsi:type="CE" code="(proteinuria)" codeSystem="TBD">
        <originalText>proteinuria...</originalText>
      </value>
    </consequenceObservation>
  </risk>
</issue>
</subjectOf>
</substanceAdministration>
</subject>
</highlight>
</excerpt>
<component>
  <section ID="Altered-Laboratory-Findings">
    <id root="f2620509-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="34075-2" codeSystem="2.16.840.1.113883.6.1" displayName="Adverse Reaction"
subsection - Altered Laboratory Findings"/>
    <title>Altered Laboratory...</title>
    <text>
      <paragraph>
        <caption>Serum...</caption> Hyperkalemia: small increases in serum
potassium,...<linkHtml styleCode="MainTitleNumber" href="#Hyperkalemia"/>....</paragraph>
      <paragraph>
        <caption>Hyponatremia:...</caption> particularly in patients receiving a low sodium diet
or...</paragraph>
      <paragraph>
        <caption>BUN/Serum...</caption> Transient elevations of BUN or serum creatinine
especially...</paragraph>
      <paragraph>
        <caption>Hematologic:...</caption> A positive ANA has been...</paragraph>
      <paragraph>
        <caption>Liver Function...</caption> Elevations of liver transaminases, alkaline
phosphatase,...</paragraph>
    </text>
  </section>
</component>
</section>
</component>

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<component>
  <section ID="OVERDOSAGE">
    <id root="f262050a-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="34088-5" codeSystem="2.16.840.1.113883.6.1" displayName="Overdosage Section"/>
    <title>OVERDOSAGE...</title>
    <text>
      <paragraph>Correction of hypotension would be of primary concern....</paragraph>
      <paragraph>While captopril may be removed from the adult circulation...</paragraph>
    </text>
  </section>
</component>
<component>
  <section ID="DESCRIPTION">
    <id root="f2638bab-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="34089-3" codeSystem="2.16.840.1.113883.6.1" displayName="Description Section"/>
    <title>DESCRIPTION...</title>
    <text>
      <paragraph>CAPOTEN (captopril) is a specific competitive inhibitor of...</paragraph>
      <paragraph>CAPOTEN is designated chemically as 1 [(2S) 3 mercapto 2...</paragraph>
      <paragraph>Captopril is a white to off white crystalline powder that...</paragraph>
      <paragraph>CAPOTEN is available in potencies of 12.5 mg, 25 mg, 50 mg,...</paragraph>
    </text>
  </section>
</component>
<component>
  <section ID="CLINICAL-PHARMACOLOGY">
    <id root="f265124c-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="34090-1" codeSystem="2.16.840.1.113883.6.1" displayName="Clinical Pharmacology"/>
    <title>CLINICAL...</title>
    <component>
      <section ID="Mechanism-of-Action">
        <id root="f265124d-f5e7-11d8-9eec-01a868e9b85b"/>
        <code code="XSS12.1" codeSystem="2.16.840.1.113883.6.1" displayName="Clinical
Pharmacology Subsection - Mechanism of Action"/>
        <title>Mechanism of...</title>
        <text>
          <paragraph>The mechanism of action of CAPOTEN has not yet been fully...</paragraph>
          <paragraph>CAPOTEN prevents the conversion of angiotensin I to...</paragraph>
          <paragraph>ACE is identical to "bradykininase," and CAPOTEN may also...</paragraph>
          <paragraph>Inhibition of ACE results in decreased plasma angiotensin...</paragraph>
          <paragraph>The antihypertensive effects persist for a longer period of...</paragraph>
        </text>
      </section>
    </component>
    <component>
      <section ID="Pharmacodynamics">
        <id root="f26698ee-f5e7-11d8-9eec-01a868e9b85b"/>
        <code code="XSS12.2" codeSystem="2.16.840.1.113883.6.1" displayName="Clinical
Pharmacology Subsection - Pharmacodynamics"/>
        <title>Pharmacodynamics...</title>
        <text>
          <paragraph>Administration of CAPOTEN results in a reduction of...</paragraph>
          <paragraph>Reductions of blood pressure are usually maximal 60 to 90...</paragraph>
          <paragraph>Blood pressure is lowered to about the same extent in both...</paragraph>
        </text>
      </section>
    </component>
    <component>
      <section ID="Pharmacokinetics">
        <id root="f2681f8f-f5e7-11d8-9eec-01a868e9b85b"/>
        <code code="XSS12.3" codeSystem="2.16.840.1.113883.6.1" displayName="Clinical
Pharmacology Subsection - Pharmacokinetics"/>
        <title>Pharmacokinetics...</title>
        <text>
          <paragraph>After oral administration of therapeutic doses of CAPOTEN,...</paragraph>

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        <paragraph>Approximately 25 to 30 percent of the circulating drug is...<linkHtml
styleCode="MainTitleNumber" href="#Dosage-Adjustment-in-Renal-Impairment"/>)...</paragraph>
        <paragraph>Studies in rats and cats indicate that CAPOTEN does not...</paragraph>
    </text>
</section>
</component>
</section>
</component>
</component>
<section ID="NONCLINICAL-TOXICOLOGY">
    <id root="f2681f90-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="XMS13" codeSystem="2.16.840.1.113883.6.1" displayName="Nonclinical Toxicology
Section"/>
    <title>NONCLINICAL...</title>
    <component>
        <section ID="Carcinogenesis-Mutagenesis-and-Impairment-of-Fertility">
            <id root="f269a631-f5e7-11d8-9eec-01a868e9b85b"/>
            <code code="34083-6" codeSystem="2.16.840.1.113883.6.1" displayName="Carcinogenesis,
Mutagenesis and Impairment of Fertility"/>
            <title>Carcinogenesis, Mutagenesis and Impairment of...</title>
            <text>
                <paragraph>Two year studies with doses of 50 to 1350 mg/kg/day in mice...</paragraph>
                <paragraph>Studies in rats have revealed no impairment of...</paragraph>
            </text>
        </section>
    </component>
    </component>
    <section ID="Animal-Toxicology">
        <id root="f26b2cd2-f5e7-11d8-9eec-01a868e9b85b"/>
        <code code="34091-9" codeSystem="2.16.840.1.113883.6.1" displayName="Animal
Toxicology"/>
        <title>Animal...</title>
        <text>
            <paragraph>Chronic oral toxicity studies were conducted in rats (2...</paragraph>
            <paragraph>Reductions in hemoglobin and/or hematocrit values were seen...</paragraph>
            <paragraph>Captopril caused hyperplasia of the juxtaglomerular...</paragraph>
            <paragraph>Gastric erosions/ulcerations were increased in incidence in...</paragraph>
            <paragraph>In the two year rat study, irreversible and progressive...</paragraph>
        </text>
    </section>
</component>
</section>
</component>
</component>
<section ID="CLINICAL-STUDIES">
    <id root="f26b2cd3-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="34092-7" codeSystem="2.16.840.1.113883.6.1" displayName="Clinical Studies Section"/>
    <title>CLINICAL...</title>
    <text>
        <paragraph>Congestive Heart Failure: In patients with heart failure,...</paragraph>
        <paragraph>Left Ventricular Dysfunction After Myocardial Infarction:...</paragraph>
        <paragraph>Baseline blood pressure was 113/70 mm Hg and 112/70 mm Hg...</paragraph>
        <paragraph>Therapy with CAPOTEN improved long term survival and...</paragraph>
        <paragraph>CAPOTEN was well tolerated in the presence of other...</paragraph>
        <paragraph>Diabetic Nephropathy: In a multicenter, double blind,...</paragraph>
        <paragraph>The CAPOTEN group had a 51% reduction in risk of doubling...</paragraph>
        <paragraph>In two multicenter, double blind, placebo controlled...</paragraph>
    </text>
</section>
</component>
</component>
<section ID="PATIENT-COUNSELING-INFORMATION">
    <id root="f26cb374-f5e7-11d8-9eec-01a868e9b85b"/>
    <code code="34076-0" codeSystem="2.16.840.1.113883.6.1" displayName="Patient Counseling
Information"/>
    <title>PATIENT COUNSELING...</title>

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<text>
  <paragraph>Patients should be advised to immediately report to their...<linkHtml
styleCode="MainTitleNumber" href="#Angioedema"/>...</paragraph>
  <paragraph>Patients should be told to report promptly any indication...</paragraph>
  <paragraph>All patients should be cautioned that excessive...</paragraph>
  <paragraph>Patients should be advised not to use potassium sparing...<linkHtml
styleCode="MainTitleNumber" href="#Hyperkalemia"/>...<linkHtml styleCode="MainTitleNumber" href="#Agents-Increasing-
Serum-Potassium"/>...<linkHtml styleCode="MainTitleNumber" href="#ADVERSE-REACTIONS"/>...</paragraph>
  <paragraph>Patients should be warned against interruption or...</paragraph>
  <paragraph>Heart failure patients on captopril therapy should be...</paragraph>
  <paragraph>Patients should be informed that CAPOTEN (captopril) should...<linkHtml
styleCode="MainTitleNumber" href="#General"/>...</paragraph>
  <paragraph>Pregnancy. Female patients of childbearing age should be...</paragraph>
</text>
</section>
</component>
</structuredBody>
</component>
</document>

```

7.3 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).

7.3.1 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.

7.3.2 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 the Appendix for a table that shows the translation between SPL RMIM class names and SPL Schema element names.

7.3.3 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

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
		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.

7.4 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
Section.Code	38056-8	SUPPLEMENTAL PATIENT MATERIAL
Section.Code	TBD	PATIENT PACKAGE INSERT*
Section.Code	TBD	MEDGUIDE*

*The Patient Package Insert and MedGuide LOINC codes can only be used as subsections for the Supplemental Patient Material Section. These two codes should not be used unless nested within a Supplemental Patient Material section.

7.5 Implementation Notes

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

7.5.1 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 3.10 *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 <i>ActCode</i> vocabulary domain – in <i>FDALabelData</i> subset of <i>ObservationType</i>) 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 <i>ActCode</i> vocabulary domain – in <i>FDALabelData</i> subset of <i>ObservationType</i>) The description is included as free text in the 'text' field
Shape	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDASHAPE (In <i>ActCode</i> vocabulary domain – in <i>FDALabelData</i> subset of <i>ObservationType</i>) The description is included as free text in the 'text' field
Color	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDACOLOR (In <i>ActCode</i> vocabulary domain – in <i>FDALabelData</i> subset of <i>ObservationType</i>) The description is included as free text in the 'text' field
Coating	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDACOATING (In <i>ActCode</i> vocabulary domain – in <i>FDALabelData</i> subset of <i>ObservationType</i>) The description is included as free text in the 'text' field
Scoring	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDASCORING (In <i>ActCode</i> vocabulary domain – in <i>FDALabelData</i> subset of <i>ObservationType</i>) The description is included as free text in the 'text' field
Logo	In <Observation> class (an observation about a <ManufacturedProduct>) Code = FDALOGO (In <i>ActCode</i> vocabulary domain – in <i>FDALabelData</i> subset of <i>ObservationType</i>) The description is included as free text in the 'text' field
[Package(s)]	
NDC	'code' in <PackagedMedicine> class (code = the code value; codeSystem = NDC). <i>Note: located as a child of <containingPackagedMedicine> in schema.</i>
Package type	'formCode' in <PackagedMedicine> class (In the <i>EntityCode</i> HL7 vocabulary domain, there is a potential set of values in the <i>ContainerEntityType</i> subset)
Package quantity	'quantity' attribute in <Content> or <MedicinePart>
Controlled substance classification or schedule (e.g., DEA number in U.S.)	'code' in <Policy> The 'code' in <Policy> 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 <Medicine>
Active ingredient name(s)	'name' in <Substance> (playing the role of <ActiveIngredient>)
Active ingredient code(s)	'code' in <Substance> (playing the role of <ActiveIngredient>)

Active moiety code(s)	'code' in <ActiveMoietyEntity>
Strength of active ingredient	'quantity' in <ActiveIngredient>
Dosage form	'formCode' in <Medicine>
Labeled route of administration	'routeCode' in <SubstanceAdministration>
Inactive ingredient name(s)	'name' in <Substance> (playing the role of <InactiveIngredient>)
Inactive ingredient code(s)	'code' in <Substance> (playing the role of <InactiveIngredient>)
Strength of inactive ingredient	'quantity' in <InactiveIngredient>

7.5.2 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.

7.5.3 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.

7.5.4 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 would be 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 institutions 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.

7.5.5 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.

7.6 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="98765-4"
    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: <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: <10.23.4567.345>
Content-Location: canned_left_hand_image.jpeg
Content-Type: image/JPEG

... Base64 image ...

--HL7-CDA-boundary--

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

7.7 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.

7.7.1 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.

7.7.2 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 <Characteristics> class (the subjectOf a <ManufacturedProduct> or <MedicinePart>) Code = FDAIMPRINTCD (In <i>ActCode</i> vocabulary domain – in <i>FDALabelData</i> subset of <i>ObservationType</i>). The code is included as free text in the 'text' field
Size	In <Characteristics> class (the subjectOf a <ManufacturedProduct> or <MedicinePart>) Code = FDAIMPRINTCD (In <i>ActCode</i> vocabulary domain – in <i>FDALabelData</i> subset of <i>ObservationType</i>)

	The code is included as free text in the 'text' field
Shape	In <Characteristics> class (the subjectOf a <ManufacturedProduct> or <MedicinePart>) Code = FDAIMPRINTCD (In ActCode vocabulary domain – in FDALabelData subset of ObservationType) The code is included as free text in the 'text' field
Color	In <Characteristics> class (the subjectOf a <ManufacturedProduct> or <MedicinePart>) Code = FDAIMPRINTCD (In ActCode vocabulary domain – in FDALabelData subset of ObservationType) The code is included as free text in the 'text' field
Coating	In <Characteristics> class (the subjectOf a <ManufacturedProduct> or <MedicinePart>) Code = FDAIMPRINTCD (In ActCode vocabulary domain – in FDALabelData subset of ObservationType) The code is included as free text in the 'text' field
Scoring	In <Characteristics> class (the subjectOf a <ManufacturedProduct> or <MedicinePart>) Code = FDAIMPRINTCD (In ActCode vocabulary domain – in FDALabelData subset of ObservationType) The code is included as free text in the 'text' field
Logo	In <Characteristics> class (the subjectOf a <ManufacturedProduct> or <MedicinePart>) Code = FDAIMPRINTCD (In ActCode vocabulary domain – in FDALabelData subset of ObservationType) The code is included as free text in the 'text' field
[Package(s)]	
NDC	'code' in <PackagedMedicine> (code = code value; codeSystem = NDC)
Package type	'formCode' in <PackagedMedicine> class (In the EntryCode HL7 vocabulary domain, there is a set of potential values in the ContainerEntityType subset)
Package quantity	'quantity' attribute in <Content> or <MedicinePart> classes
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.)	'code' in <Policy> The 'code' in <Policy> 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 <Medicine>
Active ingredient name(s)	'name' in <Substance> (playing the role of <ActiveIngredient>)
Active ingredient code(s)	'code' in <Substance> (playing the role of <ActiveIngredient>)
Active moiety code(s)	'code' in <ActiveMoietyEntity>
Strength of active ingredient	'quantity' in <ActiveIngredient>
Dosage form	'formCode' in <Medicine>
Labeled route of administration	'routeCode' in <SubstanceAdministration>
Inactive ingredient name(s)	'name' in <Substance> (playing the role of <InactiveIngredient>)
Inactive ingredient code(s)	'code' in <Substance> (playing the role of <InactiveIngredient>)
Clinical pharmacology	'Section.code'
Animal pharmacology/toxicology	'Section.code'

Clinical studies	'Section.code'
References	'Section.code'

7.8 References

Reference Information Model (RIM) References

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Other data standards references

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(<http://cap.org.html/lip/labstandards.html>)

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

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www.w3.org/1999/05/06-xmlschema-1/
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www.w3.org/Style/XSL/
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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://csrc.nist.gov/publications/fips/fips186-2/fips186.2.pdf>)

7.9 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 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.

7.10 Changes To Release 1

The following are changes from SPL Release 1. These changes reflect changes to the SPL schema itself and changes to CDA that have propagated to SPL.

7.10.1 Summary of Changes to SPL Release 1 Schema

The following changes outlines schema changes from SPL Release 1 to Release 2. Changes are grouped together by change set to identify common reasons for a set of changes.

Table 4: Changes from SPL Release 1

<u>Current Release 1 Name and Relative Location</u>	<u>New Element Name</u>	<u>Chg. Set*</u>	<u>Rationale</u>
Document	document	1	HL7 XML style for elements and attributes is having the initial letter lower case and then camelCase convention.
+ author			
+ + assignedEntity			
+ + + assignedPerson			
+ + + representedOrganization			
+ legalAuthenticator			
+ + assignedEntity			
+ verifier			
+ + assignedEntity			
+ relatedDocument			
+ + relatedDocument			
+ component			
+ + StructuredBody	structuredBody	1	HL7 XML style for elements and attributes is having the initial letter lower case and then camelCase convention.
+ + + component			
+ + + + section			
+ + + + + author			
+ + + + + replacementOf			
+ + + + + priorSectionReplaced	sectionReplaced	N	HL7 naming conventions.
+ + + + + component2	component	2	Previous versions had arbitrary use of component elements, e.g., <component1> and <component2> that were a source of confusion and errors. <component> can now be substituted by making section a choice in RMIM.
+ + + + + Observation	observation	1, 5	Observations in sections are unrelated to any subject, and are difficult to associate with components of a multicomponent product. Observations are deprecated in favor of characteristics. Observations are a choice for a component <i>with</i> a <section> or <observationMedia> rather than being a <component> of a <section>.
+ + + + + ObservationMedia	observationMedia	1	HL7 XML style for elements and attributes is having the initial letter lower case and then camelCase convention.
+ + + + + subject			
+ + + + + manufacturedProduct			

*Changes are grouped together by change set to identify a common reason for a set of changes.

7.10.2 Changes to CDA Narrative Block Propagated to SPL Release 2

The following summarize proposed changes to the CDA narrative block that have propagated to SPL Release 2. Changes in red represent additions to the current CDA schema or deprecated elements/attributes; deletions are represented by strikeouts.

Table 5. Changes to CDA Propagated to SPL Release 2

```

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

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

<!ELEMENT content (#PCDATA | content | link linkHtml | sub | sup
| br |
  footnote | footnoteRef | renderMultiMedia)*>

<!ATTLIST content
  %textAtts;
emphasis (bold | underline | italics | yes) #IMPLIED
  revised (insert | delete) #IMPLIED>

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

<!ELEMENT linkHtml (#PCDATA | footnote | footnoteRef)* >

<!ATTLIST linkHtml
  name CDATA #IMPLIED [DEPRECATE]
  href CDATA #IMPLIED
  rel CDATA #IMPLIED
  rev CDATA #IMPLIED
  title CDATA #IMPLIED
  %textAtts;>

<!ELEMENT sub (#PCDATA)>

<!ELEMENT sup (#PCDATA)>

<!ELEMENT br EMPTY>

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

<!ELEMENT footnoteRef EMPTY>
<!ATTLIST footnoteRef
  %textAtts;
  IDREF IDREF #REQUIRED>

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

<!ELEMENT renderMultiMedia (caption?)>

```

```

<!ATTLIST renderMultiMedia
  referencedObject IDREFS #REQUIRED
  %textAtts;>

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

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

<!ELEMENT item (#PCDATA | caption | content | link linkHtml |
sub | sup
| br | footnote | footnoteref | 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
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<!ENTITY % Scope "(row|col|rowgroup|colgroup)">

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<!ELEMENT tbody (tr)+>
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  renderMultiMedia)*>
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sup | br
| footnote | footnoteRef | renderMultiMedia |
  paragraph | list)*>

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8 APPENDIX -- ANALYSIS OF THE COMPONENTS OF “DOSE INSTRUCTIONS”, WITH DEFINITIONS (INFORMATIVE)

This section is an analysis of common dosage regimens and their mapping to HL7.

8.1 Dose Instructions

A Dose Instruction is the full set of information that supports the correct administration of a medication to a patient in order for it to have its therapeutic effect. Within this set of information, there are a variety of different concepts represented, such as the amount of medication to be administered, the frequency with which it is to be administered etc. These are termed the component parts of the instruction, and they themselves may have attributes, or sub-types, within them.

A single “dose instruction” may be complex, and therefore may be split into a number of separate clauses: each clause can then be split into its component parts.

Once this has been done, the clauses can be concatenated together again to reproduce accurately the sense of the instructions. So that this concatenation keeps the correct sense of the instructions, there needs to be a mechanism to put the clauses and their components together in the right order; this is Sequence Indicator (see below).

8.2 Dose Instructions Clause

Definition:

A Dose Instructions Clause is a single statement that stands “on its own” to describe a single set of dosage instruction information.

Discussion and Examples:

A clause is usually distinguished by need to describe more than one single dose quantity or by the need to describe two types of dosage actions (as in the last example) or by the need to specify more than one [sequential] frequency and/or treatment duration.

The clauses may be sequenced, with their order indicated by a sequence integer. In text, this is often indicated by the use of the word “then”

Example: “Take 1 capsule at night for 4 nights, then increase to 3 capsules at night for next 4 nights, then increase to 5 capsules at night”

Take 1 capsule at night for 4 nights – *Clause Sequence - 1*

Joining word “then”

increase to [taking] 3 capsules at night for next 4 nights – *Clause Sequence - 2*

Joining word “then”

increase to [taking] 5 capsules at night – *Clause Sequence - 3*

The clauses may be “in parallel” and “conjoined”, indicated by the use of the word “and” between the two distinct clauses, representing that both clauses are valid together, as in the following example:

“Take one capsule in the morning and two at bedtime”.

Take one capsule in the morning – *Clause Sequence - 1*

Joining word “and”

take two [capsules] at bedtime – *Clause Sequence - 2*

The clauses may be “alternatives” (disjoined) and there is a choice between which one of the two (or more) clauses is valid; this is indication by the use of the word “or” between the two distinct clauses, such as

“Take two at breakfast time, or take one at breakfast time and one at lunchtime”

Take two at breakfast time – *Clause Sequence - 1*

Joining word “or”

take one at breakfast time and one at lunchtime – *Clause Sequence - 2*

Note: a single dose instruction **must** refer to a single described medicinal product.

The following example would only be valid if the medicinal product description was given as a combination pack:

“Apply a new patch twice a week and take one tablet daily for the 12 days as instructed on pack”.

Apply a new patch twice a week – *Clause Sequence - 1*

Joining word “and”

take one tablet daily for the 12 days as instructed on pack - [Clause Sequence - 2](#)

8.2.1 Clause Sequence and Association

Definition:

The Component Sequence is the numerical (integer) value that allows each dose instruction clause to be placed in its correct order (i.e. that which the original author deemed appropriate) communicate the full Dose Instruction information.

The Component Association is the description of the association between two dose instruction clauses (and, or, etc.). This is the representation of the relationship between two or more clauses that may be an “and” (“conjunction”) or an “or” (“disjunction”).

Mapping to HL7 v3 Pharmacy Message:

Each Dose Instructions Clause should be a “sub” SBADM act, and the relationship between them will be a Component (COMP); the sequence will be indicated by the ActRelationship.sequenceNumber.

There may be a requirement to have sibling sub SBADM acts to represent complex instructions, these may share the same ActRelationship.sequenceNumber, have different ones, or have no ActRelationship.sequenceNumber, as appropriate. [Clause coming before a word such as “then” should have a lower ActRelationship.sequenceNumber than the one coming after].

Description of the Association between two (or more) Act Relationships is managed by the use of the conjunction. Code on the relevant Act Relationship between the two SBADM acts holding the dosage information.

8.3 Components in a Dosage Clause

Within any Dosage Clause, there may be any number of “Components” of dosage information. These have been identified, analysed and are described in the sections below. Within the Dose Analysis, each Component is seen as being linked to the clause. Some Components, such as Quantity, have been further sub-divided, so that there are attributes for the Component.

It is not possible, at this level of description, to specify the cardinality of Components within a Dose Clause: for example, it might seem sensible to require all Dose Clauses to have a representation of the Dose Quantity, but the common clause to use for creams and ointments is “Apply twice a day” – this has no quantity implicit in it, yet it communicates enough information for the medication to be administered.

Practical implementations of the Dose Syntax may wish to build patterns for Dose Clauses, and to make certain components, and/or certain attributes of components mandatory within these patterns, for reasons of safety and clarity.

8.3.1 Component Sequence Indicator

Definition:

This is the numerical (integer) value that allows each of the items of component information present in a particular clause of dose instruction information to be reassembled after the analysis and structuring process into the correct (i.e. that which the original author deemed appropriate) order.

Discussion and Examples:

A Dose Instruction may be entered into an application as a single process, or as a component process and the order in which the information is entered may vary according to the application. In order to keep this order and therefore the “sense” of the instruction through the process of analysis, decomposition, transmission and reassembly in another application, each sub-clause and component must “know” where it fits in relation to the others. Therefore, the function of the Component Sequence Indicator is to allow dose instruction information to be reassembled and presented in the same semantic order as was originally intended by the initiator of the dosage instructions being communicated. For example, a prescription with the following (fairly complex/detailed) Dose Instruction Clause would be analysed as follows:

“Two tablets to be taken with plenty of water, every Wednesday for three months, starting in the first week of September”

“Two tablets” – **Quantity** - [Component Sequence - 1](#)

“to be taken” – **Action** – [Component Sequence - 2](#)

- “with plenty of water” – **Instruction** - **Component Sequence** - 3
 “every Wednesday” – **Timing (frequency)** - **Component Sequence** - 4
 “for three months” – **Timing (duration)** - **Component Sequence** - 5
 “starting in the first week of September” – **Timing (Timing Start)** - **Component Sequence** – 6

Note: The Dose Syntax works to the principle that there is (currently) no requirement to “use” the exact textual representation of the original information in the receiving application, to allow for language translation and context translation (patient-friendly information may use different descriptive terms from those commonly used by clinicians referring to the same concept). However, a receiving application should *display* information as described by the information contained in the Sequence Indicator attribute. When it then comes to *using* this information further, for example information received into a dispensing system that is then used for dispense labelling, there is also (currently) no requirement for that order to be maintained, if it is more appropriate, in the new context, to have a different order. Therefore, using the example above, the receiving application may initially display the instruction as:

“Two tablets” “Take” “with plenty of water” “Wednesdays” “for three months” “starting first week in September”

but offer the following as the Dose Instruction to be used on the dispensing label:

“Take two tablets every Wednesday, swallowed down with plenty of water. Start on the first Wednesday in September and continue for three months”

Additionally, the dispensing label may wish to be make the duration very clear, and add

“until the last Wednesday in December”

to the end of the clause.

Mapping to HL7 v3 Pharmacy Message:

Currently, this does not map to a V3 message. Is there truly a requirement for this?

Action

Definition:

An Action is the verb description of the actual process of administration of the medication to the patient.

Discussion and Examples:

This concept describes the action that must be performed in order for the medication to be administered to the patient. This is a single concept but is described differently dependant on the role of the person performing the action, that is, whether that be by the patient acting on themselves, or by a parent/carer/healthcare professional.

Examples:

“Take one three times a day” – Action “Take” for a self administration

“Give one three times a day” – Action “Give” for carer administration to a child

In Secondary Care, if a dosage instruction is “written” as opposed to the more common “charting”, then “administer” is often used as the “action” word. Charted dosages do not usually have the “action” concept made explicit.

Note:

“Action” must not be confused with preparation instructions (which often contain action verbs such as “dilute” or “mix”).

Action Vocabulary:

Take
 Give
 Apply
 Administer
 Swallow
 Chew
 Inject
 Use

Traditionally, the Action information was/is described using the passive voice (to be taken, to be applied). This is becoming less widely used, as it is thought that the active voice is easier to understand and less likely to be misinterpreted. However, a particular application may wish to use the passive voice to describe Actions, or offer a choice.

NB: Currently no appropriate S-CT vocabulary appears to be available.

Mapping to HL7 v3 Pharmacy Message:

Currently, no exact mapping exists in V3 for this concept, it is all covered by the overall concept of "administration", hence the "Substance Administration" Act.
The specific information could be described as a part of the Route-Site-Method set of information instead.

8.3.2 Quantity

Definition:

The Quantity is the "amount" of the described medication to be administered to the patient at a single point in time (i.e. a single dosage act, which may itself be a dosage instructions clause).

Discussion and Examples:

Most dosage clauses will have a quantity specified: but not all do (e.g. "apply three times a day" does not, there is an implicit understanding that "some" of the medicine will be applied three times a day).

The dose quantity may be described in a number of ways:

1 (one) [each]; 2 sprays; one 5ml spoonful; 1 pair of ampoules; one drop, one to two puffs; one applicatorful, one metered dose, a quarter of a tablet, 50mg, one 5ml spoonful, 2.5ml, 750microgram/kg bodyweight, 1.2 MU, 5,000 units, 1cm, half an inch; one fingertip's worth.

For each of these, there is, usually, a numerical value and a unit of measure; although sometimes the unit of measure is implicit (e.g. the "one" in "one to be taken three times a day" is actually "one tablet" [or one capsule etc.]). This is expressed in for Dose Quantity by the use of the data type "Physical Quantity" <PQ>, which captures both the value (a real number) and the unit of measure for that number in the one expression. Unit of Measure should be expressed using UCUM units.

Within the overall description of quantity, there may be a range of values specified: e.g. 2-6 tablets, 100-200mg, one to two puffs. This can be described in the syntax using the "Interval" structure within the quantity attribute. All or a selection of the following value types may be used to describe a range using the interval structure:

"Low" – the bottom end of the range – the "two" of "two to six tablets"

"Low closed" – whether the bottom end of the range is included in the range or not (two or more, versus more than two [i.e. three or more]) - This is a Boolean field, and the default value is Y

"High" – the top end of the range – the "six" of "two to six tablets"

"High closed" – whether the top end of the range is included in the range or not (six or less, versus less than six [i.e. five or less]) - This is a Boolean field, and the default value is Y

"Width" – distance between the high and the low (4 in above example)

"Centre" – mid point between high and low (also 4 in this example)

Data Structure Population

Although the structure of the Quantity may have the six Interval attributes, there is no requirement to populate all six fields with data for any one expression of dose Quantity: indeed there are extremely few situations in which it is envisaged that there would be any requirement to populate all the fields, the one exception might be in specifying a complex dosage that is going to be administered by a device, such as an infusion given in an ITU.

If the Dose Instruction has only one value, that is, there is no *range* specified, and the majority are of this type (for example: "50mg", "one 5ml spoonful", "two capsules"), then the agreed convention is to place this in the "low" attribute of the structure: all other attributes would remain unpopulated.

As noted above, the "Low Closed" and "High Closed" attributes are Boolean, with the default as "Y", therefore signifying that, unless this is changed to "N", all ranges will be considered "inclusive".

Description and Units Consistency

The quantity description *must* be consistent with the description of the medicine: a prescription where the medication is described as "amoxicillin 250mg capsule" may have its dose quantity described as "one" [one capsule] or any multiple of 250mg [250mg, 500mg etc.]; a prescription where the medication is described just as "amoxicillin" (i.e. the VTM level concept in NHS dm+d) may only have its dose quantity described as a quantity with appropriate units, which in this case is milligrams. Medicines that are available as products where the unit can

be divided (such as scored tablets, vials etc.) may have their dosage expressed in any sensible portion or multiple of this.

This consistency is particularly important in two particular scenarios:

Firstly, if some form of manipulation (e.g. dilution or preparation) of the medicine is performed prior to its administration. For example, the instruction for salbutamol for nebulisation might be described as:

"Give 2.5mg of salbutamol in 2.5ml saline via a nebuliser every 6 hours"

The description of the **medicine to be administered** is "Salbutamol 2.5mg *inseparably mixed with* 2.5ml saline"; this may be achieved using a 2.5mg/2.5ml unit dose vial, or by dilution of a different strength of unit dose vial or the 5mg/ml respirator solution. In the latter two cases, the dilution must be described as an "extemporaneous preparation" as a single administrable medicine is made, at the time of administration, from two other preparations. In the case where an order (prescription) is described using the 2.5mg/2.5ml unit dose vial, the dose quantity could either be "one" or "2.5ml".

In the case where the order (prescription) is described using the extemporaneous preparation method, then the dosage must reflect the final preparation, so the quantity must be either "2.5ml" or "2.5mg/2.5ml". [See also below, in the Dilution/Preparation Instructions].

Secondly, if the description of the medicine to be administered is given as a such that it cannot be consistent with the units in which the dose quantity is expressed, because the description of the medicine is "a larger whole" than the dose quantity measured portion to be taken from it, then the "measured portion" must be described separate from the dose quantity. For example, if the description of the medication to be administered is a "pack" description (e.g. a 200 dose Salbutamol 100microgram/actuation Inhaler) then a dose quantity of "2" must not be interpreted as "2 inhalers", but as "2 actuations". "An actuation" is not a UCUM unit, and therefore cannot be communicated in the "units" attribute of the PQ datatype; it must be described using an additional attribute of the SBADM act, the administrationUnit attribute.

Note: when the attribute "administrationUnit" is used in a SBADM act, it must apply to all expressions of dose quantity within that act, not just the doseQuantity, but also the maxDoseQuantity and rateQuantity, as appropriate.

For example, if the description of a medicine was "Paracetamol 500mg tablets 1x100 pack", and the doseQuantity expressed as "2" and the administrationUnit expressed as "tablet(s)", and the prescriber also wished to state a maximum dose quantity, the administrationUnit of "tablet(s)" would also apply to the value stated in the maxDoseQuantity numerator attribute; therefore the maximum dose quantity would have to be stated in terms of the maximum number of tablets, not as, for example, "4g per 24 hours".

These patterns of consistency are determined by business rules that cannot be enforced by the dosage instructions syntax/structures themselves, but must be implemented within clinical applications.

Mapping to HL7 v3 Pharmacy Message:

Each Dose Quantity will be represented by dose.Quantity in a SBADM act, either the core SBADM act or a sub SBADM act joined by a Component (COMP) act relationship.

Note: where necessary, the administration unit is specified in the separate attribute "administrationUnit".

Quantity Qualifier

In the textual description of a dosage clause, for clarity of communication, there may be a modifier included in the description of the quantity, often when the unit of measure for the quantity is a standard unit rather than a "pharmaceutical" unit.

Example: "Apply 2cm of gel to the skin of the trunk every morning"

Quantity: "2" Unit of Measure: "cm" Modifier: "of gel"

Example: "Take 5ml of the mixture every 8 hours"

Quantity: "5" Unit of Measure: "ml" Modifier: "of the mixture"

Example: "Take one blue tablet every morning"

Quantity: "1" Unit of Measure: "tablet" Modifier: "blue"

Mapping to HL7 v3 Pharmacy Message:

Currently, no exact mapping exists in V3 for this concept.

Quantity Upper Bound

Definition:

The Quantity Upper Bound is the upper limit of the amount of a dosage; it is usually coupled with a period of time over which that amount is valid for within the dose clause: this time must be described using the denominator part of the ratio attribute.

Discussion and Examples:

There are types of dosage instruction that contain information on an “upper limit” for the dose quantity, for example: “Take two tablets every 4-6 hours when required, to a maximum of eight per day” – the “eight tablets” is the upper bound quantity.

When describing an upper bound quantity such as the one above, the duration of time that the dose quantity limit is set in is also described, in this case “per day” or more precisely “24 hours”. The datatype used to describe this information is a ratio, where the numerator is the maximum quantity (in units comparable to the dose quantity) and the denominator is a period of time (value + unit) – for example: “maximum dose is 50 mg per 24 hours”.

A Quantity Upper Bound is distinguished from the high point of a range because of the coupling with the thing that limits it (usually a time period). The upper bound quantity describes a total dose amount to be calculated cumulatively from more than one dose administration event occurring within the set limit, rather than the high point in a dose range appropriate for a single dose administration event.

Note:

Conceptually it would be possible to specify a “lower bound dose quantity” (for example: take a minimum of 300mg per day), no actual examples of this type of instruction have been found.

Mapping to HL7 v3 Pharmacy Message:

This information would be held in the maxDoseQuantity attribute of the SBADM act or a sub SBADM act as appropriate.

8.3.3 Timing

Definition:

The Timing describes “when” the prescribed medication is to be administered to the patient.

Dose Frequency

This is the “how often” the medication is to be administered. This information can be represented very differently, depending on the setting in which it occurs.

“Regular” Frequency Descriptions

In UK ward-based secondary (institutional) care, the “how often” a medicine is to be administered is commonly represented by the use of printed charts, where the times of the specified “medicine rounds” are represented by columns, each headed by the time of one of the rounds: the clinician marks in the appropriate column(s) when the medicine is to be administered. The representation is therefore of administration at specific times (usually throughout the 24 hour period).

e.g.:

Drug	Route Form	Dose Quantity	06.00	08.00	10.00	12.00	14.00	18.00	22.00
Gentamicin	IV	60mg	X				X		X
Benzylpenicillin	IV	1.2g	X			X		X	X

Secondary (institutional) care also uses charting to represent/communicate information about medications to be given over a period of time, such as infusions. These are discussed in greater detail below. Textual description for some information (for example, “when required” medication) is also used, usually in a separate part of the overall prescription sheet.

In other care settings, the “how often” a medicine is to be administered is usually represented by text, either by the full word description, or by commonly recognised abbreviation of this description. There are commonly two different ways to represent the “how often” a particular dose of medication should be given – firstly by specifying a time interval between doses, secondly by specifying how often during a named time period (often “a day”) the dose should/may be taken.

e.g.:

give 500mg intravenously every 6 hours [q 6 h] – specific time interval between doses
 apply three times a day [t.d.s] – how often in a specified time period

In addition, in some realms (e.g. the Netherlands), frequency of administration is commonly constructed by selecting a “number of administrations” and coupling this with a vocabulary to represent the unit of time that this number of

administrations should take place in. This is analogous with the “how often in a specified time period” but is constructed differently.

e.g.:

“2” (number) per “day” (vocabulary)

“6” (number) per “week” (vocabulary)

For all but the institutional specific times expression of frequency, it is possible for there to be expression of a range of frequency values:

e.g.:

give 500mg intravenously every 4 -6 hours

apply two to three times a day

In some cases, only the upper or lower limit of a range is expressed:

e.g.:

give 500mg intravenously not less than every 8 hours

apply to a maximum of four times a day

As with the description of Dose Quantity as an “Interval”, this information is captured using the appropriate combination of High, High Closed, Low, Low Closed, Width and Centre attributes, thus:

give 500mg intravenously every 4 -6 hours Low = “every four hours”; High = “every six hours”

apply two to three times a day Low = “twice a day”; High = “three times a day”

give 500mg intravenously not less than every 8 hours Low (only) “every eight hours”

apply to a maximum of four times a day High (only) = “four times a day”

To summarise the above, there is a requirement to represent the “how often” as:

- 1) one or more specific but repeating times throughout a period (usually 24 hours)
- 2) a “frequency” of a number of times within a period (may be a 24 hour day or a week or a month), with range
- 3) a specific time interval between doses, with range

Activity/Event Related Frequency Descriptions

The “how often” part of medicines administration instructions may also be described using phrases that seem to “tie” the administration to an event or an activity.

e.g.:

take one [tablet] at breakfast-time – “tied” to a meal time, a “daily living” activity

In order to correctly communicate the “how often” information in phrases such as these, which are commonly used, it is necessary to analyse them a little further. For example, does the example above mean:

“One to be taken once every day and by the way breakfast is the most sensible/convenient/easily remembered time to do this, but if you forget at breakfast, or you don’t have breakfast, taking one once in every 24 hour period is still absolutely what you should do”

Or does it mean:

“One to be taken after the first meal of your day, and if you don’t eat breakfast, or forget to take the medicine, give up and don’t take it for that 24 hour period because it is vital that this medicine is taken with the first meal of your day”

Although this may appear extreme, it is attempting to highlight the difference between what is truly “frequency” information and the ways in which this is expressed in common use. It highlights the difference between prescriptive information and additional supportive or suggestive information and how this is implicit in certain phrases in common use. Prescriptive instructions will require that “if event or activity X does not happen, then the medicine administration does not happen”; whereas supportive information accepts that “if event or activity Y does not happen, the medicine administration should still happen”.

If one accepts that the first interpretation of the example above is actually what is intended, then the true “frequency” of administration is implicit in the statement and can/should be made explicit in electronic communication to support such activities and decision support dose calculation checking, compliance checking and stock management. In order to do this, the common phrases found in dosage instruction should be “mapped” to an appropriate mathematical expression of their frequency, as well as a code to represent the particular activity/event information that the phrase communicates.

The following are other examples of dosage instructions where no frequency of administration is explicitly articulated, but there is timing information given:

take two tablets three days **before travelling – tied to a particular “life” activity**
 take one capsule **on days 5-10 of the menstrual cycle – tied to a particular “clinical” event**

Using the principle articulated above, these could be restated as follows:

Take two tablets *once a day* three days before travelling [and only on that day]

Take one capsule *once a day* on days 5-10 of the menstrual cycle

Therefore, in the first example, the actual frequency is “once” and the “three days before travelling” is a start time which is related to a “precondition” of travelling (in that if the travel is cancelled before the three days, then the medication need not be taken). See below in “Timing Start/Stop” and in “Qualifying Information” for a further discussion of this. The second example follows the same pattern, with the “precondition” being a clinical event.

Named Interval Descriptions

However, there will be dosage instructions clauses that, although they have information about “how often” to take the medicine, do not have any clear (mathematical) expression of frequency in terms of “how many times in a named time interval”. An example of this would be:

take one capsule **after each loose stool – tied to a particular “clinical” event**

apply **after each nappy change – tied to a particular “life” event**

Since these actually state “take one capsule *whenever* the diarrhoea occurs” and “apply at *every* nappy change” and it is impossible to know how often this will be, and in some cases for how long, this type of expression cannot have a “mathematical” frequency description. It can, however, be expressed as a coded description of the event, using a standard vocabulary.

Dose Duration

The Dose Duration is the amount of time that an individual dose takes in order for it to be administered. This information is important for infused medications, and for treatments that require a “contact time”.

e.g.: give 30mg via syringe driver **over 12 hours**
 mix into a bath of warm water and immerse body **for 30 minutes**

Because this attribute is described by an interval of time with the facility to describe a range of values, with low, low closed, high, high closed, width and centre values being specified, it is possible to represent information such as “infuse over 30-60 minutes” as well as the single length durations of the examples (where just the low value is used).

However for the majority of dose types this will effectively be instantaneous. A tablet is swallowed and there is little value in knowing how long the swallowing process takes. Therefore, for an “instant” dose, such as the taking of a tablet, the start (low) and end (high) time stamps are the same (both zero) and the width is zero, also.

Mapping to HL7 v3 Pharmacy Message:

This information will be held in the effectiveTime attribute of the relevant SBADM act or sub act.

Timing Start Stop

Definition:

The Timing Start Stop identifies “when” the administration described in the dosage clause should start and/or stop: this may alternatively be expressed as the treatment duration.

Discussion and Examples:

Although a significant proportion of all medication treatments are ongoing, with no (currently) foreseeable end point, there are instances where a particular set of dosage instructions described in a Dose Instructions Clause may have a time to start and/or a time to stop that administration.

Just as in the Timing section, there are various patterns of representation of this information:

Specific Times:

Take one tablet three times a day, starting 1 January 2004, finishing 5 January 2004.

This is rare in community practice, but does occur in secondary care, particularly when treatment protocols for chemotherapy etc. are being followed.

There may be occasion where a specific start and stop time is implicit in a phrase:

Take the contents of one sachet now and repeat after 14 days

The “start” time is implicitly “today, as soon as you can” and linked to that there is a stop time also implicit, which is 15 days hence, so this instruction could be expressed frequency of once every 14 days, with a start and stop time of today and 15 days onward.

Number of Doses

Occasionally, the end of a treatment period is marked by having reached a specified number of doses being administered:

e.g.:

Take every 2 hours, for 5 doses

The “stop time” is stated as after 5 doses have been administered, which strictly speaking could be calculated as 8 hours and 4 minutes after the first treatment was administered, if the administration takes only 1 minute to perform, but pragmatically the administration would be seen to have ended after 10 hours.

More commonly, the start and stop time of a treatment would be implied by the use of Treatment Duration:

Treatment Duration

The Treatment Duration is duration of time that a particular set of dosage instructions is to be valid for. As discussed above, a complete set of Dosage Instructions may contain one or more Dose Instructions Clauses, each of which may have a Treatment Duration. In the example (clauses) below, the Treatment Duration describes the length of time (duration) of a “Dose Quantity + Frequency” instruction.

e.g.: take one [capsule] three times a day **for five days**

In common with Dose Duration, Treatment Duration is represented by an interval of time with the facility to describe a range of values, so that such duration expressions as “for 5-7 days” or “for 4-6 weeks” can be clearly communicated.

Preconditions

Some dosage instructions have start and/or stop information that is dependent on a certain event or activity taking place; this is termed a “Precondition”.

e.g.:

take one tablet every morning **starting three days before travel**

apply twice a day, finishing **on day 21 of the menstrual cycle**

In the first example, in order for the medicine administration to start, it must be a time that is “three days before travel”, whereas in the second example, the medicine administration should stop when the time gets to “day 21 of the menstrual cycle”.

Note: Precondition may also be used as a “trigger” for a medicine administration that is possibly “intermittent” rather than continuous or with explicit start/stop times. This is often indicated by the words “if” or “when” and therefore includes some very common instructions, as well as rarer more complex examples:

e.g.:

“Take two tablets every four to six hourly, **when required for pain relief**”

“Give one tablet once daily, **only if the pulse rate is above 80 beats per minute**”

In the first example, the precondition is “the requirement for pain relief”; in the second, it is “a measured pulse with a value of greater than 80 beats per minute”.

Mapping to HL7 v3 Pharmacy Message:

Precondition information should be described using the act relationship of “has Precondition” (PRCN) linked to an Observation act describing the activity or event that forms the precondition. This requires that the thing described in the related act must be true before medicine is administered.

Maintenance

There are also dosage instructions have “maintenance” information in them, in that the dosage is designed to produce a particular maintenance level of effect, and does not automatically “stop” when that level is reached, indeed, it should continue

e.g.:

Infuse 2-5micrograms/kg/min **to maintain systolic blood pressure at greater than 70mmHg**

Mapping to HL7 v3 Pharmacy Message:

Maintenance information should be described using the act relationship of “has Continuing Objective” (OBJC) linked to an Observation act in criterion mood describing the activity or event that is the required outcome.

Final Objective

Some dosage instructions have stop information that is dependent on a certain event or activity taking place; this is termed an “Outcome” or “Final Objective”.

e.g.:

take one tablet every morning **until the bleeding stops**

In order for the medicine administration to stop, there must be the observation (event) that “the bleeding has stopped”.

Mapping to HL7 v3 Pharmacy Message:

Outcome information should be described using the act relationship of “has Final Objective” (OBJF) linked to an Observation act in criterion mood describing the activity or event that is the required outcome. It carries the connotation of “reach, then stop” for the service act (in this case the Substance Administration).

Timing Appendix:

Representation of Complex Timing Instructions

There is sometimes a mixture of different types of timing in a complete dosage instruction:

e.g.:

“Take one tablet three times a day for five days, starting on day 5 of the cycle, for three cycles”

This needs to be analysed as its component sub-clauses, then the timing attributes in each clause identified.

As stated previously, in analysis of dosage clauses, it must be noted that a single timing specification applies to a single dose quantity. Where there are multiple dose quantities, there can be a timing specification for each dosage quantity, as well as an overall timing specification that acts as an outer bound on the timings of the various dosage amounts, which in itself is a separate timing specification for the overall clause.

e.g.:

“Take 1 capsule at night for 4 nights, then increase to 3 capsules at night for next 4 nights, then increase to 5 capsules at night for 8 nights”

Take 1 capsule at night for 4 nights – Clause Sequence – 1; Timing “once daily (at night) for 4 nights increase to [taking] 3 capsules at night for next 4 nights – Clause Sequence – 2; Timing “once daily (at night) for next 4 nights increase to [taking] 5 capsules at night – Clause Sequence – 3; Timing “once daily (at night) for next 8 nights

Overall Timing Clause – Treatment Duration = 16 days (4 + 4 + 8)

8.3.4 Route-Site-Method

Definition:

Route-Site-Method describes “where” and “how” the prescribed medication is to be administered to the patient.

Discussion and Examples:

These components describe the route into the body, where on the body the medicine makes its entry or the method of administration to be used. They allow the prescriber to give specific direction to the patient and/or parent/carer/healthcare professional about “where” or “how” to administer their prescribed medication.

Route-Site-Method is composed of the three separate components allowing each to stand alone if required. All, one, two or none of the components may be used dependent on the medication prescribed and the intent of the prescriber.

Examples:

Take one [tablet] three times daily (none)

Inject 100mg/5mL IV (route)

Apply to the right eye twice a day (site)

Apply to the affected area with gentle massage (site and method)

Route

This describes which route the administered medication takes into the body and constitutes part of the “where” (the other part being site – see below). It is the “way in” or the course the medication must take to get to its’ destination (i.e. its’ site of action).

Examples:

oral, rectal, ocular, IV, SC, IM

Route can be implied from the dose form and would therefore not need to be specifically articulated

Examples:

Paracetamol 500mg tablets

Take two [tablets] four times daily

Implied route – Oral

In other cases, route must be explicitly stated at time of prescribing where confusion may otherwise arise.

Example:

Betnesol 0.1% ear/eye/nose drops

Two drops every three hours

Prescriber stated route – aural

Mapping to HL7 v3 Pharmacy Message:

Route of Administration information should be described using route.Code attribute in the appropriate SBADM act or sub act.

Site

This describes the specific area of the body “where” the medication is administered to. The site can be seen as the particular location where an activity is happening (or has happened). It can be specific including for example laterality (e.g. apply to the **right eye**) or more general (e.g. apply to the **affected area(s)**)

Some directions to a patient to simply perform an action are ambiguous without qualifying these directions with further instructions as to “where”. Without the “where” qualifier (i.e. site) certain directions are useless.

Examples:

Apply (**action**) the cream – *apply it where?*

Apply the cream to the **right arm** (**site**)

Sometimes, even when route is detailed in the instruction, there is still a need to further qualify the instruction by defining the specific site.

Examples:

Inject (**action**) 15mg IA (route) – *inject into which joint?*

Inject 15mg IA to the **left knee** (**site**)

As seen in the last example there is a distinct boundary between route and site; route being the “way in” to the body and the site the specific area in/on the body where the “way in” is located

Examples:

Route – ocular site – right eye

Route – IV site – antecubital fossa

Mapping to HL7 v3 Pharmacy Message:

Site of Administration information should be described using approachSite.Code attribute in the appropriate SBADM act or sub act.

Method

This gives further information as to “how” the medication should be administered (see “Action”). Method is the particular way for carrying out or approaching a procedure i.e. it further defines the way the medication is to be administered to the patient, whether that is by the patient or by the parent/carer/healthcare professional.

Method can be an adjective that directly defines the action giving more information as to “how” the prescriber intends that medication to be administered:

Example:

Apply (**action**) **sparingly** (**method**)

Or it can be a further act added to the original action in order to fully define the exact method of administration required:

Example:

Apply (**action**) with **gentle massage** (**method**)

Or a method can be inherently linked to the route of administration, further defining how the medication should be administered via that route:

Example:

Administer (**action**) a **slow** (**method**) intravenous (**route**) **infusion** (**method**)

Mapping to HL7 v3 Pharmacy Message:

Currently, no exact mapping exists in V3 for this concept.

Route-Site-Method Vocabulary

SNOMED CT values for Route and Site are currently available

Certain Method values are currently available in SNOMED CT but “method of administration of drug” would require population in order to satisfy the requirements of the model.

Suggested Additional Method Vocabulary:

Gentle massage

Vigorously

Sparingly

Liberally

3 Definition:

7 Discussion and Examples:

1 e.g.:

SC Infusion, to be given at 10ml/24 hours

9 e.g.:

Currently, the datatype for Rate information is a Physical Quantity, therefore the description of the units must be a compound expression based on UCUM: for example “ml/minute” or “litres/hour”. Therefore the last two examples given above could only be messaged in the Rate attribute if made unitary (500ml over 6 hours = 83.3ml/hr; 10ml over 24 hours = 0.417ml/hr). Non unitary rate information could be messaged using a dose quantity and a phase attribute in Timing also.

The Rate of Administration information should be held in the rate.Quantity attribute in the SBADM act.