



SPL Webinar Series: Part 2

Implementation Approaches to SPL



Webinar - 2

Introductions

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Octagon Research Solutions, Inc. is a development partnering organization that offers regulatory, clinical, process and IT solutions to the life sciences industry

The Octagon Advantage:

- Deep Domain Knowledge
- Cross-functional eSub Expertise
- A Holistic Process Approach
- Creative Use of Technology

- “Compliance and profit are not mutually exclusive.”
 - Web Service Technology and Consulting company formed in 1998.
 - Medical products manufacturing solutions delivered by medical products manufacturing professionals
 - Patented web service technology delivering value in months not years
 - Affordable and scalable solutions.

- SPL Overview
- SPL Tools/Services
- SPL Tool Vendors
- ELIPS
- Wrap Up/ Q & A

- **Structured Product Labeling (SPL)**
 - Human readable (via Style Sheet); Machine processable
 - Facilitates the review, editing, storage, dissemination of, and access to product labeling document content
 - Models the structure and semantics of labeling content, **not** the presentation (eg. As found in package inserts)
 - In the U.S., SPL will be submitted in XML format (XML is built according to the SPL XML schema)
- **3 aspects of SPL:**
 - Header – metadata about the document
 - General information about the label and product
 - Sections – label content
 - Divide the label into blocks of text (e.g., indications section, contraindications section, warnings section)
 - Data elements – controlled data content that will facilitate indexing, searching of documents
 - Drug Listing elements will be handled via the data elements

SPL – What is Required and When?

- **What?**
 - Submission of the content of labeling in electronic format for marketing applications (even for paper applications!)
 - Submission of proposed and final content of labeling. Note: this is an area that could change
 - Submitting some Drug Listing information through SPL. Note: Information still needs to be submitted via the form 2657
- **When?**
 - Now
 - Most sponsors are complying by submitting in PDF
 - October 2005
 - SPL required for all approved prescription pharmaceutical products
 - Initial submission of SPL for a pharmaceutical product can take place:
 - Dependant on the implementation of ELIPS (Electronic Labeling Info Processing System) at FDA. Currently on schedule for October.
 - SPL can be sent in lieu of PDF
 - Voluntary SPL “test” submissions can be sent

SPL – What is Different?

- Information displayed through SPL will not look like the printed label
 - Purpose of SPL is to facilitate the dissemination of labeling content and data
 - Purpose is not to replicate the format of the final printed label
- Drug Listing information will be need to be coordinated
 - New processes will need to be put in place.
 - Processes to maintain consistent information between the Drug Listing form and the information submitted via SPL

SPL – What is Not Required Now or is Outstanding?

- **What is Not Required Now**
 - Lifecycle management for each individual piece
 - *For the moment*, the entire content of labeling text is submitted each time
 - SPL will not replace the various methods used for negotiating labeling changes (for example, MS Word files using track changes)
- **What is Outstanding?**
 - If proposed labeling via SPL will truly be required in October 2005
 - How the sponsors will insure that the final labeling text is appropriately updated at the National Library of Medicine
 - How labels with multiples of one section, such as Indications and Usage, should be handled/converted
 - If the Drug Listing form will go away in the future (potentially phase 2, targeted for 2006)

SPL: XML Sample

```

<?xml version="1.0" ?>
- <Document xmlns="urn:hl7-org:v3" xmlns:voc="urn:hl7-org:v3/voc"
  xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
  xsi:schemaLocation="urn:hl7-org:v3 PORR_MT050015.xsd">
- <!--
  -----
  SPL Header
  -----
  -->
  <id extension="a129" root="2.16.840.1.113883.3.933" />
  <code code="11488-4" codeSystem="2.16.840.1.113883.6.1"
    codeSystemName="LOINC" displayName="Human prescription drug label" />
  <!-- Note that there is no <title> element, so no title will be rendered -->
  <effectiveTime value="200212" />
  <availabilityTime value="200212" />
  <confidentialityCode code="N" codeSystem="2.16.840.1.113883.5.25"
    codeSystemName="Confidentiality" />
- <author>
  <time value="20021201" />
  - <assignedEntity>
    <id extension="PH00017" root="2.16.840.1.113883.3.933" />
    - <representedOrganization>
      <name>Pharmacia & Upjohn Company, A subsidiary of Pharmacia
        Corporation</name>
      <addr>Kalamazoo, MI 49001, USA</addr>
    </representedOrganization>
    </assignedEntity>
  </author>
- <legalAuthenticator>
  <time value="20021208" />
  <signatureCode code="S" />
- <assignedPerson>
  <id extension="PH00017" root="2.16.840.1.113883.3.933" />
  - <assignedPerson>
    - <name>

```

SPL – XML viewed using Style Sheet

SINGULAIR (MONTELUKAST SODIUM) TABLETS, CHEWABLE TABLETS, AND ORAL GRANULES
EXAMPLE DOCUMENT. NOT FOR MEDICAL REFERENCE

DESCRIPTION

Montelukast sodium, the active ingredient in SINGULAIR®, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene (CysLT₂) receptor. Montelukast sodium is described chemically as [R-(2R)-1-[[[1-(3-[2-(7-chloro-2-quinolinyl)ethoxy]phenyl)-3-[2-(1-hydroxyethyl)phenyl]propyl]butyl]butyl]hydroxypropyl]acetic acid, sodium sodium salt. The empirical formula is C₂₃H₂₇ClO₄Na and its molecular weight is 408.18. The structural formula is:

CC1(C)C(O)C(C2=CC=CC=C2)C(C3=CC=CC=C3)C(C4=CC=CC=C4)C5=CC=CC=C5C6=CC=CC=C6C7=CC=C(C=C7)N=C8C=CC=CC8Cl.[Na+].[O-]C(=O)C1=CC=CC=C1

Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Each 10-mg film-coated SINGULAIR tablet contains 10.4 mg montelukast sodium, which is equivalent to 10 mg of montelukast, and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and vanillin wafer.

Each 4-mg and 5-mg chewable SINGULAIR tablet contains 4.2 and 5.2 mg montelukast sodium, respectively, which are equivalent to 4 and 5 mg of montelukast, respectively. Both chewable tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

Each packet of SINGULAIR 4-mg oral granules contains 4.2 mg montelukast sodium, which is equivalent to 4 mg of montelukast. The oral granule formulation contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action

The cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These leukotrienes bind to the cysteinyl leukotriene (CysLT) receptor. The CysLT type-1 (CysLT₁) receptor is found in the human airway including airway smooth muscle cells and airway macrophages and in other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLT₁ have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. In allergic rhinitis, CysLT₁ are released from mast cells and eosinophils.

SPL – What are the Impacts?

- Implementing a solution
 - Implement Technology?
 - Outsource Conversions?
 - Validation
 - Training
- Up front impact will vary depending on the number of marketed products...sponsors will need to convert all in-use labels to SPL format
- Ongoing impact – fundamental process changes

- Three major choices
 - Outsource
 - Full outsourcing on an on-going basis
 - Single instance conversion?
 - ASP
 - Hosted Application
 - Insource
 - Technology Implementation

- Full outsourcing
 - Vendor converts/creates sponsor's content of labeling in SPL format
 - Vendor manages SPL within the vendor's environment on an on-going basis
 - Sponsor accesses the SPL in the vendor's environment using vendor-provided tools
- Single SPL Instance
 - Sponsor provides source documents/files in paper, MS Word, PDF
 - Vendor converts sponsor's labeling into SPL format and returns to sponsor
 - Sponsor manages the SPL themselves

SPL – Outsourcing Vendors

- DC Labs
- i4i
- Innodata Isogen
- Octagon Research Solutions
- TAKE Solutions
- ThinSpring
- Thomson/Liquent

Factors to Consider - Outsource

- Turnaround time for conversion using a vendor
- Subject matter expertise of vendor
 - Pharma-specific expertise
 - XML expertise
- Size and location of vendor
- Ability to support SPL life cycle management

Factors to Consider – Outsource (cont'd)

- **Implementation of processes to effectively work with outsourcing vendor**
 - Transmission of labeling between sponsor and vendor
 - How is content provided
 - How is Drug Listing information provided
 - How are changes communicated
 - Vendor's QC process
 - Technical validation against schema
 - Validation against delivered content
 - Internal QC process
 - 100% verification of all data
 - Verify LOINC codes, symbols, tables and figures
 - Verify Drug Listing information

ASP

- Down time
 - Maintenance & upgrades
 - Communication plan
- Training
- Support
- Intellectual Property Protection (Security)
 - Physical & Logical Security
 - Part 11 open system
 - Needs encryption

SPL – Internal Light/Mid-Weight Solution

- **XML authoring tools are used to create and validate a single instance of SPL**
 - Some tools use an MS Word-like interface to create XML files
 - Some tools have their own interface
 - Some tools convert the MS Word label into XML files
 - Tools store the SPL in a database and/or on a fileshare
- **Most tools do not clearly address the author, review and approval process**
 - Conversion rather than creation
- **May be a single user application rather than an enterprise solution**
- **Integrated with your DMS?**
- **Desktop application?**

SPL – Fully Integrated Solution

- **Fully integrated solution including XML authoring and lifecycle management**
 - Tools facilitate authoring and validation of single instances of the SPL
 - Tools facilitate managing the lifecycle of the label (tracking/managing the SPL sections) via integration with the EDMS
 - Tools have the ability to manage multiple labels
 - Solution would include the author, review and approval process

SPL Tool Vendors

- **Large full-scale applications – global label management, manages labels at the section level**
 - FCG - FirstDoc R&D with XML (Documentum-based)
 - Glemser - XmLabeling (Documentum-based)
 - Arbortext - Product Information Enterprise Publishing Pack
 - Concise - Concise Global Drug Labeling (Documentum-based)
 - I4i - ALiCE 4 Labeling (A4L) Enterprise
 - Thomson/Liquent - ??
- **Midsize applications – server based, manages entire label**
 - I4i - ALiCE 4 Labeling (A4L) Professional
 - ThinSpring - SPLServer
- **Small applications – single user desktop, manages entire label**
 - TAKE Solutions - Submit SPL
 - In.Vision - Xpress Author

Factors to Consider - General

- Number of labels that need to be managed
- Frequency of labeling submissions
- Formats of current labels
- Who is responsible for compiling and submitting drug listing information
- DMS
- Where will you store? Native XML – what do you need to render to html, pdf, doc ...

Factors to Consider – Internal Solution

- **Subject matter expertise of vendor**
 - Pharma-specific expertise
 - XML expertise
- **Size and location of vendor**
- **Resource requirements for implementing a tool or set of tools**
 - Vendor selection
 - Software validation
 - Training
 - Support
- **Ability to support SPL life cycle management**
- **Implementation of processes for author, review and approval**

SPL Action Items - Now

- **Identify SPL strategy team**
- **Determine short-term approach, interim & long-term approach**
- **Investigate vendor options**
 - Product demonstrations
 - Services discussions
 - Costs
 - Possibly a proof of concept
- **Identify list of existing labels and planned labels (scheduling)**
- **Identify first label(s) to be submitted after October 31, 2005**
- **Perform label analysis**
 - Map existing labels to SPL headings and address any issues
 - Review table formats for ease of conversion
 - Review graphics for ease of conversion (availability in jpeg or gif, 75 dpi)
 - Identify source of drug listing information

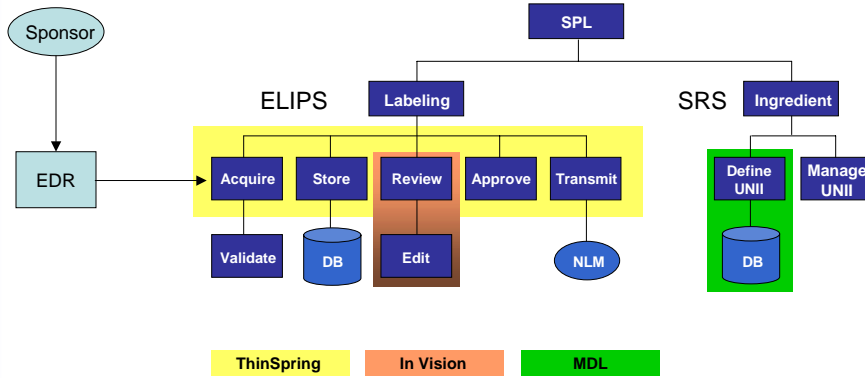
SPL Action Items – On-going

- **Monitor the agency activities for SPL:**
 - Monitor ongoing updates to the schema and Implementation Guide
 - Determine impact to organization
 - Tools
 - Processes
 - Share information with the appropriate functional groups
- **Review strategy as new/additional information becomes available**
- **In 2006, verify short-term strategy for its long-term appropriateness**

SPL Initiative Benefits

- Public health and safety – Improved decision support
- Sponsor process efficiency - Drug Listing via SPL submission
- FDA Form 2657 will not be required in phase 2
- Sponsor process efficiency – Submit only labeling elements that have changed in annual reports, not entire labeling content file
- Sponsor process efficiency – New models for negotiation process possible

FDA ePS – Electronic Prescribing Support System



Source: HL7 Working Group Presentation, Jim Shugars, FDA CDER/OIT, Gaithersburg, MD, March 18, 2005

SPL Validation Checks

Validation Summary: Ambriflex Bloxlnato

✔ Passed Validation
 ⚠ Will Be Flagged For Review (click for details below)
 ❌ Will Be Rejected (click for details below)

| Header | Product | Imprint |
|---------------------|---------------------------|-----------|
| ✔ III | ✔ Proprietary Name | ✔ Imprint |
| ✔ SetID | ⚠ Established Name | ✔ Color |
| ❌ Title | ✔ Active Moieties | ❌ Shape |
| ✔ Effective Time | ✔ Inactive Ingredients | ✔ Size |
| | ✔ Dosage Form | ⚠ Scoring |
| Section | ✔ Route of Administration | |
| ✔ III | ❌ Package Type | |
| ✔ Title | ✔ Quantity | |
| ⚠ Code | ⚠ Quantity Unit | |
| ✔ Text | ✔ NDC Code | |
| ✔ Active Ingredient | ✔ DEA Number | |



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