



SPL Webinar Series:

Introduction to Structured Product Labeling



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

ThinSpring Overview

- “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.

Agenda

- SPL Goals and Partners
- Regulatory Background and Requirements
- SPL as a Standard
- SPL Overview
- SPL vs. PIM
- FDA Tools
- Resources
- Wrap Up/Questions

Goal of Structured Product Labeling

FDA Drivers:

- Electronic labeling information to support Medicare Prescription Drug, Improvement and Modernization Act of 2003
 - Electronic prescribing, electronic health records, and Daily Med Initiative
- Improve Drug information
 - Better organization
 - Consistent structure
 - Computer format
 - Standard terminology and code sets

SPL Overview – Regulatory Background

- Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Content of Labeling (Final Guidance April 2005)
 - Final Rule 11 Dec 2003 requiring submission of the content of labeling in electronic format for marketing applications [68 FR 69009]
 - Electronic Labeling Rule: NDA - 314.50(1); ANDA - 314.94(d); BLA - 601.14(b); Annual Reports – 314.81
 - Effective 8 June 2004
 - Can be sent as pdf file until automated system is in place
 - FDA Goal to transition to SPL format (XML) in 2005 [ELIPS implementation date is 10/31/2005]

SPL eventually to affect all drug labels including OTC and VetMed

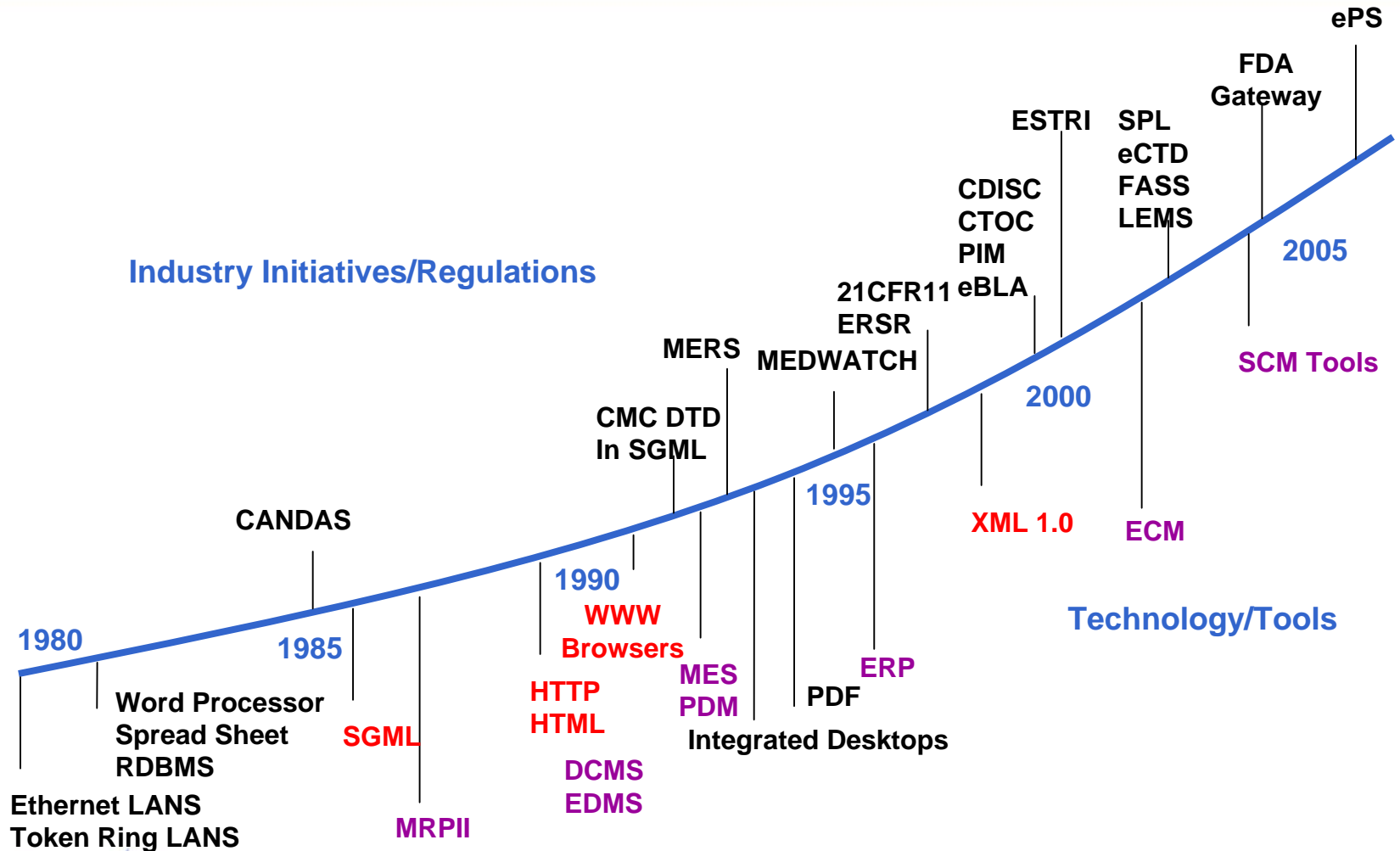
SPL Standard

- Based on Clinical Data Architecture (CDA) developed by Health Level Seven (HL7)
 - American National Standards Institute (ANSI) accredited organization
- CDA allows information to be exchanged in extensible markup language (XML)
- SPL v1.0 schema has been ‘balloted’ as an HL7 standard
 - v2.0 schema has passed HL7 committee-level balloting and now is in reconciliation stage
 - It is expected that it will be submitted to ANSI for approval by September 2005
 - FDA is implementing schema v2a. Full v2.0 will be implemented once the Physicians Labeling Rule is finalized

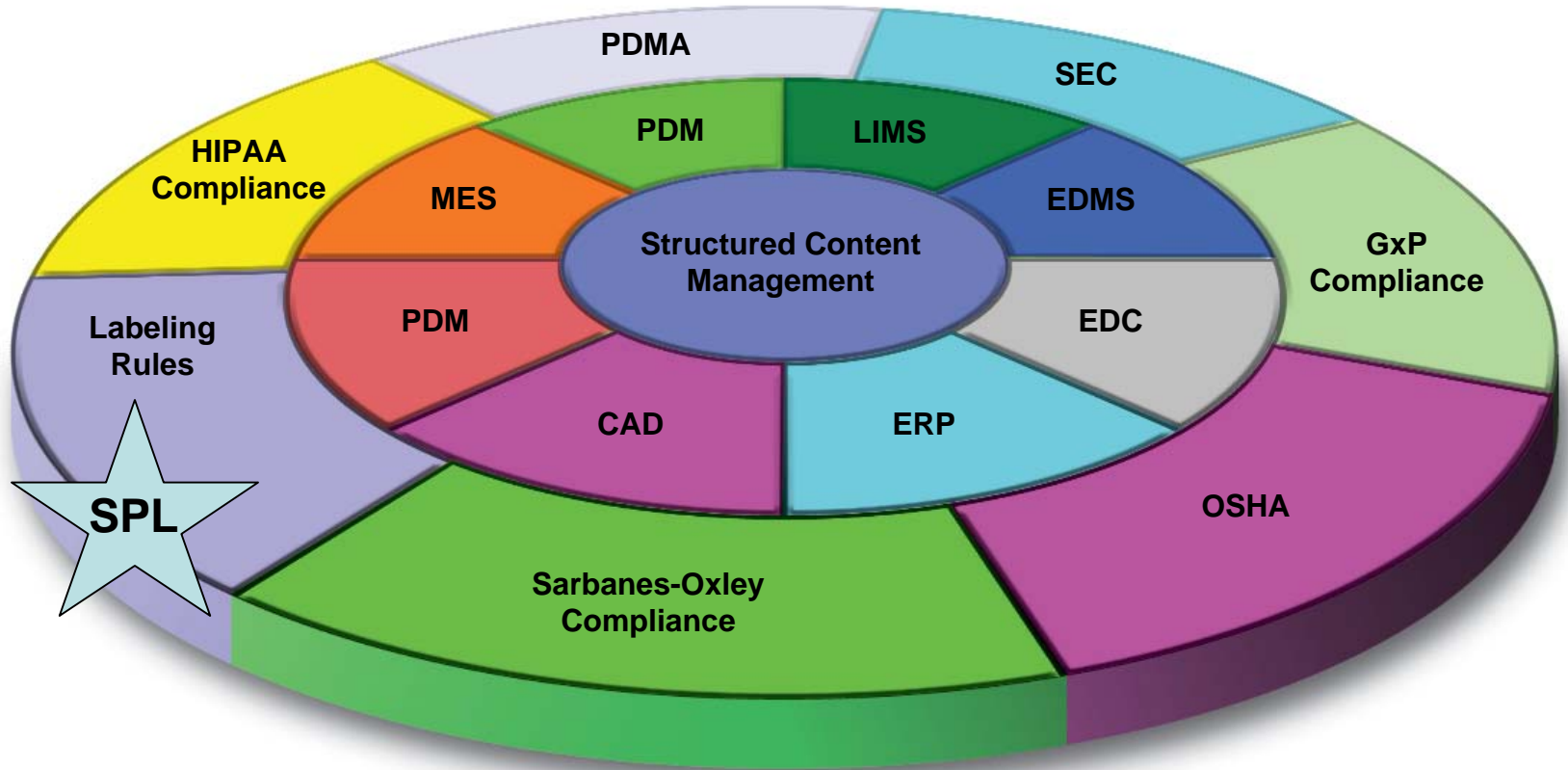
Partners in SPL

- **Manufacturers**
 - Provide up to date product information in electronic format (Structured Product Labeling, product listing)
 - HL7 SPL Implementation Working Group
- **National Library of Medicine**
 - The DailyMed database will be hosted by NLM and will make up-to-date product information available to health information suppliers (doctors/pharmacies)
- **Health information suppliers**
 - Use in systems (e.g., electronic prescribing, decision support)

Where does SCM fit in the alphabet soup?



Where Does SPL Fit?



SPL Advantages

- Standard for product information
 - Electronic file leveraging the power/promise of XML
 - Information can be used between computer systems
 - Consistent organization of product information
 - Information for each type of product in same location
 - Automation of comparison of text by section and drug data elements
 - Flexible to accommodate different labeling requirements
 - Directly impacts public health and safety by providing most current/accurate product information

SPL Overview – What is it?

- ‘Content of Labeling’ as required by 21 CFR 201.100 (d)(3) including
 - All text, tables and figures
 - As provided in original submissions, supplements and annual reports
 - This includes paper submissions
 - Does not apply to carton and containers

<http://www.fda.gov/cder/guidance/6719fnl.pdf>

SPL Overview – What is it?

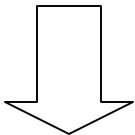
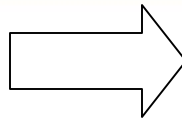
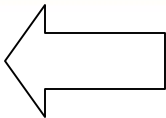
- ‘Content of Labeling’ in XML format
 - Replaces *proposed.pdf*, *current.pdf*, *approved.pdf*
- Based on schema – strict set of rules
- Human readable (via Style Sheet); Machine processable
- Models the structure and semantics of labeling content, not the presentation
- In addition to labeling text, SPL contains drug listing data elements
 - Drug Listing elements currently submitted via FDA Form 2657 will be submitted with SPL
- Structure will allow sponsors to submit labeling updates in ‘pieces’, rather than having to resubmit the entire label; initial implementation will require full label be submitted

Structured Product Labeling

- SPL has three basic parts
 - Header
 - General information about the label and product
 - Sections
 - Divide the label into blocks of text (e.g., indications section, contraindications section, warnings section)
 - Define list of acceptable sections based on regulations and needs
 - Data elements
 - Specific information about the product (e.g., active ingredient, dosage form, how supplied)
 - New data elements can be added



Labeling



Boxed warning

Indications and Usage

Dosage and Administration

How Supplied

Contraindications

Warnings and Precautions

Drug Interactions

Pregnancy

Labor and delivery

Lactating women

Pediatric use

Geriatric use

Adverse reactions

Drug abuse

Over dosage

Description

Mechanism of action

Pharmacodynamics

Pharmacokinetics

Other pharmacology

Carcinogenicity

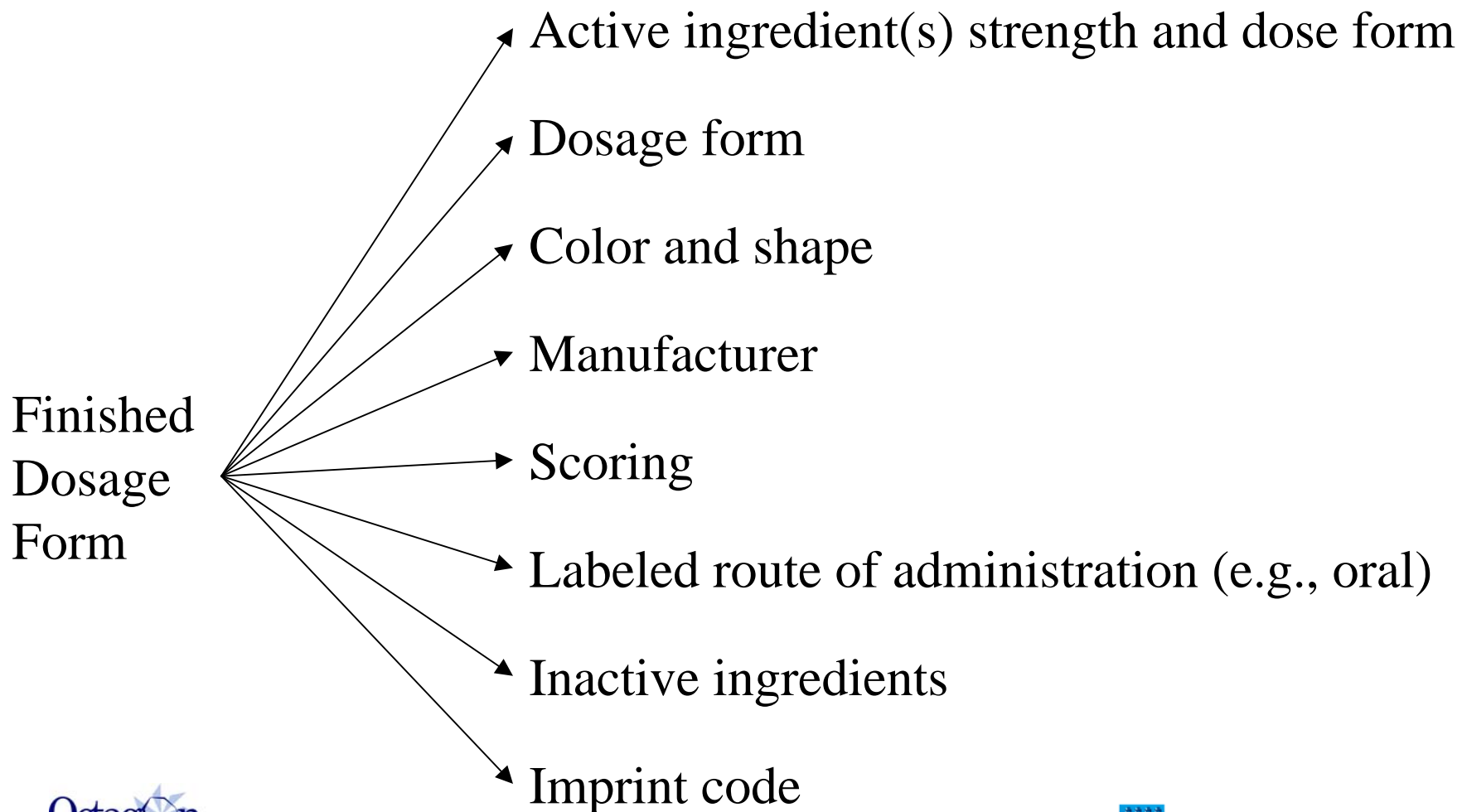
Animal toxicology

Clinical studies

Patient counseling

References

SPL Data Elements



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="a123" 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" />
  - <assignedEntity>
    <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 - N - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Address <http://www.fda.gov/oc/datacouncil/singulair/singulair.xml>

powered by **NETZERO** Yahoo! search Type 'Search' Here **Go Search!** **Inbox** **MegaMail** **HiSpeed** **Connect**

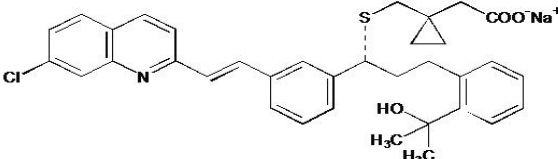
SINGULAIR (MONTELUKAST SODIUM) TABLETS, CHEWABLE TABLETS, AND ORAL GRANULES EXAMPLE DOCUMENT- NOT FOR MEDICAL REFERENCE

DESCRIPTION

Montelukast sodium, the active ingredient in SINGULAIR[®], is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT₁ receptor.

Montelukast sodium is described chemically as [*R*-(*E*)]-1-[[[1-[3-[2-(7-chloro-2-quinoliny)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt.

The empirical formula is C₃₅H₃₅ClNNaO₃S, and its molecular weight is 608.18. The structural formula is:



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 carnauba wax.

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 eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT₁) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs 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, CysLTs are released from the mast cells after allergen exposure, leading to the characteristic allergic reactions and are associated with symptoms of allergic rhinitis. Treatment challenges with CysLT₁ block...

Done Start **Inbox** - Microsoft Outl... **Core Process Team** **FDA Responses - 200...** **Document2 - Microsof...** **SINGULAIR (MONTE...** **eCTD training and intr...** Internet 11:22 AM

Creating and Submitting SPL

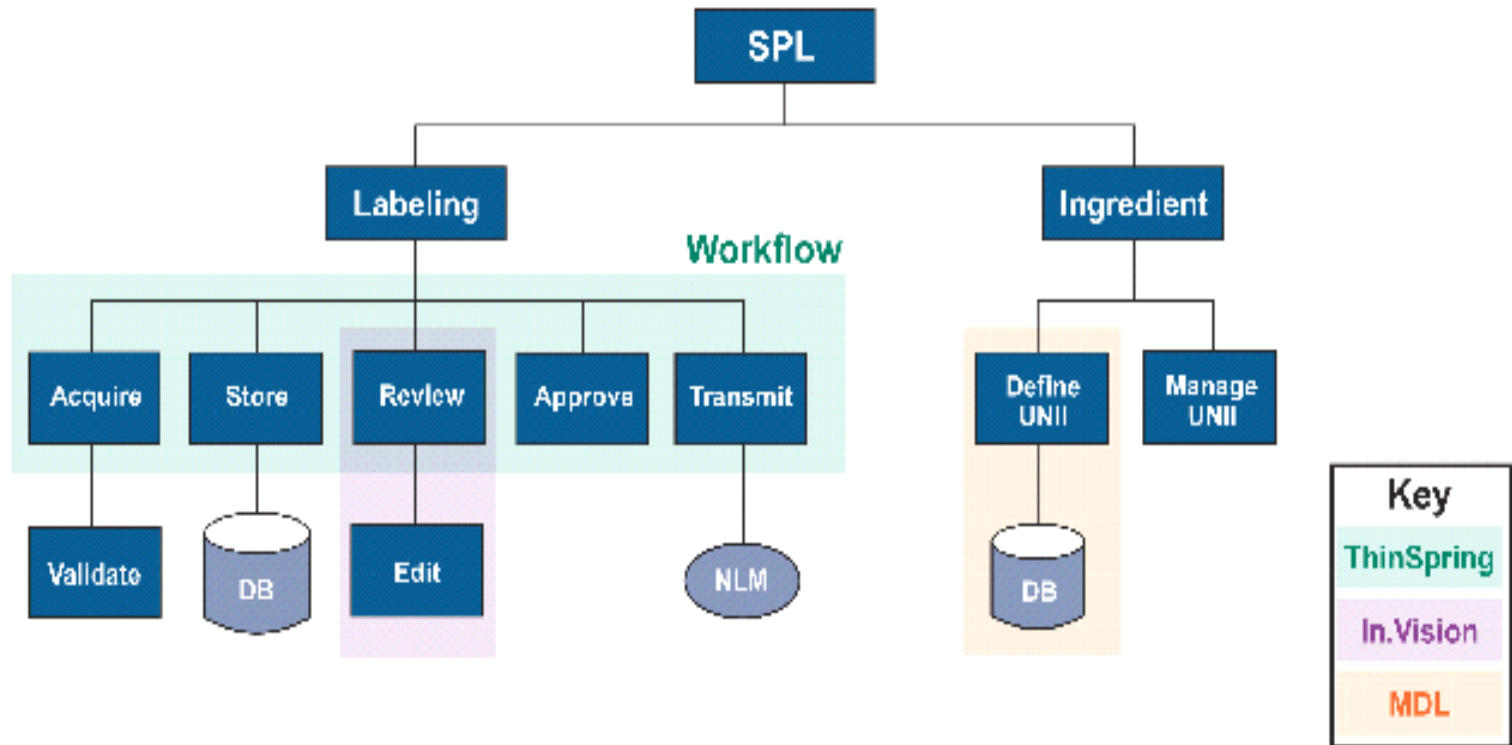
- SPL Implementation Guide for FDA Content of Labeling Submissions
 - Details for creating SPL document, headers, body and data elements
 - GO TO GUIDE, all 100+ pages!!!
- MUST be submitted through the Electronic Document Room (EDR)
 - Central Room per public docket
- SPL files places in a folder titled *sp/*
 - If accompanying a paper submission it will be a single folder
 - If accompanying an electronic submission it will be within the labeling folder (eNDA/eBLA) or M1 (eCTD – more guidance to follow)

SPL Tools and Technology

- SPL will require the conversion of WORD processed or PDF documents to XML
 - Conversion services
 - Conversion tools
 - XML Authoring tools
 - Hosted environments
- Tool and Technologies selection should take into account number of labels, infrastructure of company and existing processes

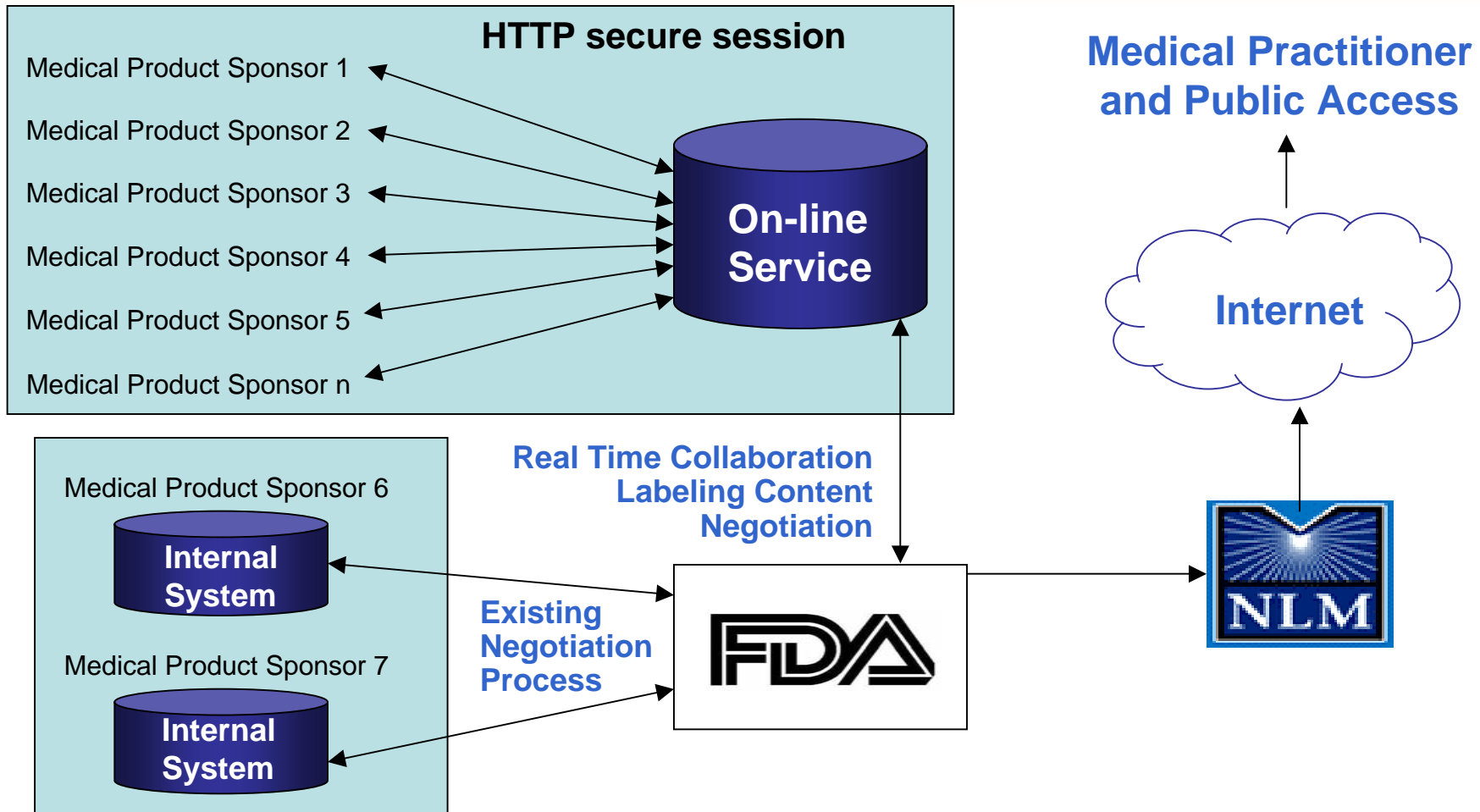
SPL Government Support

ThinSpring's Key Role in Building the FDA's ePS Solution



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

Structured Product Labeling Initiative Update



What about PIM?

- PIM Initiative started in 1999 as a way to handle product information for registration of human medicines via Centralized Procedure
- Joint European Medicines Agency (EMA) and European Federation of Pharmaceutical Industries and Associations (EFPIA)
- PIM is XML based standard for product information
- Implementation targeted for November 2005 – Voluntary
- Mutual Recognition (MRP) and Decentralized (DC) at a later date
- Supports 21 languages of the EU (increasing to 24 in 2007)

GOAL of PIM

- EMEA Drivers:
 - Product information documents associated with single Trade Name is between 650 and 1000 documents
 - Creating and managing this magnitude of documents is difficult for sponsors and agencies alike
 - New Medicines Legislation require a reduction in time from opinion to submission of opinion documents from 45 days to 15 days
 - Improve the quality and consistency of the published product information

Key PIM Objectives

- Electronic-only Submissions
- Selected automated validation checks
- Compliance with templates
- Focus on content and NOT format
- Elimination of repetition of checks on the same information
- Improved commenting process
- Submission and review of changed information only
- Easier adoption of new template versions

Buxton, T. and Marr, A., Regulatory Rapporteur
2005

How are PIM and SPL Related

- Although designed around different needs that are closely related
- Both SPL and PIM leverage XML and allow for repurposing and reuse of content
- A single PIM file includes definitions for:
 - Multiple documents for various strengths and dosage forms
 - Multiple documents for all required European Union languages (~27)
- SPL and PIM define very rigid and structured XML tags
 - Every section has a separate tag
 - Section sequencing is controlled

Key Learning Points

- SPL format is required for US Submissions beginning October 2005
 - Between 10/2005 – 10/2006, SPL will need to be submitted for ALL prescription drug products
 - First submission to contain labeling
 - Or, annual report
 - Transition requires education and training on new technologies & processes
 - Companies must develop strategy to support SPL lifecycle
 - Build internal capabilities
 - Develop outsourcing strategy
- Global companies should consider SPL Strategy along with PIM Strategy
- PIM and SPL are SIMILAR but DIFFERENT!!!

References/Resources

SPL Specification and Implementation Guide : www.hl7.org

SPL stylesheet, sample and updates:
www.fda.gov/oc/datacouncil/spl/html

PIM: <http://pim.emea.eu.int/>

Glossary of Abbreviations

- CBE – Changes being effected
- CDR – Central Document Room
- CID – Chemical Ingredient Dictionary
- COMIS – Center wide Oracle Based Management Information System
- DARRTS – Document Archiving, Reporting and Regulatory Tracking System
- DocRoom – Paper document room
- ELIPS – Electronic Labeling Information Processing System
- eLIST – Electronic listing system
- FDA – Food and Drug Administration
- NLM – National Library of Medicine
- OTC – Over the Counter
- SPL – Structured Product Labeling
- SRS – Substance Registration System
- UNII – Unique Ingredient Identifier

Question & Answer



Part 2

Please join us for the SPL Webinar Series Part 2:

Focus on SPL Implementation and Strategies

August 17, 2005 at 11 am EDT

To register please call Kathy Bouldin at 610.535.6500 ext 556
or send an email to kbouldin@octagonresearch.com

Thank You

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