The Challenge of Change in Drug Product Labeling

A US-market perspective

July 2011

Introduction

Drug product label production is changing. Some changes represent continued evolution. Others are new factors needing attention.

Major regulatory regimes, specifically the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), need labels submitted in a variety of formats. These include PDF, Microsoft© Word (Word), and XML. Formatting and submission requirements have evolved, and will continue to do so.

All regulatory regimes are working to streamline their expensive approval processes. Also, new markets are emerging. And new marketing media is voraciously consuming information. These and other factors are creating demands on content creators and managers. New demands are pushing old systems beyond their capabilities.

The Challenge of Change

A label management system must be built on a sound infrastructure, have an architecture that can anticipate change, and be based on standards that are designed to outlive proprietary formats. It must efficiently manage:

Document review and approval. Each label, in each of its variant formats and languages, has a review and approval cycle that must be managed and documented.

Variants. The system must manage all possible label variants, which are created to satisfy the diverse requirements of the different label consumers. These variants can exist in different formats and languages. For instance, the internal authoring and review process uses Word, the regulator review process needs PDF, and the packaging process requires desktop publishing (DTP)[1] documents.

Translations. Multilingual markets need the system to manage translations of each Word, PDF, and DTP document.

Content organization. Add to this volatile mix the fact that each regulatory regime has different requirements for label content organization. The US market requires the all-in-one SPL (Structured Product Label) while Europe needs a collection of QRDs (Quality Review of Documents), the size of which depends on a product's profile and the number of target languages.

Variant dependencies. To add more complexity, there are dependencies between label variants:

- Translations cannot be submitted for internal approval until the base English version receives regulatory approval.
- A variant label cannot be approved before the approval of the change request document that triggered the variant's creation.
- The comparison of the DTP document against the base Word document must be approved before the DTP document is approved for production.

1 Adobe Systems Inc.'s InDesign® and Quark Inc.'s QuarkXPress® are examples of DTP tools.

The permutations are varied and complex.

And the system must manage all of this while maintaining information agreement—where what is said in one place is materially consistent with what is said in another.

One Solution

i4i provides a solution to the challenge of change in the form of A4L,[2] a state-of-the-art technology suite that combines the latest advancements in the use of XML and the Internet. A4L is an out-of-the-box solution for authoring, managing, and publishing drug product labels, with all of their complexities.

Content of Interest

A cornerstone of the A4L design is the ability to identify and manage a piece of *content of interest* in the complex context of drug product labeling.

Content of interest is content that serves a distinct purpose or has a specific role within a larger context. It is usually textual but can be multi-media, and can also be recursive. Examples:

- Within an indications section, each indication is *content of interest*.
- Within a drug product label, the indications section is *content of interest* (e.g., an SPL's LOINC 34067-9).
- Within an Electronic Common Technical Document (eCTD), a product label is *content of interest*.

The problem of duplication

About 80% of drug product labeling content is duplicated. One simplistic notion sees content reuse as the entire solution, with its reliance on a central library of reusable pieces of content of interest (a.k.a. fragments or chunks). This idea ignores the reasons for the duplication.

In labeling, one of the key reasons for duplication is format. That is, the same content exists in different formats such as Word, PDF, InDesign, or different flavors of XML (e.g., SPL, DITA[3]).

Another reason is that content is expected to change: it is being translated or is being adapted for a specific product configuration. Over time, the textual content (words) will change but the materiality must remain the same—so fragment reuse as a management strategy will not work here.

To specify a content of interest's materiality, the system needs the ability to apply defining metadata to the content. It then must track both the content and its metadata, throughout the content of interest's life cycle. The tracked content must include the base content and all of its versions, copies, variants, and translations.

2 ALiCE (Authoring Lifecycle Collaboration Environment) for Labeling.

3 The Darwin Information Typing Architecture is an XML-based architecture for authoring, producing, and delivering information.

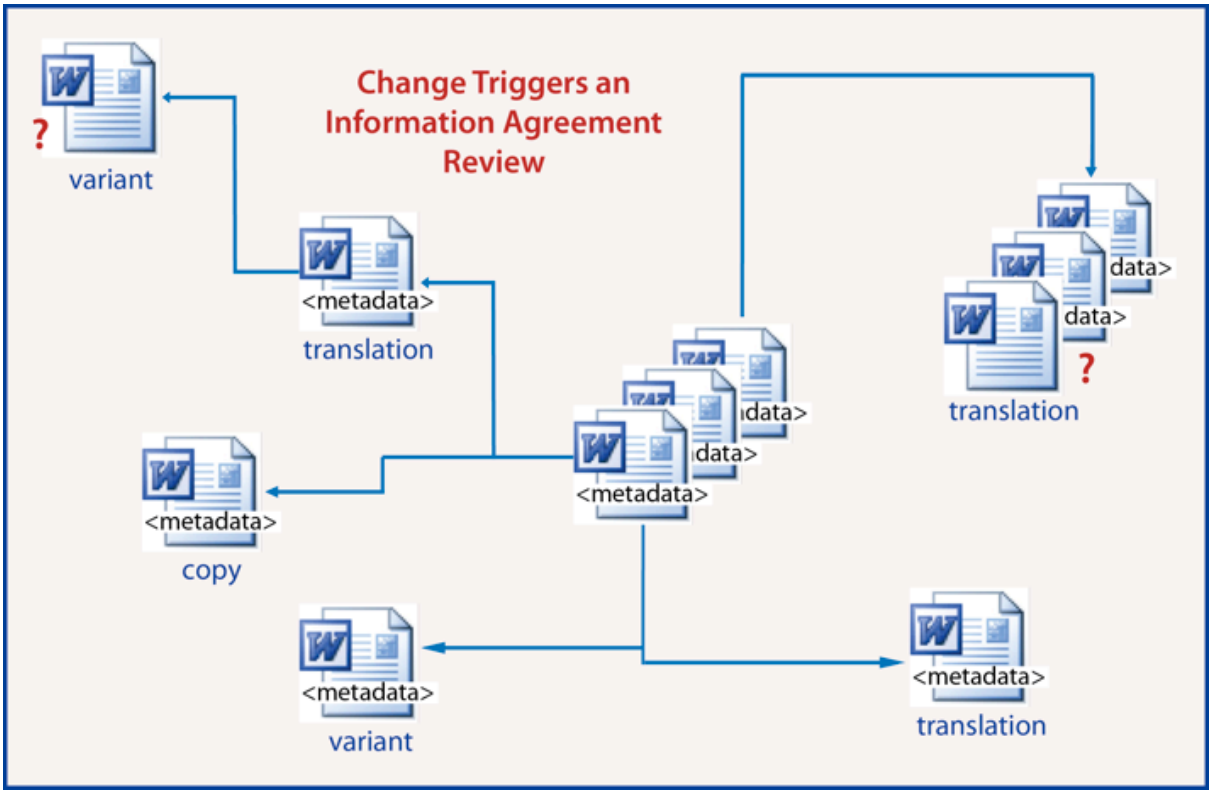

Figure 1

Change triggers an information agreement review. For example, figure 1 would raise the question: Why is the metadata dropped from a translation of the document or from a variant of a translation?

Fragment reuse still has a role to play, but only as part of an effective information agreement strategy. For some content of interest, like a corporate disclaimer, reuse from the content library can be the starting and ending points of the strategy. For other content of interest, such as adverse events for a class of products, reuse from the library is only the starting point.

Dealing with complexity

A4L is designed to deal with these complex issues. A core element of its design is based on the importance of getting it right at the beginning. So the starting point for working with A4L is content authoring. A4L has implemented, in the ubiquitous authoring tool Word, an XML layer that supports:

- Repurposing of Word content to:
  - » regulatory XML targets such as SPL.
  - » desktop publishing tools such as InDesign.
  - » review formats such as PDF.
- Content reuse and tracking.
- Fragment management.
- Application of metadata to *content of interest.*
- Content exchange between labeling documents, corporate documents, and content databases.

A collection of web services supports this functionality. These services track and manage the content in all of its formats and variants, from initial authoring to regulatory submission to the creation of print-ready copy.

Standard desktop productivity tools such as Word and Internet Explorer can access these services.

Customer Scenario

To put this into perspective, consider the hypothetical Aardvark Life Sciences (ALS), a small innovator that also markets some related generics.

ALS markets in the U.S. and is considering expansion into Europe. To date, ALS has managed its label authoring, approval, and publishing processes on the desktop—with no integrated enterprise component.

Despite the best efforts of its small group of professionals, ALS has suffered the embarrassment of a product recall—due to an information agreement error between its approved PDF and its printed label. This has prompted a review of current practices and the implications of European expansion.

ALS currently uses i4i's A4L desktop software product to create its SPL submissions, and is aware that its supplier also has the A4L Enterprise offering. So, in the interest of leveraging their investment, they are presenting to i4i a set of high-level requirements.

Immediate Requirements	
1	Author labels in Word.
2	Submit Word or PDFs for review exchange with the FDA.
3	Create Package Inserts, Med Guides, and SPLs from the Word document.
4	Manage the life cycle of documents so that only approved versions of Word, PDF, or SPL labels are sent to the regulator.
5	Manage the submission cycle of approved documents.
6	Manage the life cycle of Changes Being Effected (CBEs).
7	Create and manage Change Request documents for authorizing label versions and variants.
8	Manage the interdependencies between documents and their variants, including CBEs.
9	Manage the Reference Listing Drug (RLD) labels for the generic products.
10	Create and manage RLD variants.
11	Create InDesign artwork documents from Word documents.
12	Manage the life cycle of InDesign label documents.
13	Manage information agreement between Word, InDesign, and SPL documents.

Anticipated Future Requirements	
14	Author European QRDs in Word for different jurisdictions and approval procedures, including DCP (Decentralised), MRP (Mutual Recognition), and CP (Centralised).
15	Create PDFs of QRDs for approval procedures.
16	Create InDesign artwork documents from approved QRD documents.
17	Manage the life cycle of InDesign documents.
18	Create translations of documents.
19	Manage the life cycle of translation documents, including interaction with in-house translators, contract translators, and translation memory systems.
20	Manage the synchronization of source and translation documents.
21	Manage Type I and Type II variants.
22	Manage information agreement between Word, PDF, InDesign, and QRD labels.
23	Manage the life cycle of labels so that only approved versions of Word, PDF, or QRD labels are sent to the appropriate regulator.
24	Support collaborative authoring.

Note: The ALS profile is based on typical scenarios that i4i has encountered with its own customers.

i4i's Response

i4i described the major pieces of required functionality, including with each description a reference to the ALS requirements that are addressed.

Content development

The i4i solution for managing drug product labels has two layers:

1. Content Authoring. ALS is familiar with this from using the A4L desktop solution.
2. Specialized XML Content Services. These manage document life cycles, relations, and information agreement strategies.

Drug product labels are complex documents that are typically authored in Word. The solution enables "getting it right" from this authoring starting point, which is more cost effective than layering on "fixes" after the fact.

A4L embeds an XML layer into Word authoring templates for SPL, QRD, and other document classes as required.

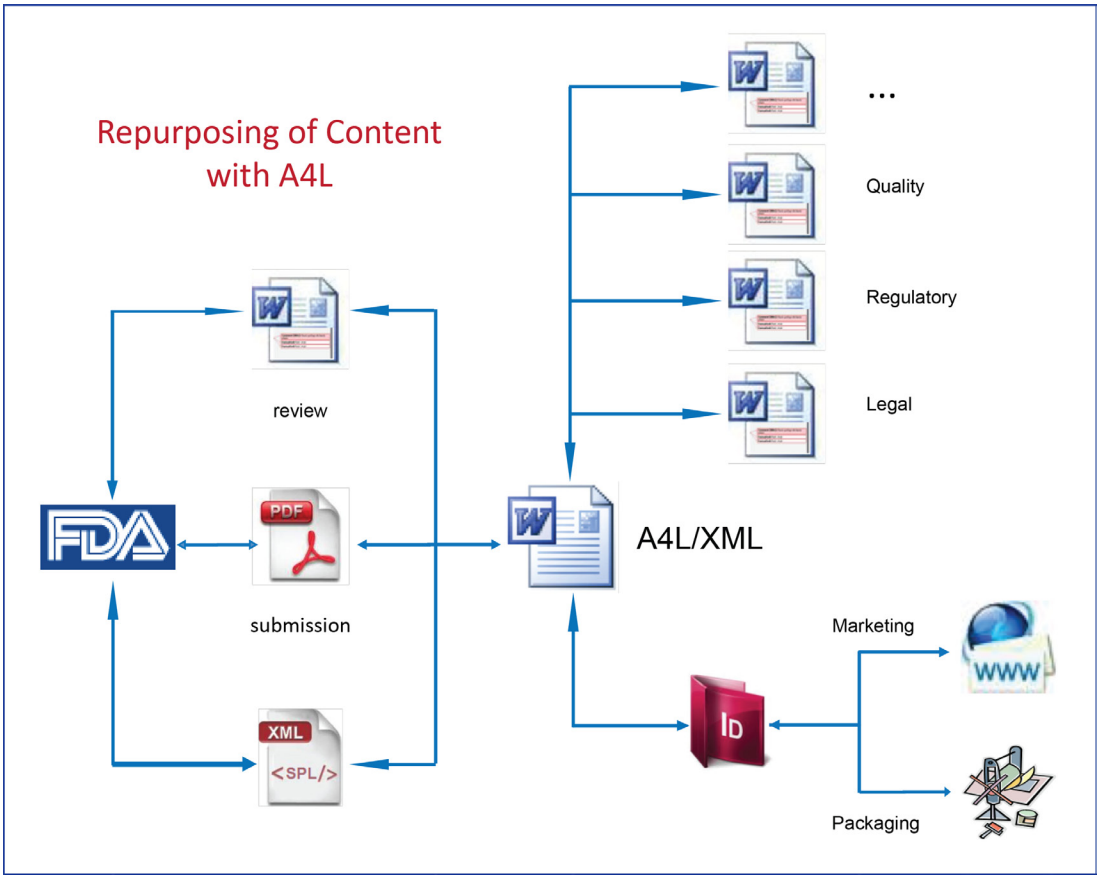

Figure 2

This XML layer serves two purposes:

1. Allows the document to be treated and managed as a mini-database with a custom application, specific to the objectives of its template (e.g., proper creation of an SPC or SPL, or facilitating downstream business processes that ensure information agreement).
2. Enables the accurate export/import of content between Word and a regulatory XML format such as SPL, or the repurposing of content between Word and InDesign.

As seen in figure 2, A4L's use of Word and XML allows the repurposing of a single label document.

For regulatory purposes:

- A Word document, supported by an XML infrastructure, is authored that meets FDA regulatory requirements for drug product labels.
- A Word or PDF rendition can be exchanged with a regulator, with the comments made by the regulator flowing back into the working Word document.
- A PDF rendition can be sent to a regulator.
- A Package Insert, Med Guide, and SPL can be created from the same Word document and submitted to the regulator as part of the submission package.
- Using QRD XML templates, the same objectives that are realized in the U.S. market can be realized in the European CP, MRP, and DCP procedures.

For print purposes:

- XML provides the necessary intermediate form to repurpose content for different applications. This form also lets users compare content from nominally different formats and identify information agreement problems.

Response to requirements: 1, 2, 3, 11, 14, 15, 16.

Business process applications

A suite of web services, organized into business process applications, support content development and repurposing.

A4L's applications for managing complex life cycles use the paradigm of the digital dashboard to deliver the required functions. This provides a consistent metaphor to the user. Each dashboard is configured to provide a single point of access to the business objective's required functionality.

A role-based security model controls all user interaction with the applications and documents.

Version management

Version management is the most commonly used application, ensuring that all documents go through a controlled life cycle process.

For instance, it verifies that an authorized system user has digitally signed a Word, PDF, or SPL label document before it is sent to the regulator. It also ensures that versions of documents are properly sequenced and easily discoverable, with each document's metadata determining the method of its discovery.

A4L documents appear in folders according to their metadata,[4] thus providing a simple yet effective means of routing them to their appropriate workspace.

For example, one folder is designated to gather all documents awaiting signature. The signing officer does not have to search the system for documents needing review and sign-off, but can instead simply open the *waiting signatures* folder and digitally sign off the documents.

The act of signing off changes the document's metadata, causing the system to automatically route the document to the next appropriate folder cum task: *submit to regulator*.

Response to requirements: 4, 5, 10, 12, 17, 23.

4 Folders are dynamic searches. Popular examples of this organizational paradigm are smart folders in the Apple© iTunes digital media application or search folders in the Microsoft© Outlook email application.

Change request management

Change request management naturally builds on version management.

This application manages the change requests that may be required between a document's versions or variants.

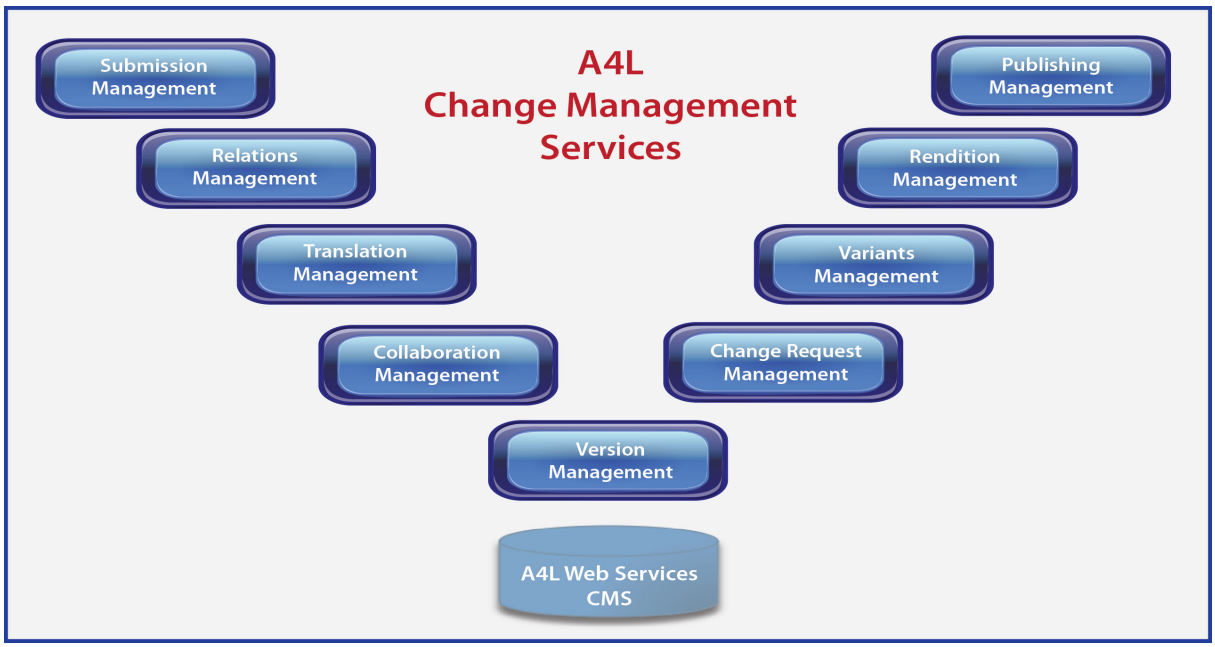

Figure 3

Response to requirements: 7.

Variants management

Variants management leverages both version and change management. Document variants are created, distributed, tracked, and if necessary, merged into a single document.

A4L's email sub-system[5] distributes variants (e.g., CBE-30, Type 2 variations) to system users, with instructions about the next expected action.

A variant process manages the life cycle of a document and its variants. At certain points in the process, users must evaluate and reconcile updates to the base document content against updates to the variant content.

The variants dashboard provides services to effect the evaluation, to remove documents from and add documents to a variant process, and to close a variant process.

Figure 4 shows a sample view of this dashboard.

5 This sub-system integrates with the customer's enterprise email system.

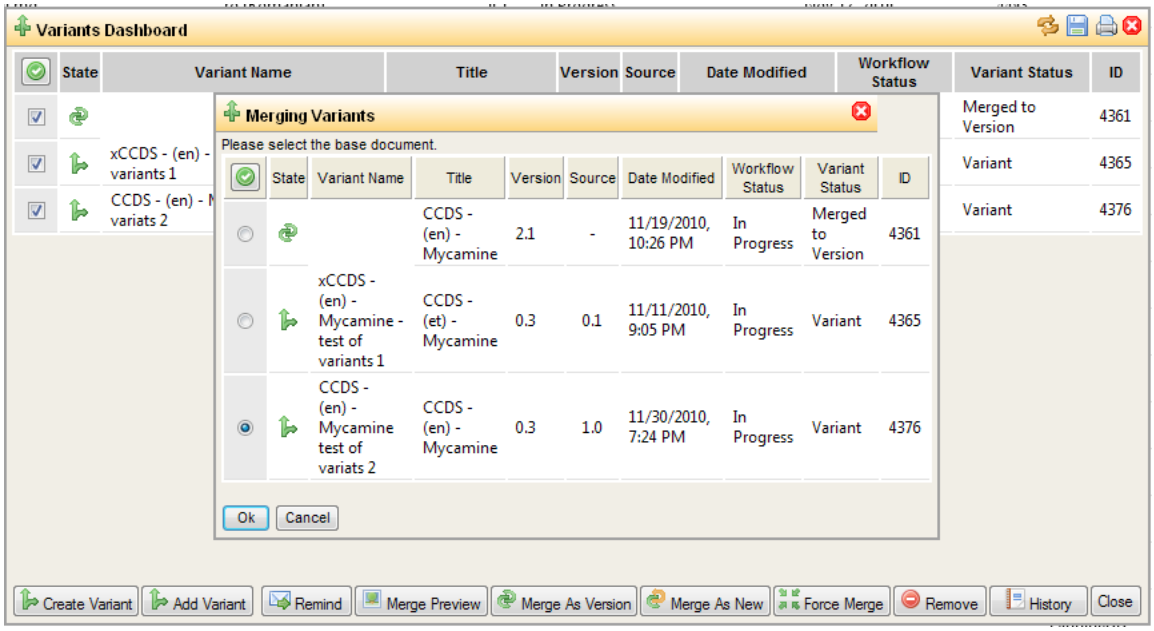

Figure 4

Response to requirements: 6, 8, 21.

Collaboration management

Collaboration management lets a document owner distribute copies of a document to other system users, for review and editing.

Collaborators can stay current with each other's work: other collaborators' changes can be automatically incorporated into the current collaborator's copy of the document.

Collaboration documents have a life cycle specific to the collaboration process, within which A4L's email system can prompt delinquent editors.

When the process is complete, the documents are reconciled into a single document.

Response to requirement: 24.

Translation management

Translation management lets the owner of a document distribute it for translation into one or more languages, and monitor the progress of each translation.

Each translation can have its own translator: a person, an outsourced service, or a translation memory system. And each has its own life cycle to help manage this complex multi-document process.

The translation process can run concurrent to the development of the base document. At selected points in the process, the application facilitates updates of the translation documents with new content from the base document.

Figure 5 shows a sample view of this dashboard.

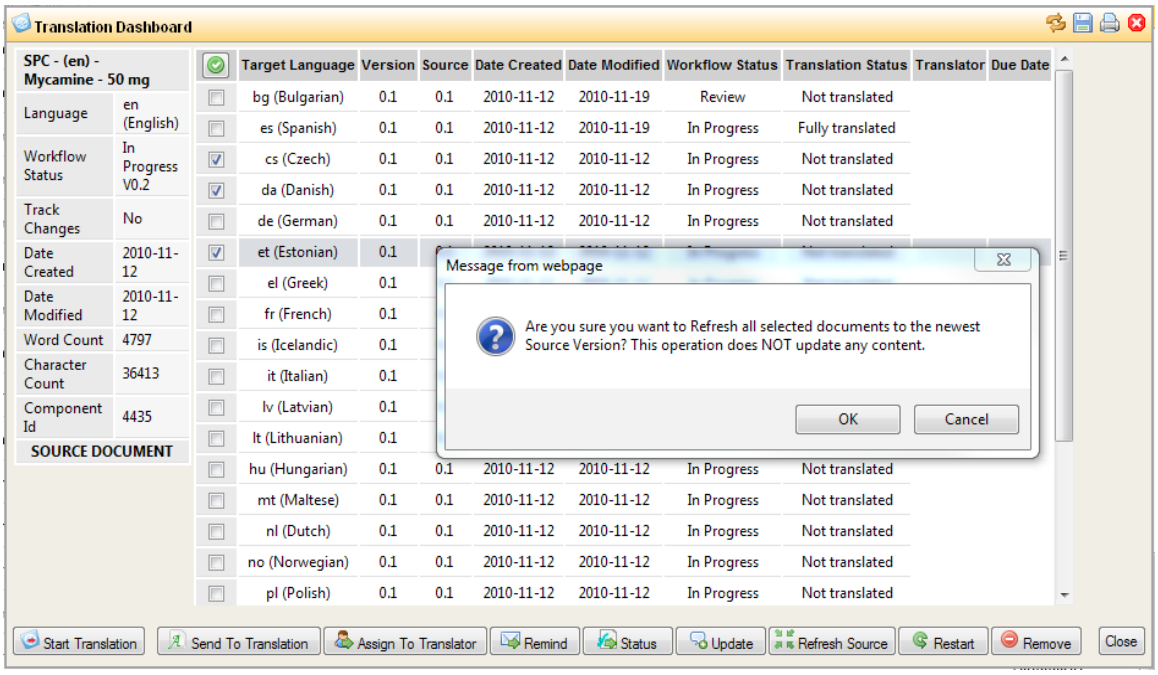

Figure 5

Response to requirements: 18, 19, 20.

Publishing management

Publishing management uses renditions, which are copies of a document in different formats. For example, a PDF of a label is a rendition of the source Word document. Renditions exist because a document's original format is often inappropriate for the target consumer. Format examples:

- Regulator needs the reviewer to work with PDF documents.
- Content database is populated from XML documents.
- Art department needs InDesign documents.

Renditions are created from the authored Word documents to satisfy the needs of these different consumers.

Renditions are not static documents. They can be modified and have a life cycle specific to their intended use. Like variants, renditions with life cycles need to be reconciled against the source document as part of the information agreement process. Because a rendition is by definition in a different format, only its content is tested—not its "look and feel".

The publishing management application facilitates this reconciliation. It also lets the user select target formats, create renditions in the chosen formats, and distribute the results to other users.

Response to requirements: 2, 11, 15, 16.

Submission management

All of the above complexities are managed to get to this final point: the creation of a label submission to the regulatory authority. The submission management application lets the user view the history of submissions and schedule upcoming submissions. In situations where submissions are shared, such as an establishment registration SPL with the content of a labeling SPL, the application tracks the sharing process and reports to the user as required.

Response to requirements: 5.

Relations management

A document relation is created when a *copy* of a document is made. The simplest type of relation is that of a copy, where a document is copied outside of a formal business process (i.e., has no context explaining the reason for the copy). When a business process is used to create a copy, it assigns a *type* to the relation. So relations are assigned types such as *Translation* or *Variant*.

A single interface, called a *constellation,* presents all of a document's relations and provides details about each relation. It is *transitive*, meaning that it lets the user navigate relations of relations.

As seen in figure 6, the base document has many related documents, which are all potentially impacted by a change to the base. The constellation's comprehensive view enables both informed decisions on change and apt consideration of information agreement issues.

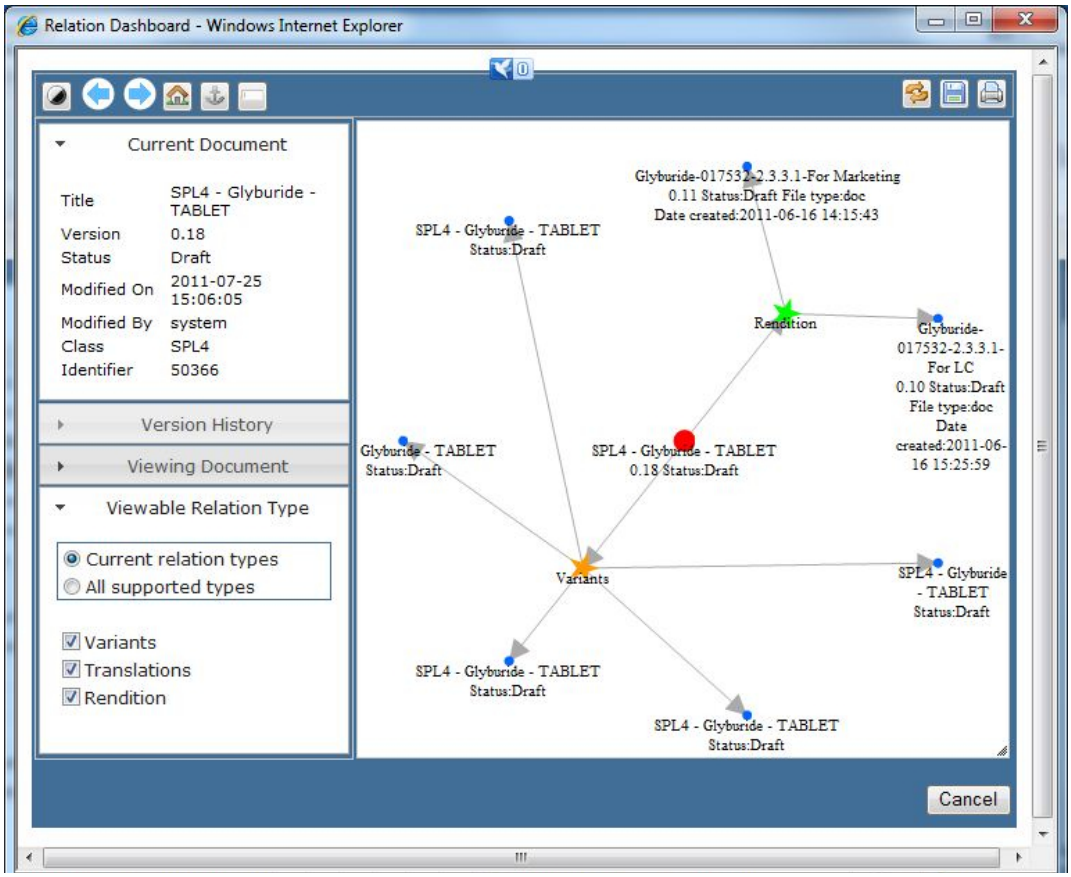

Figure 6

The constellation is supported by a tracking mechanism for *content of interest*, which is identified using its XML metadata. It can track content at a gross level (i.e., the entire document), or section or paragraph or word level. The tracking can account for language and format.

The relations management application can produce a report that identifies which documents have or have had the tracked content of interest and whether it has changes.

This application is a key tool for managing information agreement. It provides an immediate view to the impact of change. It also shows details about any changes that have occurred within a constellation.

Response to requirements: 13, 22.

Summary

A4L can meet all current ALS requirements. It also ensures that ALS can adapt to both expected and unexpected change.

Drug providers need not fear their markets' plethora of changes and new demands. Software solutions exist today that will put their businesses in a position to thrive.

The only threat is inertia. Delay will only exacerbate a drug provider's situation, as new challenges appear and competitors modernize their infrastructures.

History teaches us that change is inevitable and must be embraced.

ALS's speed of adoption to change and their readiness for future change will directly affect their bottom-line results.

Other A4L Functionality

i4i's A4L provides the business process applications, discussed above, in support of drug product label development.

In addition, it offers a number of targeted functions that support the overall business objective of producing drug products within an information agreement framework.

The following table describes some of A4L's additional functionality.

Function	Description
Discussion threads	Allow users to develop discussion threads about documents. These threads are managed externally to the document.
Annotation	Builds an annotated version of a Word/XML document. The document is turned into a table column, each part in its own cell. Users can add secondary columns for commentary on the content of the first column. They can also drag and drop content from other Word documents into the secondary columns, for easy side-by-side comparison.
Version clean-up	Certain system configurations require only major versions of approved documents. A4L can be configured to delete all minor versions of a document, once it reaches a predefined approval state.
Security	A4L provides role-based security driven by document metadata. The user interface is self-configuring, and only authorized functionality is visible to the user.
Signatures	A4L supports document signing. Users must authenticate themselves when signing. This is in addition to the document audit trail that tracks who did what and when to which document.
21CFRp11	A4L provides the functionality required to meet 21CFRp11 compliance, when supported by SOPs and operating practices.
Integration	A4L has special services for integration with document management systems like EMC's Documentum, or publishing tools like Adobe's InDesign. In addition, A4L integrates with translation memory systems such as those by TransPerfect and Lionbridge. The integration automatically routes requests for documents to these systems or submits documents to these systems, based on their metadata state.
EULM (European Label Master)	A special document class that contains all of a product's QRDs in a single document. Individual QRDs can be *derived* from an EULM, on demand. QRDs can go through a complete editorial process and update their source EULM automatically. The EULM is often used for translation. Rather than sending many documents to translation, with the exact number determined by the product configuration, a single EULM with all information for all configurations is sent. This significantly reduces the complexity of translation management.
Validation	A4L is a fully validated system. Prior to customer delivery, i4i runs a full system validation. i4i provides the customer the necessary IQ and OQ validation documents for validation in their specific environment.

Infrastructures for Information Inc. (i4i)

116 Spadina Ave. 5th Floor

Toronto, Ontario, Canada M5V 2K6

www.i4i.com