Creating, Managing and Delivering Regulated Content in Pharma

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DitaExchange Inc.
DitaExchange simplifies the way organizations create, manage, deliver, and re-use important content through structured content authoring and management solutions.
DitaExchange is the ONLY solution building on three de-facto, GLOBAL standards

DITA XML is the standard for *Information Architecture*,
Microsoft Word is the standard for *authoring and review*, and
Microsoft SharePoint is the standard for *content management* in the cloud and on premise
About Me

• VP of Life Sciences at DitaExchange since 2014
• Over 20 years of experience in regulated healthcare technology companies
  • 10+ years at Liquent (now part of Parexel) where we focused on Life Sciences industry and the tools and processes that facilitated new drug application submissions to healthcare authorities around the world
• My inspiration is my family
  • While at Liquent, we were part of the process of getting a new drug approved that my prematurely born granddaughter needed when she was born
Structured Authoring in Life Sciences
The Life Sciences Challenge

- Traditional document authoring in (semi-)narrative form
- Highly controlled regulatory document management systems
- Wide array of contributors, reviewers and approvers
- All focused on approval from healthcare authorities

- But opportunities do exist where using a structured authoring approach can yield improved quality, greater efficiencies and better accessibility
There’s a story to tell
The Narrative Approach

• Complex structure
• Evolve over long period of time
• Authors can change
• Part of a larger related collection
The Road to Re-use & Clinical Documentation

<table>
<thead>
<tr>
<th></th>
<th>ES</th>
<th>Protocol</th>
<th>TDF</th>
<th>Protocol Amendments</th>
<th>SAP</th>
<th>KRM</th>
<th>CSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended Synopsis</td>
<td>N/A</td>
<td>25%</td>
<td>10%</td>
<td>10%</td>
<td>21%</td>
<td>26%</td>
<td>21%</td>
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<td>Protocol</td>
<td>N/A</td>
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<td>40%</td>
<td>37%</td>
<td>7%</td>
<td>31%</td>
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<tr>
<td>TDF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Protocol Amendments</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>SAP</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1%</td>
<td>12%</td>
</tr>
<tr>
<td>Key Results Memo</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>15%</td>
</tr>
<tr>
<td>CSR</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Control, Control, Control
What is “21 CFR Part 11”? 

• 21 CFR part 11 requires that all systems that govern any cGXP process - including Good Manufacturing Practices (GMPs), Good Laboratory Practices (GLPs), and Good Clinical Practices (GCPs), should be validated. FDA issued a very comprehensive guidance on systems validation.
And then Annex 11

• “Should” = “must“, validate the applications, qualify the infrastructure, no decrease in quality or increase in risk introduced by the computer system
  • Risk Management – Document a risk–managed approach to the system lifecycle
    • Patient safety, data integrity, product quality
  • Personnel – Appropriate qualifications, access levels and assigned responsibilities
  • Suppliers and Service Providers – Appropriate agreements, audits based on risk assessments
    • More stringent than personnel requirements
The Risks of Non-Compliance

- Criminal penalties
- Civil penalties
- Recall, suspension, advertising
- Pharmacovigilance audit, testing
- Regulated entity communication & management
Risk Mitigation with Content

- Regulated or regulatory documents are kept in a controlled environment that has complex mechanisms built-in to ensure full control of the information.
It takes a village
It Takes Time & Money

- $2.6 billion on average

*The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

It Takes People

- Chemists
- Biologists
- Physicians
- Statisticians
- Medical Writers
- Researchers
- Clinicians
- Regulatory
Seeking approval
A (Somewhat) Familiar Map

- The eCTD is
  - A backbone (map)
  - Organizing leaf files (topics)
A Long Process

On average the EMA takes around six months more than the FDA to approve a new drug or new indication for a drug. This is mainly due to the time lost to clock stop and the delay between getting a positive CHMP opinion and approval from the European Commission. Furthermore, in the US almost all cancer drugs are approved under priority review, whereas accelerated assessment is rarely used by the EMA.


* Day 150 for accelerated assessment; Rap – Rapporteur
The Bottom Line

• Provide information in expected format
• Provide information in defined location
• Provide information with needed context

• Optimized the reviewer’s experience for best possible outcome
The Promise of Structured Authoring
## Real-world Data...

<table>
<thead>
<tr>
<th>'Document'</th>
<th>Document World</th>
<th>Reused topics</th>
<th>Authoring in the SCA World</th>
<th>Review in the SCA World</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended Synopsis</td>
<td>64</td>
<td>-</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Clinical Study Protocol</td>
<td>254</td>
<td>64</td>
<td>190</td>
<td></td>
</tr>
<tr>
<td>Statistical Analysis Plan</td>
<td>131</td>
<td>78</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Clinical Study Report</td>
<td>227</td>
<td>141</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td><strong>Workload</strong></td>
<td><strong>676</strong></td>
<td>-</td>
<td><strong>393</strong></td>
<td></td>
</tr>
<tr>
<td>Content Architecture</td>
<td>?</td>
<td>-</td>
<td>~+15%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Reduction in workload</td>
<td>-</td>
<td>-</td>
<td>~-27%</td>
<td>-42%</td>
</tr>
</tbody>
</table>

- Improve collaboration with Third Party (CRO)
- Faster Submission Turn Around Time
- Reduce Compliance Risk
Reduce, Re-use, Recycle

• By using an approach to document authoring that is designed and architected for maximum re-usability, significant time can be saved.
  • Reduce – write once
  • Re-use – use many
  • Recycle – use across
Considerations for an Information Architecture

• Give thought to
  • Topic types needed
  • Final outputs desired
  • Required vs recommended metadata & properties
  • Designing for re-use
  • Enabling author productivity
  • Possible translation needs
The “Tiny Topic” Risk in Life Sciences

• Initial analysis of content can lead to over-granularizing your architecture
  • ...if you believe that re-usability ONLY comes from re-using entire topics

• What happens?
  • Authors become overwhelmed by the idea of building documents from a large number of “tiny topics”
  • Structured authoring initiatives can fail
There’s More Than One Way...

- Re-use comes in several shapes and sizes
  - Topic Based Reuse
  - Filter Based Reuse
  - Fragment Based Reuse
  - Variable Based Reuse
The Most Basic Approach

- Topic Based Reuse
  - Identical reuse
  - Same topic is needed in different final documents
  - Same topic used in multiple maps
Filter Based Reuse

• Filtered Reuse
  • Conditional Reuse
  • Variation of content in the same topic
  • Tag portions/variation in topic with metadata
  • Use Filters when publishing to include or exclude content

<US Market>
This is information I want for the US Market
</US Market>

<EU Market>
This is information I want for the EU Market
</EU Market>
Filter Based Reuse Example

- Use Case – Metadata – Choose certain metadata values and include or exclude respective content

8 MARKETING AUTHORISATION NUMBER(S)
EU/134/345/748

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- Each Authorisation Number is tagged for the correct country
- Only the EU Authorisation Number is published
### Fragment Based Reuse Example

- **Use Case – Reference content from another topic**

The text tagged as instructional text (in blue) is for instructional purposes. It explains what type of content to include in each topic section.

### Active ingredients

**warehouse**

The text tagged as instructional text (in blue) is for instructional purposes. It explains what type of content to include in each topic section.

<table>
<thead>
<tr>
<th>Active substance: Kamuslo is a purified concentrate of blood coagulation factor XIII (FXIII). It is derived from human plasma, presented as a white powder.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2500 IU</strong></td>
</tr>
<tr>
<td>Human plasma fraction with a factor – XIII activity of total protein: 24-64 mg</td>
</tr>
<tr>
<td><strong>1250 IU</strong></td>
</tr>
<tr>
<td>Human plasma fraction with a factor – XIII activity of total protein: 120-320 mg</td>
</tr>
<tr>
<td><strong>500 IU</strong></td>
</tr>
<tr>
<td>Human plasma fraction with a factor – XIII activity of total protein: 72-100 mg</td>
</tr>
</tbody>
</table>

*Like copy/paste but the relationship stays intact*
Types of Reuse with Fragments

- Fragment Reuse (2)
  - Utilize an existing complete document (CCDS)
  - Create Topics for new document by referencing content
  - Placing a fragment of content in topic from document
    - The content is maintained in the source document but referenced by other topics
    - Content updates in the source document are reflected in the referencing topic
  - Content References within topics “replaces” copy & paste
Fragment Based Reuse Example

* Use Case – Add content from existing CCDS
Variable Based Reuse

- Variable Reuse
  - Replace word or small phrases with a value from a file
  - Variable placeholders are created within topics
  - Variable resolved at publishing time from variable file
  - Can change variable value by changing the variable file referenced

In this market, the brand name for my product is <product_brand_name>.
Variable Reuse Example

- *Use Case - Consistency* - Enter a value for a variable once and fill in all occurrences of the variable in the protocol.
Focused On Key Regulatory Needs

The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region-specific and modules 2, 3, 4, and 5 are intended to be common for all regions.
Templates Still Work!

• Offers familiarity PLUS structure
• Decreases authoring and administrative time to convert documents to new regions
• Faster turnaround time for ROW registrations
• Easier identification of differences between approved applications
• History of changes contained within single file
Quality Overview (Modules 2 & 3)

- Nomenclature
- Structure
- General properties
- Manufacture
  - Description of Manufacturing Process and Process Controls
  - Control of Materials
  - Control of Critical Steps and Intermediates
  - Process Validation and/or Evaluation
  - Manufacturing Process Development
  - Characterization
  - Elucidation of Structure and other Characteristics
  - Impurities
  - Control of Drug Substance
    - Specification
    - Analytical Procedures
    - Validation of Analytical Procedures
    - Batch Analyses
    - Justification of Specification
    - Reference Standards or Materials
    - Container Closure Systems
  - Stability
    - Stability Summary and Conclusions
    - Post Approval Stability Protocol and Stability Commitment
  - Stability Data
    - Stability
    - Stability Summary and Conclusion
    - Post-approval Stability Protocol and Stability Commitment
    - Stability Data
    - Appendices
    - Facilities and Equipment [name, manufacturer]
    - Adventitious Agents Safety Evaluation [name, dosage form, manufacturer]
  - Novel Excipients
  - Regional Information
  - Batch Record
    - Executed Batch Record
    - Manufacturing Batch Record
    - Packaging Batch Record
    - Comparability Protocols
    - Method Validation Report
    - SOPs
    - Literature References
Clinical Documentation

- Abbreviations
- Administrative Rules
- Assessment of Investigational Product
- Discussion and Overall Conclusions
- Drug Product
- Effects in Humans
- Efficacy Evaluation
- Ethical and Regulatory Standards
- General Information (title, study roster)
- General Precautions and Warnings
- Handling of Patient Withdrawal
- Introduction
- Introduction and Rationale
- Investigational Plan
- Nonclinical Studies
- Patient Safety
- Pharmacokinetics and Product Metabolism in Humans
- Physical, Chemical and Pharm Properties
- Possible Risks/ADRs, Contraindications
- Safety and Efficacy
- Safety Evaluation
- Selection of Patients
- Statistical Considerations
- Study Design
- Study Monitoring
- Study Objectives
- Study Patients
- Study Procedures
- Study Treatments
- Summary of Data and Guidance for Investigator
- Toxicology
In Summary
Remember Re-Use Comes in Many Shapes & Sizes

• Avoid “tiny topics” and the risk of non-acceptance by authors
  • Keep topics meaningful on their own

• Avoid copy & paste
  • Sure, technically it’s re-use but you have no traceability or audit trail
  • Use ‘content reference’ instead

• Start with the end in mind, but...
  • Plan your information architecture realistically
  • Focus on key collections of documents AND their places in history
“The nuts and bolts...”
Real-life Lessons Learned

• Deploying the DITA information model in a +100,000 employee global enterprise makes user adoption priority 1, 2 and 3. Nothing works without user adoption
• Complexity kills – Simplicity succeeds
• The users are often doctors, researchers, statisticians etc. and they use Word and Word only!

• Substitute DITA XML topics with OXML topics
• Leverage tagging in Word
• Enable Conditional Publishing
### The DitaExchange Approach

<table>
<thead>
<tr>
<th>&lt;diita&gt;</th>
<th>A framework for a planned information architecture designed for re-use</th>
</tr>
</thead>
<tbody>
<tr>
<td>SharePoint</td>
<td>A platform for user-friendly content management, version control, workflow, audit trail and metadata management</td>
</tr>
<tr>
<td>Word</td>
<td>The world’s leading authoring tool that offers familiarity and extensibility</td>
</tr>
<tr>
<td>DitaExchange</td>
<td>The leading structured authoring and document publishing solution that unifies and streamlines</td>
</tr>
</tbody>
</table>
Q&A
For More Information

• Contact me
  • Jim Nichols – jim.nichols@ditaexchange.com

• Visit us
  • www.ditaexchange.com