userBridge.09

Parallel eCTD Submission to EU, US, CA

Practical Experience from a Service Provider

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Electronic Submission Services

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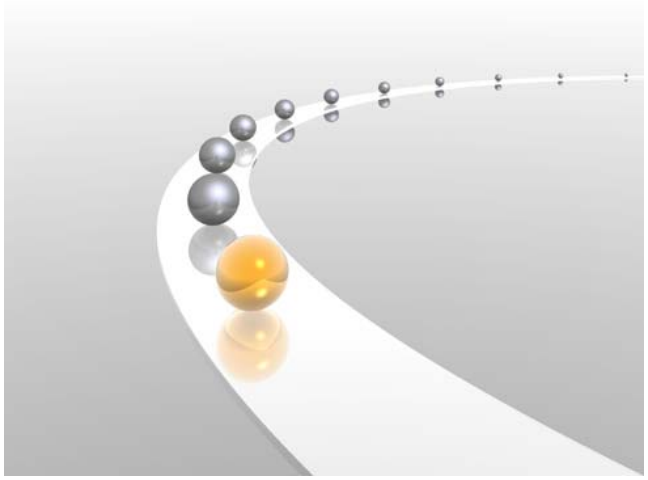

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Some Facts Numbers

- **NCE submitted in EU, US, CA (& RoW) of significant size**
  - EU: ~ 800.000 pages, 7.5 GB
  - CA: ~ 1.2 Mio pages (incl. CRFs), 25 GB
  - US: ~ 1.2 Mio pages (incl. CRFs), 75 GB (50 GB datasets)
- **US eCTD – documents, bookmarks and hyperlinks**
  - ~ 7.500 Files (6.367 in M5 - documents, datasets, CRFs)
  - ~ 20.000 Bookmark nodes (bookmarks in dB not included if possible)
  - ~ 7.500 Hyperlinks defined in docuBridge (~ 6.300 Module 2)
  - ~ 420.000 Hyperlinks in total

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Some Facts
Outsourcing Scenario

- **Interaction client - service provider**
  - Submission hosting - full outsourcing of eCTD compilation
  - Exchange of documents via secure connection (VPN)
  - Submission plans including document IDs from client DMS -> allows check against submission content report
  - Review and approval of published eCTD on file share (alternatively remote view access to docuBridge possible)
  - On request: Report publishing, document formatting, PDF processing

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Compilation Strategy
Maximizing Synergies

- **Synergies by placing compilation "into one hand"** (instead using e.g. local US, CA service providers)
  - Option to re-use parts of the compilation
  - Efficient communication, clarification of questions

- **Start with 2 "part submissions": for Safety & Efficacy**
  - M4 & respective M2 and M5 & respective M2
  - Hyperlinking only once (however – few "open" links to e.g. Quality)
  - Late documents, not included: 2.5, 2.7.3, 2.7.4
  - M4 & M5 with nodes for reports -> required for defining US STFs

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Compilation Strategy
Maximizing Synergies

- **Quality sections**
  - As Module 3 and QOS differ between regions the rationale for "part submission" is rather process time (e.g. parallel editing) time than reusability
  - Only limited number of hyperlinks
- **Merging of "part submissions"**
  - Identify best point in time to continue with region specific eCTD
  - Best case: part submissions compilation almost complete
  - Consider submission deadline – time to start e.g. with US specific items (STFs, Datasets, CRFs, ISS & ISE)

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US Specific Compilation Items

- **M4 & M5 - STFs (Study Tagging Files)**
  - STFs required for all reports in M4 and M5 (latest style sheet: ich-stf-stylesheet-2-2a, not 2-2)
  - M5 “Full Study Tagging” was only required for pivotal and supportive clinical reports (to be agreed with FDA)
  - STF definition for “Non E3 reports” may require input from clinical department
  - For reports located e.g. in M4 and in M5 (via reference node), STF was assigned only once (to avoid redundant STFs)
  - Study title used in STF is defined via node title (-> consider for part submission)

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US Specific Compilation Items

- **M5 – Study Data - Components**
  - Data tabulation datasets (CDISC: SDTM – Study Data Tabulation Model)
  - Analysis datasets (CDISC: ADaM - Analysis Data Model)
  - Program files for ADaMs (pdf and txt)
  - Data definition file (define.xml, define.pdf)
  - Subject profiles
  - Annotated CRFs
  - Annotated ECG waveform data (specific FDA Viewer available, upload outside eCTD)

US Specific Compilation Items

- **M5 – Study Data**
  - Published to folder M5/datasets. In FDA guidance “Analysis” folders are required (not “Analyses”) -> configuration item in docuBridge
  - Define.xml with links to additional files -> file names should be limited to 40 characters (current dB limit for file names)
  - Clarify (with CROs) which style sheet(s) should be used for define.xml
- **M5 – CRFs (Case Report Forms)**
  - CRF bookmarks for domain & visit and hyperlinks (e.g. query sections) expected by FDA (plan *very* early)
  - CRFs located under respective study folder; hyperlinked CRF TOC placed in section 5.3.7

US Specific Compilation Items

- **M1 – SPL (Structured Product Labeling)**
  - Consists of XML and graphic file(s) expected in folder “spl”
  - Feedback from FDA: Recommended to not link the labeling image files into the us-regional.xml (if software tool allows)
  - Submission contained SPL and JPG (invalid eCTD file format) – accepted
  - No style sheet required - reference to style sheet on FDA website
- **M1 - Miscellaneous**
  - Fillable Form 356h with eSignatures used for lifecycle submissions via ESG (Electronic Submission Gateway) -> PDF 1.6 and protection accepted
  - FDA Form 3674 (compliance ClinicalTrials.gov) should be placed in cover letter section (until update of US M1 specification)

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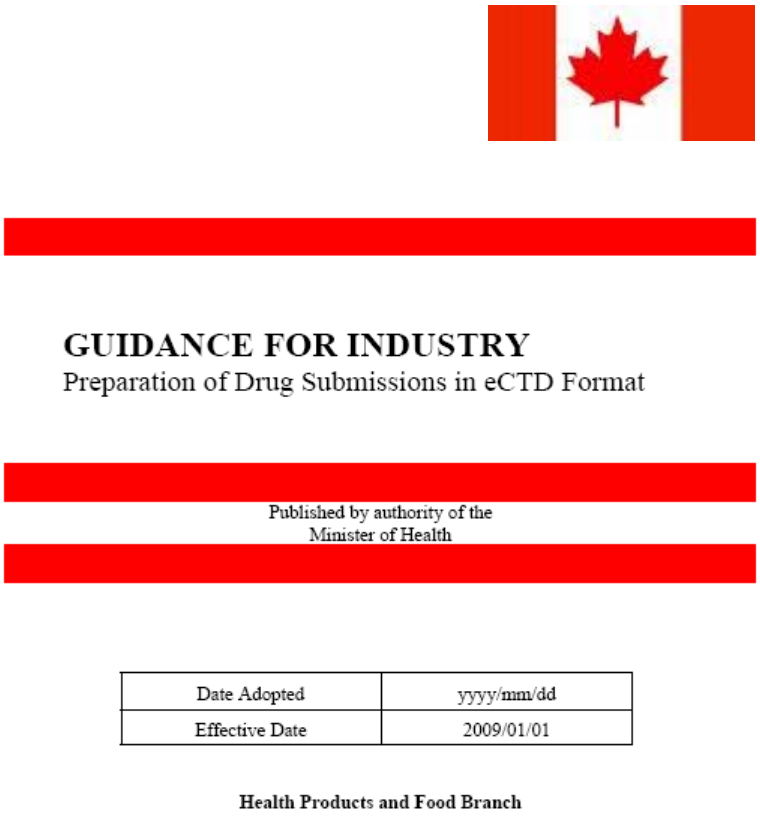
CA Specific Compilation Items

- **New eCTD Guidance**
  - Distributed by HC, but not yet available on HC website
  - Info from HC (Jun-2009):
    "The updated eCTD guidance document should be published on the Health Canada website in the next few weeks. We have released copies of the draft version before this date because no content changes will occur before publication."



GUIDANCE FOR INDUSTRY
Preparation of Drug Submissions in eCTD Format

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Health Products and Food Branch

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CA Specific Compilation Items

- **eCTD – hybrid submission**
  - Complete eCTD submission (First filing: sample eCTD required)
  - Paper copy for Modules 1 and 2 (letter of attestation – identity to eCTD)
  - Request for participation in “Hybrid Filing Format Pilot” needed
  - Note: Electronic-only submission is addressed in guidance; however, it is not yet accepted
- **Compilation, Validation**
  - Copy from EU submission (STFs “not encouraged”, no datasets)
  - External hyperlinks to information pertinent to the review will result in a failure of technical validation (Q&A in preparation)

CA Specific Compilation Items

- **M5 – CRFs**
  - CRFs expected in section 5.3.7 using node extensions for studies
  - Publishing with node extensions creates backbone nodes for study reports (if nodes defined for reports) -> “post publishing” of index.xml
- **M1**
  - No CA M1 style sheet exists -> docuBridge style sheet just for viewing
  - Life Cycle Management Table needed (subject to validation)
  - Checksum required in Appendix II to cover letter (only in paper)
  - Hyperlinking of Annotated PM and Bioequivalence Summary
  - Datasets for Bioequivalence in eCTD section 1.2.8 (.inf and .dat files)

Experience - Summary docuBridge

- **“Part Submissions”**
  - Efficient concept when compiling eCTDs for different regions
  - Structure of M4 & M5 has to be carefully planned regarding creation of nodes for reports, assignment of titles
  - Merging of submissions worked stable when submissions were closed and re-opened before moving nodes
  - QC approach to be planned for hyperlinks to merged sections (not defined in part submission) and late documents

Experience - Summary docuBridge

- **Improvement of process time for “big” submissions**
  - “Publish source file unchanged” (e.g. CRFs, Study Reports) significantly speeds up publishing time
    -> submission ready PDFs required
  - Bookmarks in dB not included, respectively removed
    -> “Publish source bookmarks” has to be re-activated
  - Support of later lifecycle by deleting “unused” hyperlinks prior to creation of 0001
    -> administrator task, tested and documented (check with Lorenz)
    -> ~ 360.000 “unused” links of in total ~ 420.000 links removed

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Experience - Summary
Client Interaction

- **Communication and information exchange**
  - Awareness of project team regarding eCTD (regional) requirements -> know-how transfer via training sessions
  - Ongoing communication and regular TCs are crucial, especially in the last weeks prior to submission
  - Transparent tracking of discussed topics and decisions
  - Process for managing new versions of documents respectively submission plans. Transfer of client's DMS IDs supports clear identification and tracking of documents
  - VPN connections allow seamless working; similar to company internal processes

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Backup Slides

Backup Slides
Granularity M3

- **All regions accepted higher M3 granularity than (explicitly) defined in eCTD specification** (see ICH granularity doc)
- **docuBridge: eCTD "sub keys" for multiple docs available for**
  - Analytical Procedures (3.2.S.4.2 and 3.2.P.5.3)
  - Validation of Analytical Procedures (3.2.S.4.3 and 3.2.P.5.4)
  - Appendices (3.2.A.1, 3.2.A.2, 3.2.A.3)
- **However, multiple docs were submitted for various sections**
  - File name (title in DB) should start with eCTD section and add. info, e.g.
    Stability Data 36 months
    Stability Data 60 months
    …

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Backup Slide
US

- **M5 & M2 – ISS, ISE (Integrated Summary of Safety, Efficacy)**
  - ISS / ISE: Consisted of two physical documents:
    - “Tables and Figures Report” (identical for all regions)
    - Narrative part (see below)
  - ISS: Different narrative part in M5 & M2 (2.7.4)
  - ISE: Identical narrative part in M5 & M2 (2.7.3) - reference node in M5
  - (2.7.3 and 2.7.4 identical in all regions)