Lecture 5:
IT and Regulatory Publishing

Ashley Burt
Kinapse Ltd
This presentation

• Introductory remarks
• Overview of electronic submissions
  • eCTD, NEES and RPS
• Best practices for document and submission management
• Other applications of IT in regulatory affairs
• Conclusions
What is eCTD (1)?

• eCTD is the electronic version of CTD
• Specification developed by ICH (Topic M2) in parallel with Topic M4 (CTD)
• There is no difference between the two in terms of scientific, technical and clinical content
• Specification was finalised in November 2003
• Regional differences in implementation
What is eCTD? (2)

A standard electronic format for sending data from the applicant to the regulatory authority

Vendor and system independent, in terms of both creation and use

- in theory!
- issues with interoperability of eCTD tools have been reported (ETICS)
Benefits of eCTD

- Greatly reduced duplication and shipping costs
- Time saved by avoiding high volume printing
- Ease of storage and distribution
- Integrates life cycle management

Note: Not everybody regards this as a benefit!
eCTD Organisation

There are four components to an eCTD:

- The scientific and technical contents
- A folder structure
- An XML backbone
- Study Tagging Files (US only)

An eCTD consists of discrete sequences:

- The initial submission is sequence 0000
- Subsequent amendments and supplements are provided as sequences 0001, 0002, 0003, etc.
Scientific and technical content

Multiple files, usually PDF

Granularity as per ICH M4 annex (as for the paper CTD)

- A document is defined for a paper submission as a set of pages, numbered sequentially and divided from other documents by a tab
- A document can be equated to a file for an electronic submission
Scientific and technical content: Granularity

In general, ICH M4 specifies coarsest granularity that is considered acceptable

- Often, the applicant has the option to choose a finer granularity

In a full CTD

- Module 2 will be broken down into at least 18 discrete documents
- Module 3 will be broken down into 50+ discrete documents
- Module 4 study reports are presented as one discrete document per report
- Module 5 study reports are broken down into at least three discrete documents per report (a synopsis, a body, and one or more appendix documents)

FDA requires fine granularity for clinical study reports
Folder structure

- Follows the CTD hierarchical structure
- A "warehouse" that stores the files making up the scientific content
XML backbone

- Effectively an "inventory" or "catalogue" of the submission contents
- Displays as a hyperlinked table of contents for the submission
- Contains version control information to support life cycle management
XML backbone (Contd)

- XML is a powerful format for storing structured information
- An XML file is a simple text file that contains text information organised into "elements"
- The eCTD XML backbone has a structure that includes "heading" elements for each CTD section
  - Organised hierarchically just like the CTD
- "Heading" elements contain leaf elements
- In general, there is one leaf element for each file in the eCTD
eCTD works like IKEA

- Folder structure = WAREHOUSE
- Folder = LOCATION in the warehouse
- File = ITEM stored in a certain location in the warehouse
- XML backbone = INVENTORY
- Leaf element = INVENTORY ENTRY

- In a warehouse, you can find the location and description of each item from its inventory entry
- In the eCTD, you can find the location and description of each file from its leaf element in the XML backbone
Study Tagging Files

Contains descriptive information on nonclinical and clinical studies in Modules 4 and 5.

Information required depends on CTD section, and can include the following:

- Study title
- Study type
- Duration of study
- Species
- Route of administration
Viewing eCTDs

Â It is possible to use a web browser with Adobe Acrobat installed
  ï view individual sequences in isolation only
Â Dedicated review tools are superior
  ï provide a consolidated view of current documents across all sequences
Â Low-cost viewing software is commercially available
NEES

ÅNEES are similar to eCTD except:

- no XML backbone
- hyperlinked PDF tables of contents included as sections 1.1, 2.1, 3.1, 4.1 and 5.1

Å these sections are not required in eCTD as the XML backbone does this job

ÅNEES have most of the advantages of eCTD

- but without the benefits or complexities of eCTD life cycle management
Acceptance of eCTDs in Europe

- Slow start: almost no progress 2003-2007
- Initial versions of EU NEES and eCTD guidance published 2008-2009
- Guidance has been refined with experience: current versions:
  - TIGes NEES guideline v3.0 (Aug 2011)
  - TIGes NEES validation criteria v2.1 (Feb 2011)
  - TIGes eCTD guideline v2.0 (Sept 2011)
  - TIGes eCTD validation criteria v3.1 (Feb 2011)
  - CMD(h) Best Practice Guide for eCTD in MRP/DCP v3.0 (Nov 2011)
EU Centralised Procedure

Â Since 1 July 08, EMEA has accepted electronic submissions
Â This has applied to all application types
  ï new applications, supplementary information, variations and renewals
  ï preparation of a "baseline" updated Module 3 in eCTD format is encouraged for existing MAs, to facilitate electronic maintenance in future
Â Since 1 January 2010, eCTD has been the only acceptable electronic format
Â Paper submissions are still acceptable, but strongly discouraged
Â EMA eSubmission gateway currently in pilot (as of January 2012)
EU National/MRP/DCP

Most agencies will now accept electronic submissions for National and Mutual Recognition Procedures.

Current requirements are published on the CMD(h) website.

- Most recent version (July 2011) indicates that only Finland, Lithuania, Slovakia and Slovenia still require paper.
- eCTD is the only acceptable electronic format in Czech Republic and Latvia.
- Published requirements not always reliable or up to date; best to check with local affiliates and/or agencies prior to submission.
eCTD in MRP/DCP

- The principle of a single comprehensive eCTD is enshrined in the CMD(h) Best Practices document.
- EU Module 1 specification allows for designation/segregation of common and country-specific information for each territory.
- Member states need only receive eCTD sequences relevant to them.
- A tracking table is included in Module 1 of each sequence, which provides a full sequence submission history.
- National translations are handled outside of the eCTD.
Acceptance of eCTDs in USA

- FDA will accept eCTDs from companies that have submitted a test submission which is of acceptable quality
  - Pilot submission for technical testing only
  - FDA will look at conformance with ICH specification and local requirements
- FDA does not like paper submissions
- eCTD mandatory for new e-submissions from 1 Jan 2008
  - guidance for NEES-type submissions withdrawn
- FDA provides an eSubmission gateway
Regional differences: EU vs. US

- Same differences in content as for paper CTDs
- Technical differences:
  - FDA has certain preferences relating to the XML backbone (node extensions not allowed)
  - SPL (structured product labelling) mandatory in USA
  - Study Tagging Files required for USA
  - Clinical and certain nonclinical study data in CDISC formats required for USA
Regulated Product Submission (RPS)

A Message specification to cover regulated product submissions

A XML used to catalogue the contents of the submission

- Extensive use of controlled vocabularies (codes) to describe contents of the message

A HL7 (Health Level Seven) standard

- Will become eCTD Next Major Version (NMV)
- ICH Steering Committee endorsed decision to work with HL7 in October 2008
- Will become an ISO/CEN standard eventually
RPS concept: eCTD v.3.2.2 vs RPS

å eCTD
  ï Message format for submitting CTD dossiers to agencies in ICH regions
  ï Supports lifecycle management

å RPS
  ï As above, plus:
    ñ Supports other types of regulated submission e.g. veterinary, devices, food supplements etc
    ñ Bi-directional communication
    ñ Potential to support exchange of content common to multiple products
RPS paradigm

Å Application
  • Covers all regulatory activity that occurs under a given procedure or application number

Å Submission
  • Represents a specific regulatory activity associated with a given Application
    • e.g. a new application, renewal etc

Å Submission Unit
  • Represents a single communication relating to a given Submission
    • e.g. Initial submission by applicant, questions from agency, responses from applicant etc.
RPS progress

RPS R2 reached Draft Standard for Trial Use (DSTU) in January 2010
  - Driven by requirement of FDA to meet PDUFA IV commitments
RPS next version development began in late 2009
  - Driven by need to include eCTD NMV requirements
    - ICH website provides a requirements list dated 9 June 2010
  - As of May 2011, earliest approval est. Sept 2012 with earliest FDA adoption est. late 2013
  - EU/JP will not implement until approved as ISO standard
  - Current situation is opaque - no newer information appears to be available (current version is R2.2)
Implications of RPS

Å The RPS/NMV re-use paradigm has profound implications for content management
Å Vendors whose systems already have good support for content re-use will be best placed to deal with the challenge of RPS/NMV
Å New investment in systems upgrades and/or replacements is likely to be required by both applicants and agencies
Å Vendors are likely to have to support RPS and eCTD concurrently
Å Currently unclear when RPS will be implemented
EU Product Information (PIM and EudraVigilance XEVPRM)

Â PIM

ï Contained product information in an XML file
ï Allowed for exchange and editing of product information between applicant and agencies
ï Benefits included reduced duplication of information, ease of review, (especially with regard to translations) and enhanced quality (enforced compliance with QRD)
ï PIM died on 28 March 2011é RIP! 😞
ï Waiting for resurrectioné 😐

Â EudraVigilance XEVPRM

ï Message specification for submission of product information to EudraVigilance
ï Contains information necessary to identify medicinal products uniquely
ï Product information included as attachments (unstructured)
ï MAHs must submit product information in XEVPRM format by 2 July 2012
US Structured Product Labelling (SPL)

- XML file containing labelling information, mandatory in the USA

SPL was introduced because:
- It supports exchange of information between different computer systems e.g. different health info systems
- It makes labelling changes easier to check
- It supports easier comparison with other labels

FDA plans to add indexing information to SPL labels to support rapid access, searching and analysis
- Indexed-based searching avoids limitations of full-text searching
- A simple text search for "hepatotoxicity" would miss references to "liver toxicity" etc.
Best Practices for eCTD

Aspects that need to be considered
- Preparing for eCTD
- Business processes
- Document authoring
- Document management
- Granularity
- eCTD publishing
Managing and publishing electronic submissions

Best practice is to use an integrated document management and publishing system for eCTD and NEES

- Well-developed market with >25 vendors

eCTD requires a publishing tool

- impractical to prepare XML backbone manually

NEES can be compiled manually

- using Acrobat and Windows explorer
- not the best option, as this is time-consuming and error prone
eCTD practicalities: General

Some issues are common to CTD, namely:
• Employing a robust and verifiable process for document authoring and version control
• Complying with the ICH M4 Annex regarding granularity
• Inserting the right document in the correct location in the submission
• Ensuring that documents are well-formatted, complete and legible
  • Old legacy reports can be particularly problematic
eCTD practicalities: General

Some additional issues are specific to eCTD:
- Ensuring adequate hyperlinking and bookmarking for ease of navigation
- File naming
- Font issues
- Text versus scanned PDF
Managing authoring and dossier content

- Operate to Good Regulatory Practice
- Procedures to ensure information authenticity and the ability to confirm origin of all information included in the dossier
- Rigorous procedures for internal review and approval
- Benefits include improved dossier quality, resulting in fewer questions and fewer delays in assessment
Controlled documentation

GMP (manufacturing and controls)

GLP (non-clinical safety evaluation, analytical methods and validation)

GCP (clinical research)

CTD / eCTD submission

Summary documentation

(Mainly Module 1-3)
The reality in some cases!
Document identification and version control (1)

Best practice:

Å Use a document management system
   ï Allows far greater control and traceability than a file system
   ï BUT it is still possible to make mistakes
      Å The wrong document or wrong version can still be checked in
   ï Control risks by ensuring that read/write access is restricted to appropriately trained staff who require access

Å Always check the final submission carefully to match document titles/numbers/dates vs the ToC
Document identification and version control (2)

If you must use a file system:
Å Give read/write access only to those who need it most
  ï Read access only for others
Å Maintain a read only area for final, approved versions
Å Agree and enforce rules for file naming/version control
  ï Set up a tracking spreadsheet or similar system to ensure traceability of files
  ï Maintain an up-to-date ToC that includes full titles and dates for each document
Å Use dates or version numbers to identify files
  ï Avoid the use of final in file names
Document identification and version control (3)

If you must use a file system:
Å Avoid cryptic file names
Å Be aware that the risk of misidentification is heightened in certain circumstances:
   ï Reports with very similar titles or study numbers can be mixed up
   ï The same applies with literature references
      Å Smith & Jones 1990a, Smith & Jones 1990b

Å Check documents in your submission for correct identity
   ï Check title, author and date versus the ToC
Granularity

Top tips:
• Make an early decision on granularity
  ï ICH M4 allows a degree of choice between a coarser or finer granularity
• Choose a fine granularity for sections that may change in future e.g. Module 2.3 and Module 3 subsections
  ï Life cycle management only allows whole documents to be replaced, not individual pages
• Generate your documents at the correct granularity
  ï Splitting or combining is time consuming and error prone, and will affect intra-document hyperlinks
Legibility and completeness

• Check scanned documents for completeness and legibility
• Common problems
  ï Quality issues with legacy documents
• Tools are available for dealing with cosmetic problems with scanned documents
• Top tip: avoid automatic tools for cleaning up scans
  ï Automatic de-speckling tools play havoc with scatter plots etc.
Document authoring

Best practice:
- Use Word templates set up with styles, auto captioning and electronic cross-referencing
  - Promotes consistent formatting and introduces a professional "corporate" look to the submission
  - Automates creation of bookmarks and hyperlinks when the Word documents are rendered to PDF
- Train users to use MS Word properly!
  - Do not use Word as a typewriter; it can do so much more for you
Hyperlinking and bookmarking

Å Recommendation

- Bookmark headings, tables and figures
- Hyperlink cross-references to anything not on the same page as the cross-reference
- Use Word templates with styles, electronic captions and electronic cross-referencing
  - Automatic creation of bookmarks and hyperlinks when rendered to PDF

Å Top tip:

- Be aware that changing file names and relative locations will break inter-document hyperlinks
Font issues

Å Lack of portability of Microsoft Word documents
Å PDF font substitution
Å Best practice
  ï Use standard Windows fonts ONLY
  ï Preferable for the author to be responsible for rendering Word to PDF
    Å or use a validated PDF rendering engine
  ï Create PDF with fonts embedded
Text versus scanned PDF

Text PDF is:
  • Searchable
  • Supports cut-and-paste
  • Recommended in the ICH M2 eCTD specification, and in EU NEES guideline

Scanned PDF is:
  • Not searchable
  • Does not support cut-and-paste
Optical Character Recognition

Å Acrobat supports insertion of a hidden layer of OCR text behind the visible scanned page
Å OCR is error prone and performance is poor with poor quality scans
Å Authorities take different viewpoints with regard to hidden OCR text
  ï FDA requires 100% accuracy (very difficult to achieve, even with careful proof reading)
  ï UK MHRA does not insist on proof reading or correction
Colour figures

• If using colour figures, ensure that they are still interpretable if printed monochrome
  ✓ Assessors may print off copies in monochrome
  ✓ Use different line types and/or symbols, as well as different colours, to differentiate data series

• EU NEES guideline recommends monochrome
Other common uses of IT in regulatory affairs (1)

Â Regulatory intelligence
  ï Agency websites
  ï Commercial providers e.g. IDRAC, Tarius etc.
  ï Social media e.g. Yahoo groups, LinkedIn etc.

Â eLearning
  ï Webinars
  ï Training

Â Electronic collaboration tools
  ï Online conferencing
  ï Document review tools
Other common uses of IT in regulatory affairs (2)

Â· Project management
  ï· MS Project etc.

Â· Submission tracking applications
  ï· Status reporting
  ï· Planning for deadlines

Â· Workflow applications
  ï· Review/approval workflows
  ï· Change controls
  ï· Artwork / advertising
Challenges for regulatory affairs professionals

Paper submissions are now almost "history"

Regulatory affairs professionals can be slow to embrace change
- fear, uncertainty and doubt result in a "if it ain't broke, then don't fix it" mentality

However, proactive implementation of appropriate IT solutions leads to tangible benefits and added value to our businesses
Rewards

Application of IT solutions can add value to regulatory affairs activities in the following ways:

1. Using MS Word properly
   - Speeds up authoring
   - Helps to avoid errors and inconsistencies in documents
   - Improves the cosmetic appearance and consistency of documents

2. Managing content appropriately
   - Effective document management eliminates problems with version control
   - Well-managed content makes publishing submissions easy

3. Using specialist publishing tools (or using a contractor)
   - Use of specialist eCTD/NEES publishing software is superior to manual publishing, in terms of speed, efficiency and lower potential for errors

4. Moving to all-electronic submissions
   - Saves time and money, and benefits the environment

5. Implementing appropriate systems to support business needs in other areas
   - Solutions for regulatory information, eLearning, collaboration, project management, tracking, workflows etc. promote efficiency, information visibility, collaboration and communications
Key References

Â ICH eCTD Specifications
  ï http://estri.org/eCTD/

Â EMA Notice to Applicants Vol 2B

Â EMA eSubmission Website
  ï http://esubmission.ema.europa.eu/

Â FDA eCTD Guidance
  ï http://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm153574.htm