Health Products *and* Food Branch

Your Health and Safety - Our Priority

@-Review

Experience with eCTD format - Validation Issues and Errors

Presentation to CAPRA

Lili Hajiesmaili

February 21-22, 2006

Toronto

Canada

eCTD Validation Issues and Errors

Some Statistics (Co-submission Filing Format, Sept 2004 – Feb 3rd 2006):

- – Total number of Submissions received: 28
- – Total number of Sequences received: 66
- – Number of Sequences received per Submission: Max. 5
- – Total number of Sequences passed IT Validation: 45
- – Total number of Sequences failed: 21

Pass rate: 68%
Fail rate: 32%

E-Review

2

Different Categories of Issues

➢ Module 1-Related: 39%

➢ ICH Specification Compliancy: 37%

➢ Life Cycle-Related: 2%

➢ Defective Media (CD / DVD): 7%

➢ Viewing Tool Limitations: 15%

Module 1-Related Issues

➢ Canadian Module 1 backbone invalid against the current version of the DTD (CA M1 DTD)

➢ Invalid Canadian Module 1 backbone name:
  Correct: ca-regional.xml   Incorrect: ca-index.xml

➢ Invalid ICH defined folder path for the regional module:
  Correct: 0000/m1/ca/cover.pdf   Incorrect: 0000/ca
                                                                                    or 0000/m1/cover.pdf

➢ eCTD Identifier should be used as top level folder structure:
  Correct: Incorrect:
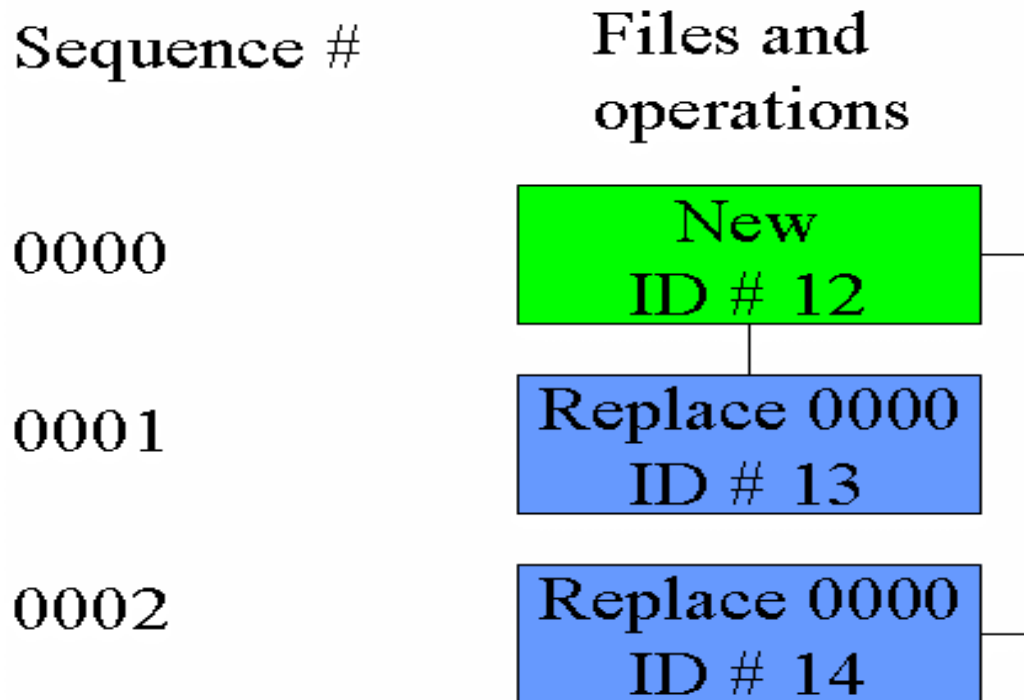
Module 1-Related Issues

➢ HC-3011 form naming convention
Correct: hc-sc-3011-en.pdf   Incorrect: 1-2-1-drug-submission-app.pdf
or 3011.pdf

➢ Invalid HC-3011 form operation attribute. It should always be "new",
unless the sponsor is asked to correct an error and resubmit, in that case,
the attribute should be "replace". The replacement would be submitted
under a new sequence number.

➢ Empty Related-sequence-number when submitting response to a Clarifax,
a Deficiency Notice, etc. (it should point to the correct parent submission
sequence number)

➢ Sequence numbers not incremental
Incorrect: 0003 submitted after 0004 was submitted and accepted

E-Review

ICH Specification Compliancy Issues

➢ ICH eCTD backbone invalid against ICH eCTD DTD
➢ Incorrect MD5 checksum value for leaf documents
➢ PDF files in submission folder not referenced in the backbone
➢ Leaf document naming convention
  - Extra space in the name:
    Correct: mytoc.pdf   Incorrect: my toc.pdf
  - Case sensitivity:
    cover.pdf in backbone, cover.PDF in file system
    Not an issue in Windows, but a problem in UNIX

➢ Invalid file path (xlink:href) in index.xml
  Correct: "m1/ca/ca-regional.xml"
    Incorrect: "/m1/ca/ca-regional.xml" (starting "/" shows an absolute path)
    Incorrect: "m1\ca\ca-regional.xml" (UNIX cannot load due to "\")

E-Review

6

Life Cycle-Related Issues

Multiple replaces to the same leaf document:

Sequence #	Files and operations
0000	New ID # 12
0001	Replace 0000 ID # 13
0002	Replace 0000 ID # 14

E-Review

Defective Media Issues

Not readable media:

- Broken CD's on arrival
- Unloadable DVD-RAM

Viewing Tool Limitation Issues

➢ Backbone loading failure in the viewing tool due to a large number of leafs (over 10,000) under one heading element in the backbone (index.xml)

➢ Backbone loading failure in the viewing tool due to a mixed order of leafs and node-extensions:
    Unloadable order: <leaf > <node-extension> <leaf> <node-extension>
    Loadable order: <leaf> <leaf> <node-extension> <node-extension>

eCTD Validation Issues and Errors

Recommendations:

➤ Prepare Well:

- Review Health Canada Guidances and Q&A
- Refer to ICH Specification and Q&A

➤ Follow the Process:

- Notify Health Canada when intend to submit in eCTD format
- Request for technical pre-submission meeting
- Submit sample eCTD first

➤ Conduct Quality Control:

- Apply satisfactory quality control when building eCTD submissions

For more information, please visit:

- Health Canada Website
  www.hc-sc.gc.ca
- Therapeutic Products Division
  http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_e.html
- Biologics and Genetic Therapies Directorate
  http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/index_e.html
- Veterinary Drugs Directorate
  http://www.hc-sc.gc.ca/vetdrugs-medsvet/index_e.html
- Natural Health Products Directorate
  http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/index_e.html
- E-Review Website
  http://www.hc-sc.gc.ca/hpfb-dgpsa/er-ee/index_e.html
- Questions about E-Review?
  ereview@hc-sc.gc.ca

E-Review

Questions ?