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Update eCTD Implementation in the EU

CAPRA 'Getting Ready for the eCTD' Symposium
2-3 April, 2003
Toronto, Canada

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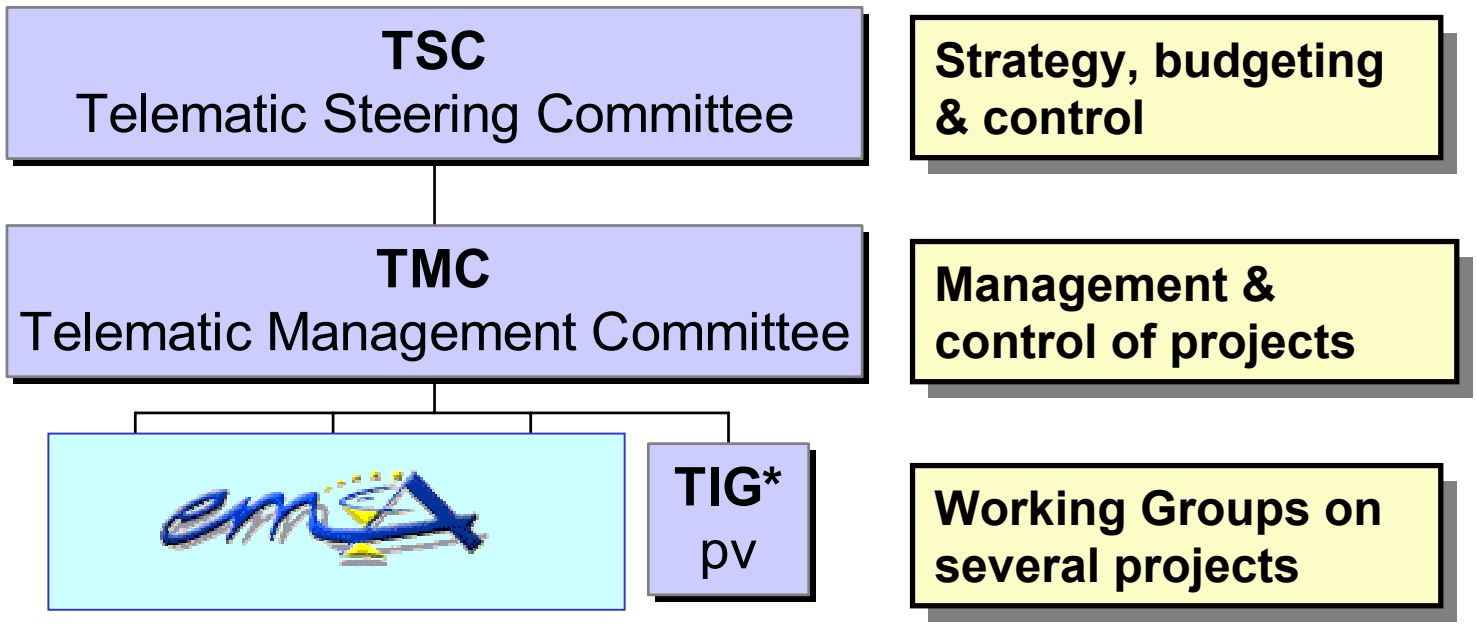
Process Manager MEB
EU ICH M2 Topic Leader

Agenda:

- EU ICT Management Structure
- eCTD Status in the EU + ICH issues
- Update EU eCTD Implementation
  - Module 1 Specification
  - EU Review System (EURS)
  - EU-IND Working Group
- Conclusions

EU ICT organisation (1)

- EU ICT Management Structure:



‘Mandate’ of TIGes

- ‘Organise’ EU regulatory in-put in ICH process
- Develop EU Module 1 Specification
- Develop other standards, i.e. Application Form, PIM, etc.
- Develop tools for review
- Communication and training on eCTD
- Establish contact with other EU regulatory groups, e.g. NtA
- Co-operate with industry: **EU-IND Working Group**

The eCTD Specification Status in the EU

- ICH SC approval: September 2002
- EU CPMP in November 2002
- Step 5 published
- EU implementation date: 1 July 2003:
  - Voluntary basis for industry, i.e. NOT REQUIRED
  - This means ‘mandatory’ for regulators
- Next step: incorporate standards in legal framework, i.e. the Notice to Applicants

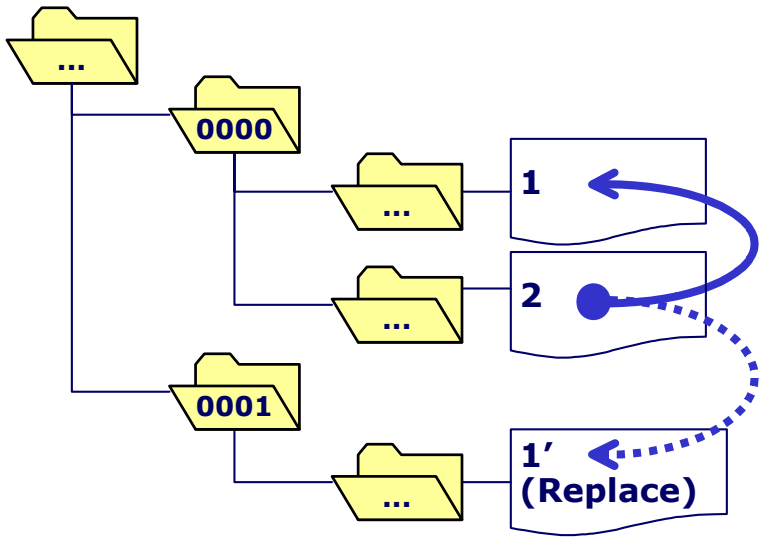
What are *the* eCTD issues for the EU?

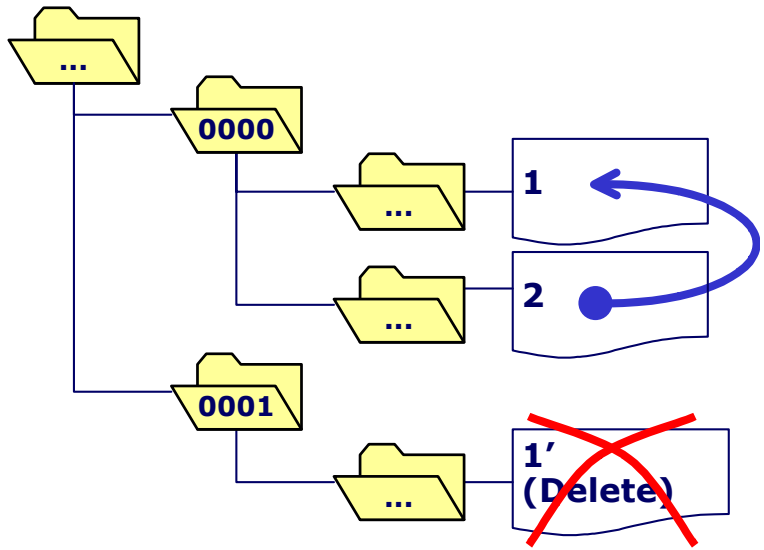
- **Solution Study Report issue of the FDA (!!!)**
- Adequate ICH Change Control Process
- Handling Questions & Answers
- Understanding technical issues:
  - Life-cycle management (REVIEW TOOL)
  - 'Broken-link issue' (REVIEW TOOL)
  - Third party information e.g. Drug Master Files

BIG QUESTION: how are we going to manage ‘Life-Cycle’ in the REVIEW TOOL or SYSTEM??????

Life cycle management

-the Broken Link Issue-





The link from Document 2 still points to Document 1 which has been replaced

The link from Document 2 still points to Document 1 which has been 'deleted'

What are the eCTD *implementation* issues for the EU?

- Development EU Module 1 Specification
- Development EU Review System
- Co-operation with industry

The EU Module 1 Specification

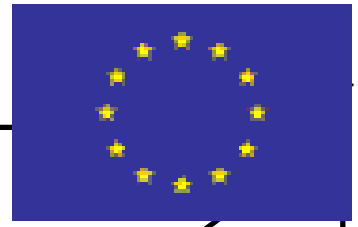
- Content: Notice to Applicants
- Technical components:
  - XML backbone (**`eu-regional.xml`**)
  - directory structure + files (PDF, XML, RTF)

  ICH
  - XML envelope for submission meta-data
- Document topics:
  - Description concepts and technical components
  - Change Control Process (regulators *and* industry)
  - Future topics
- Status: version 0.91 (final version April 2003)

EU Module 1 content and main XML elements

NtA	EU Module 1 XML element
1.1 ToC	<m1-1-other>.
1.2 Administrative forms	<m1-2-administrative-forms>
1.3 Product Information	<m1-3-product-information>
1.4 Info on Experts	<m1-4-information-about-experts>
1.5 Specific requirements	<m1-5-specific-requirements>
ANNEX: ERA	<annex ERA>
	<eu-envelope>

EU Module 1 Architecture:



<applicant>
<agency>
<agency-number>
<approval-date>
<product-name>

<submission>:
“submission-type”
“submission-date”
“sequence-number”

EXAMPLE

Document topics (1)

-Change Control Process-

- Specific for Module 1, but resembles ICH Change Control
- Change request by Form:
  - national authorities
  - national or international industry associations
- Form: contact info, problem statement, testing (?) and proposed solution (?)
- Meetings: proposal for REG-IND Working Group
- Decision: approved, testing, deferred or rejected
- Publication: Specification and Change Request Tracking Document

Document topics (2)

-Future issues: PIM project-

- Proof of Concept for data-base to data-base approach proven with an Oracle iFS/Arbortext system
- **Big question**: can it be transformed into a production system which adds value to the entire business process around product information documents
- Question to be answered in 2003 and eventually incorporation of PIM standard into Module 1
- *Information provided on PIM in symposium*

Document topics (3)

-Future issues:administrative Information in XML-

- Purpose: meta-information at the submission level (replacement of the envelope) and re-use of information
- XML DTD (version 0.94) available for Application Form (NtA version July 2002 = 30 page form)
- Status: final version DTD foreseen in March 2003
- Two Member States already developing implementations: AFSSAPS and MEB
- *Reference to presentation later in symposium*

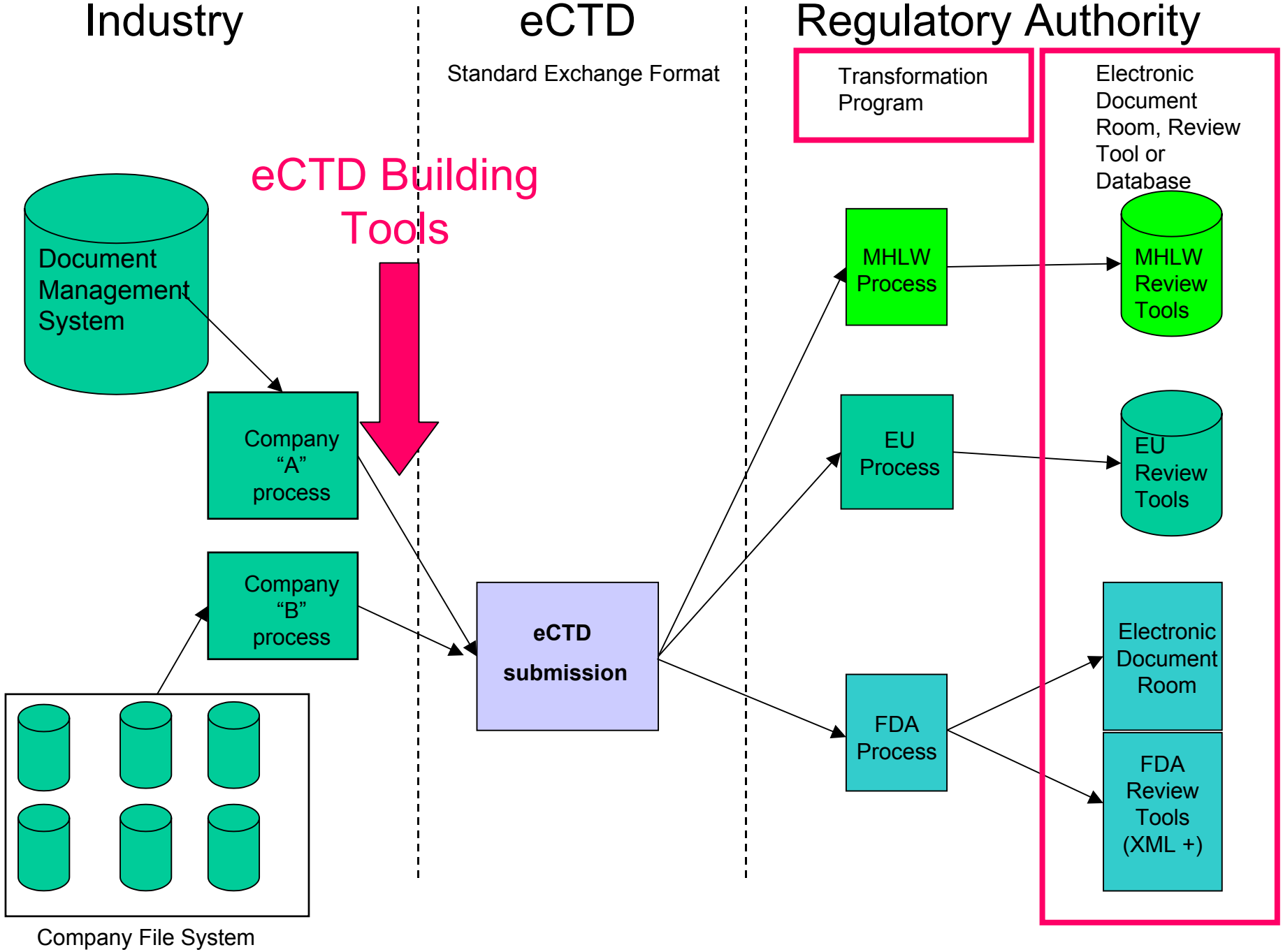
Document topics (4)

-Future issues: pure electronic communication-

- EudraVigilance: up and running in most MS
- For eCTD:
  - inventory of status of electronic signature
  - inventory of status national PKI initiatives
- EDI (two-way communication: R-to-I and I-to-R)

EU Review System ??

The reason why each region need a review system lies within the ICH concept of the eCTD being an exchange standard.


Industry
eCTD
Standard Exchange Format
Regulatory Authority
Transformation Program
Electronic Document Room, Review Tool or Database
eCTD Building Tools
Document Management System
Company "A" process
Company "B" process
Company File System
eCTD submission
MHLW Process
EU Process
FDA Process
MHLW Review Tools
EU Review Tools
Electronic Document Room
FDA Review Tools (XML +)

EU Review System (EURS)

-Initial user requirements (1)-

- Scope:
  - Phase 1: validation/processing + review
  - Phase 2: life-cycle, including regulatory out-put, cross-applications, pure electronic
- Review functionality:
  - viewer
  - search
  - print
  - off-line
  - review assistant

http://esubmission.eudra.org/ectd

EU Review System (EURS)

-Initial user requirements (2)-

- Viewer:
  - navigation (e.g. expandable / collapsible)
  - meta-data view
  - view document (including functionality from application, e.g. Acrobat 5.0)
- Search:
  - through meta-data
  - full text search

EU Review System (EURS)

-Initial user requirements (3)-

- Print:
  - single or batch
  - info on size before printing
- Off-line:
  - download
  - synchronisation
- Review Assistant:
  - annotations

Demo's during symposium

EURS: development process steps

No optimistic view on ***EU*** eCTD implementation and therefor, several Member States started national initiatives to *fully* implement the eCTD, for an example reference is made to a later presentation in the symposium (alternative T3PR?????)

No EU funding available for 2003-2004!!!

EU-Industry eCTD Working Group

- Participants:
  - representation of TIGes
  - EFPIA eSubmission Taskforce
  - generic associations
  - individual companies
- Agenda of the Group:
  - Specifications change requests
  - Implementation status
  - Business protocols & Life-cycle management

Specifications Change requests

- **Objective:** common EU position
- Examples high priority:
  - Excipient & container section
  - Optional file names
  - MD5 deleted files
  - Modularization of the DTD
- Examples low priority:
  - Understanding operation attributes
  - Value of optional document attributes
  - Multiple envelopes *(regional)*
  - Renewal documents *(regional)*

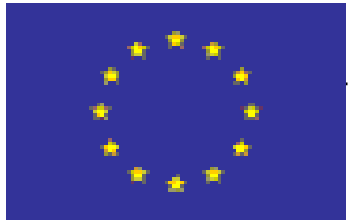
Implementation status

- **Objective:** define status within EU Member States *and* the pharmaceutical industry
- Status update per Member State: *document*
- Industry questionnaire:
  - When ready to prepare and file eCTDs?
  - After that, eCTD only or other types of eSubmissions?
  - What are company drivers for the eCTD?
  - What are external factors influencing progress on eCTD?
  - Issues around enabling business process for eCTD?
  - What are obstacles producing eCTDs?
  - Once-electronic-always-electronic?

Business process & LCM (1)

- **Objective:** define in detail the EU business process around the Centralised Procedure (EMEA) and the Mutual Recognition Procedure (MRP) and how it relates to eCTD submissions
- First conclusions:
  - Centralised: quite straight forward
  - MRP: complex

Business process & LCM (2)



First country	*First MRP round*	*Second MRP round*	*Comments*	
RMS	*CMS A*	*CMS B*	*CMS C*	
0000				**Original national dossier**
0001				Responses to RMS questions
0002				Responses: Final SPC
0003				Variation to support shelf life extension
0004	0004-**Q1**	0004		**Submission of the MR updated dossier for a MRP that involves CMS-A and CMS-B**
0005	0005	0005		Responses to CMS questions
0006	0006	0006		Withdrawal from CMS B Possibly 007 contains only the letter of withdrawal-**Q2**
0007	0007	0007-**Q3**		Responses to CMS questions
0008	0008	0008		Responses: Final SPC
0009	0009			**Variation to support a SPC change**
0010	0010			Responses to CMS questions
0011	0011			Responses: Final SPC
0012	0012			**Post approval commitment: submission of long term stability data**
0013	0013	0013		**PSUR**
0014	**Q4**	0014	0014	**Submission of the MR updated dossier for a MRP that involves CMS-B and CMS-C**
0015		0015	0015	Responses to CMS questions
0016		0016	0016	Responses: Final SPC
0017	0017	0017	0017	**Extension to support a new indication**
0018	0018	0018	0018	Responses to questions
				Extension is rejected – **Q5**
0019	0019	0019	0019	**Renewal**

Business process & LCM (3)

- Many questions to be answered:
  - Start MRP: updated dossier or cumulative view of history?
  - How to indicate that updated dossier supersedes all prior once?
  - One single submission to all CMS?
  - How to handle gaps in the life-cycle?
  - Is correspondence part of the eCTD?
  - ……...
- EFPIA has build a Mock eCTD with 12 life-cycles:
  - see http://www.euro-ectd.org

EU Summary (1)

- Standardisation process:
  - ICH considered successful
  - EU TIGes; good progress, several examples of DTD developments, e.g. EU Module 1, PIM, administrative forms
  - Issues: Study Report, Change Requests, further understanding

EU Summary (2)

- Implementation:
  - Step 5 published; voluntary date set at July 2003
  - EURS; will be very basic and general due to lack of sufficient funding and ability to serve all EU infrastructure
  - National initiatives
  - Initiated co-operation with industry; great potential

Thank you for your attention!

Reference to:

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