Human and veterinary pharmaceuticals regulation

Towards EU accession: Serbia's regulatory challenges, expectations and opportunities

29-30 November 2010

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Republika Srbija
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Medicines and Medical Devices Agency of Serbia

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

E-Submission

An European perspective

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Agenda

- Rationale for e-submission
- Managing eCTD Life cycle management (LCM) in the CP, MRP, DCP and national procedures
- EU NeeS guidelines, validation, the future of NeeS
- eCTD current status and expected implementation dates

eSubmission: rationale

- Reduction of the administrative burden
- Reduction of physical archive space
- Reduction in shipment fees both for applicants and agencies
- Facilitation of automated processing (workflow, automated mails)
- Facilitation of the review process
- Re-use of former information, economy of scale
- Facilitates centralisation, both at applicants and agencies (platforms, portals).
- Automated reporting, KPI's
- Creation of authentic sources (e.g. Eudrapharm)
- Facilitation of dynamic offices
- Facilitation of tele work

Some theory first

ICH 3.2.2 specs: The primary focus of the eCTD is:

- A data interchange message between industry and agencies.
- Industry prepares the initial submission in terms of an electronic CTD.
- Through out the life cycle of this process, additional information will be submitted to update or modify the information contained in the initial submission (e.g., supplement, amendment, variation.)
- The agency can submit acknowledgements, queries and requests to industry. (Future 2 way communication)
- The overall architecture of the eCTD is designed to provide a commonly agreed upon submission and submission structure that imposes minimal restriction to the industry and agencies.

Life cycle management – LCM (1/2)

The LCM describes the additional information (e.g. variations) in the dossier by means of *sequences*.

- Technically: The XML (index.xml) super structure with the CTD folder and file structure is the eCTD, similar to a table of contents.
- Each PDF file in the CTD structure has an attribute in the index.xml. It is the value of each attribute which defines the position of the PDF file in the life cycle.
  - Attribute is new: means that file has no link with any previous file.
  - Attribute is replace: this file replaces a previous one, can be some sequences back.
  - Attribute is delete: that PDF file is not relevant for submission.
  - Attribute is append: the PDF file associates to an existing PDF file. (not recommended operator, especially in combination with other operators)

Life cycle management – LCM (2/2)

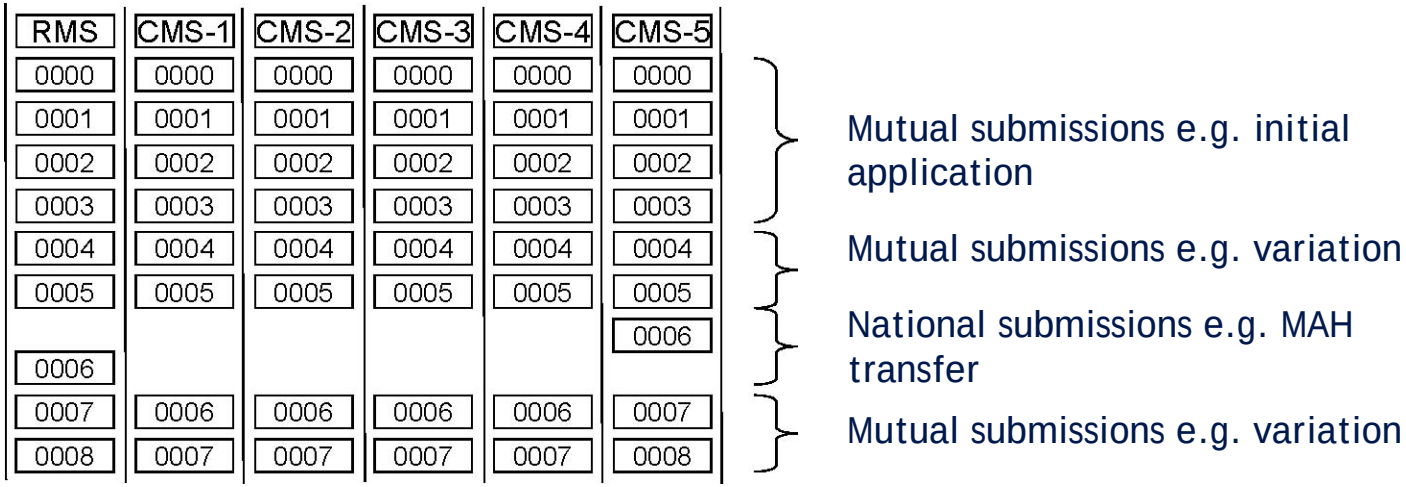
- When an eCTD is opened in the Internet explorer: the reviewer sees the current submission with the value for each attribute.
- When used in a eCTD viewer: the reviewer chooses between the delta view (i.e. the difference with previous sequences), the cumulative view (all documents ever submitted) and especially the current view (updated view using all attributes).
- Assessors appreciate the LCM: the updated dossier, baseline submissions but also functional intra document and inter document hyperlinks (new application), bookmarks.

- A NeeS (Non eCTD electronic Submission) is the folder and file structure of the CTD. This is identical to an eCTD where the index.xml is not present.

Managing the Life cycle management (1/5)

- There are 4 licensing procedures in the EU: centralised, MRP, DCP and national procedure:
  - **Centralised procedure**: From 1st july 2009: eCTD only, or paper. EMA is working on a gateway for applicants to the central repositories.
  - **MRP and DCP**: all but a couple of agencies accept fully electronic submissions/ NeeS or eCTD (and eCTDs backwards compatible with NeeS).

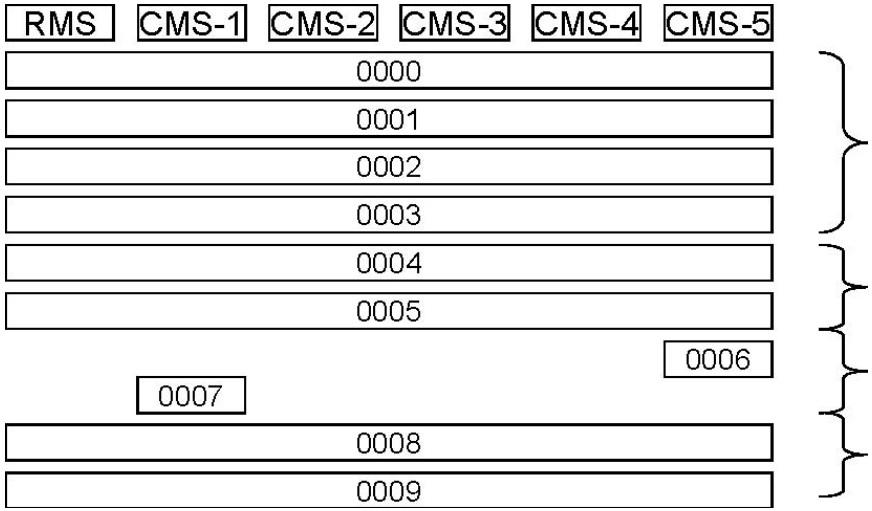
The Parallel National Model for the use of eCTD in MRP/DCP (2/5)



This model is complicated (i.e. resource intensive), both for applicants as for agencies. Numbering of sequences is different per CMS – Industry has to see this model only as an interim measure.

The Comprehensive Model for the use of eCTD in MRP/DCP (3/5)

Single LCM in EU



Mutual submissions e.g. initial application

Mutual submissions e.g. variation

National submissions e.g. MAH transfer

Mutual submissions e.g. variation

Applicants are advised to use this model but it requires a corparate or centralised way of working: This may not be obvious for affiliates.

Agencies: Requires central architecture (Central repositories).

Managing the Life cycle management (4/5)

- There are 4 licensing procedures in the EU: centralised, MRP, DCP and national procedure:
    - **National procedure:** baseline submissions (clean up of previous state into a single first sequence) can be expensive for older medicial products. National survey indicates (smaller) applicants prefer the NeeS.

Life cycle management – LCM (5/5)

Points to consider building eCTDs:

- Start with submission strategy: the granularity: one eCTD per strength/pharmaceutical form or one eCTD for the branch (difficult to split later), Granularity at the level of a PDF: larger files or multiple smaller files. Once started, **very** difficult to change the granularity.
- Hyperlink strategy: links must be maintained (updated) during the LCM.

MRP/DCP:

- Organise first the flow and tracking of documents (which document is used where and when) – choose dedicated system
  - Corporate and central medium to large size organisation and submitting moderate volumes: consider eCTD for new application, make them backwards compatible with NeeS. Use the comprehensive model. Organise with affiliates for the local documents (e.g. SPC's).
  - Corporate and central medium to large size organisation and submitting very large volumes: start with the NeeS until upscaled.
  - Organisation (affiliate) without any central support: consider starting with NeeS, move away from paper. Consider eCTD later on.

Validation of eCTD and NeeS (1/2)

Topic of the NeeS and eCTD harmonisation group: writing both guidances and defining validation criteria under auspices of the TIGes.

The validation criteria: Notice published 13th sept 2010 on EMA esubmission page to review the existing validation criteria to allow more automation in the processing and coherence of handling according the following principles:

- Each identified criterion must be a check for a single item.
- Each criterion must be defined in an unambiguous way that leaves no room for interpretation
- The criteria must be defined in a way that is tool and vendor independent

Validation of eCTD and NeeS (2/2)

This results in 2 cathegories of criteria:

- A. Acceptability Criteria. These will either Pass or Fail and be used to determine whether an eCTD/NeeS can be accepted into a review process.
- B. Reviewability/Best Practice Criteria. These will not form the basis of the acceptability of an eCTD/NeeS.

-> NeeS validation criteria will be reviewed in parallel to the eCTD criteria, according the same principles, to allow interoperability between NeeS to eCTD.

For consultation till 26.11.2010:
http://esubmission.emea.europa.eu/new.htm

Is also the place where a large library regarding esubmission can be found.

eCTD current status and expected implementation dates

Useful document: eCTD readiness questionnaire on the HMA site (www.hma.eu).

Conclusions of 2009Q3-Q4:

Readiness of authorities: The eCTD implementation report covering the period july 2009-till dec 2009 shows: 10 EU authorities were testing tools to work electronically, 18 EU authorities had tools in full production. Meanwhile, from the EU chart, almost all agencies accept electronic submissions.

Readiness by applicants: Half of the volume submitted in the EU are electronic formats. Remark: Very large majority of the submissions are national and MRP variations. Of the electronic part: 86% is in NeeS or other.

14% is eCTD (corresponds with 7% of all submissions in eCTD). For the new applications in MRP/DCP during 2009Q3-Q4: 40% is in eCTD.

-> These scores are slightly increasing (nov 2010) but not all data are available.

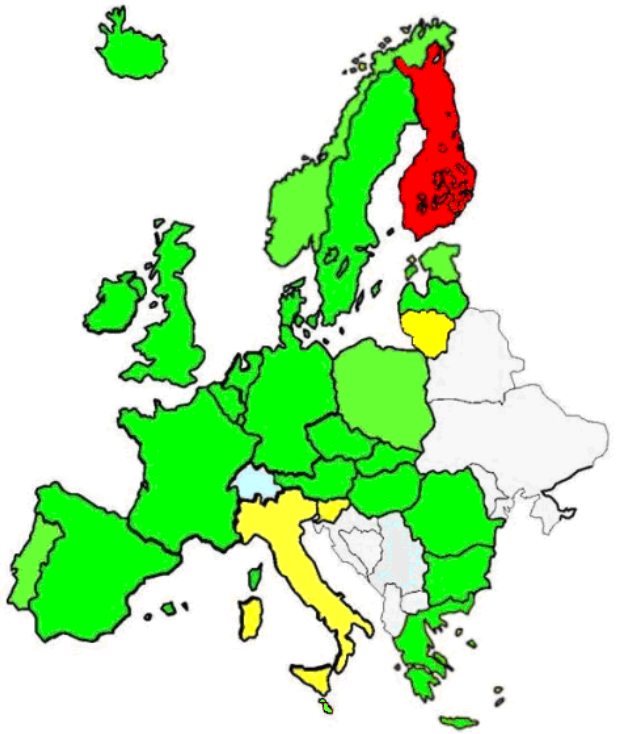
Acceptation of esubmissions (Human)

Dossier requirements in MRP/DCP and national procedures for medicinal products for human use

Electronic-only dossier (optional or mandatory)

Mixed electronic/paper dossier (only some modules needed in paper)

Complete paper dossier



- Finland (Green July 2010)
- Italy (Green Sept 2010)
- Lithuania (Green January 2011)
- Slovenia (Green January 2011)

- Austria
- Belgium
- Bulgaria
- Cyprus
- Czech Republic
- Denmark
- Estonia
- France
- Germany BfArM
- Germany PEI
- Greece
- Hungary
- Iceland
- Ireland
- Latvia
- Liechtenstein
- Luxembourg
- Malta
- Netherlands
- Norway
- Poland
- Portugal
- Romania
- Slovak Republic
- Spain
- Sweden
- UK

Status in April 2010, as presented at the HMA (Spain)

eCTD current status and expected implementation dates

Possible reasons:

Hesitation at applicants to change format (clean up, baseline eCTD's) for older existing products

Variation in tools, maturity of tools, interpretation of validation results, which leaded to the harmonisation of the validation criteria and to large efforts to construct a HMA Common Esubmission platform CESP (single validation in EU, single LCM, comprehensive model).

Thank you !