EU experience in eCTD implementation

- current status on transition, challenges & lessons learned, eCTD adoption timeline and considerations, eCTD through centralised procedure (CP) & DCP, MRP.

Karin Gröndahl
Business Development Manager
Swedish MPA

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

eCTD implementation in EU

An eCTD EU M1 Specification was published in 2004 and eCTD was then stepwise implemented. Additional hard copies in paper were required for a long time.

To facilitate electronic-only submissions in a harmonised way in all member states, a new intermediate EU format called NeeS (Non-eCTD electronic Submission) was introduced.

To speed up the implementation of eCTD, an EU eSubmission Roadmap was agreed in 2014 by HMA and EUTMB with stepwise mandatory use of eCTD for all submissions.

EU eSubmission Roadmap

The EU eSubmission Roadmap is a text document with objectives and milestones in different areas and the timelines are visualised in a flowchart. There are also an annex document with details on implementation for each area.

HMA eSubmission Roadmap

- Final HMA eSubmission Roadmap - **Updated**. The final updated version of the eSubmission Roadmap 2.1 was adopted by the EU TMB and endorsed by the HMA on the 28th of February 2018. The summary of main changes is available in the Release Notes. The updated Annexes to the Roadmap are being published as they become available to reflect further details on the practical implementation steps.
- eSubmission Roadmap (visual representation) The final updated version of the eSubmission Roadmap v2.1 visual representation of the timelines.

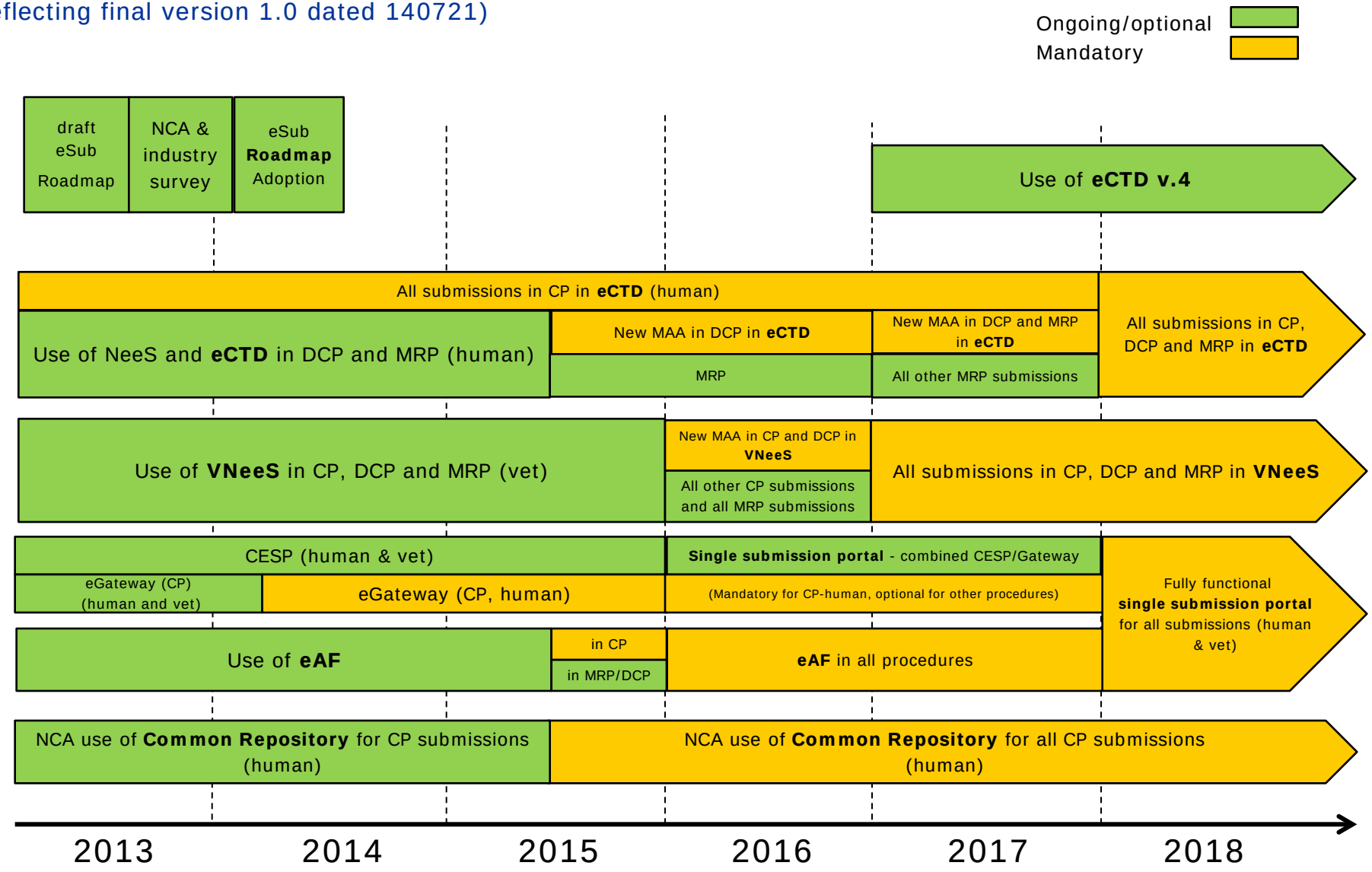
Annexes to the eSubmission Roadmap

- Annex 1 to the HMA eSubmission Roadmap on the implementation of **eCTD version 4.0**.(Adopted by the eSubmission CMB on 04.05.2018.)
- Annex 2 to the HMA eSubmission Roadmap on the implementation of mandatory use of **eCTD format** for Human regulatory submissions. (Adopted by the eSubmission CMB on 04.05.2018.)
- Annex 3 to the HMA eSubmission Roadmap on the implementation of mandatory **VNeeS format** for Veterinary regulatory submissions. (Adopted by the eSubmission CMB on 18.05.2018.)
- Annex 4 to the HMA eSubmission Roadmap on the **replacement of the current PDF electronic application forms** (eAFs) **with** the CESP Application Dataset Management Module (**CESP Dataset Module**). (Adopted by the eSubmission CMB on 18.05.2018.)
- Annex 5 to the HMA eSubmission Roadmap on the mandatory use of the **Common Repository** for EMA led procedures (Adopted by the eSubmission CMB on 18.05.2018.)

Link to the eSubmission website - CMB Documents

eSubmission Roadmap

(reflecting final version 1.0 dated 140721)



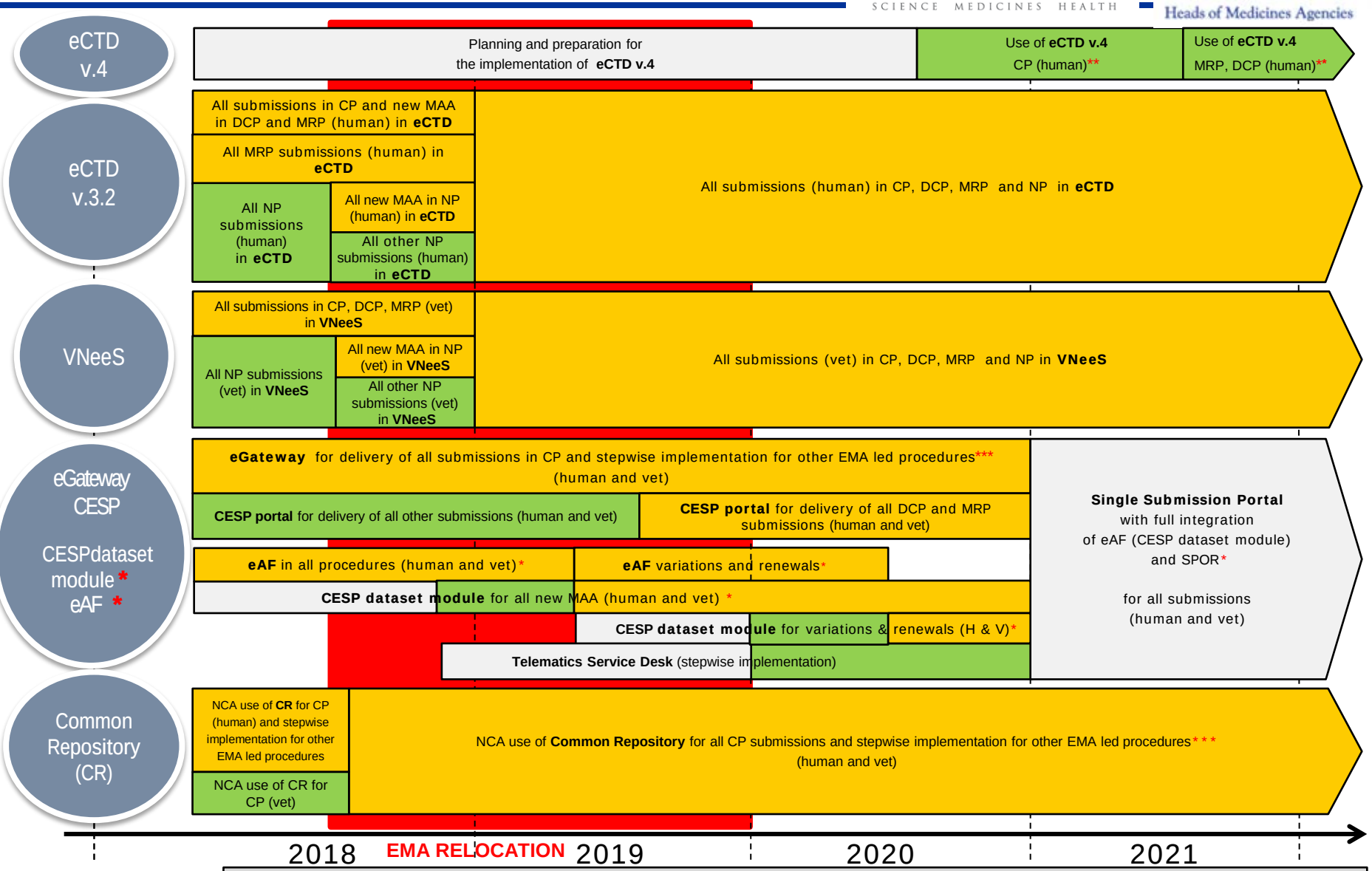
eSubmission Roadmap Timelines

eSubmission Roadmap - timelines

(reflecting version 2.1 dated 28 February 2018)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies



Planning in progress
Ongoing or optional
Mandatory

*) The SPOR project will stepwise (see specific Roadmap) deliver master data services (RMS, OMS, SMS, PMS) to be integrated with the eAF and CESP dataset module. Currently, the mandatory use of OMS is planned for Q4 2018, subject to outcomes of further planning exercise.

) Timelines subject to planning *) Some procedure types are excluded

EU Guidance Documents

Close collaboration between regulators and industry representatives has been crucial for eCTD implementation in EU and drafting of documents has been done together, e.g.

- EU NeeS Technical Guidance
- EU eCTD Technical Guidance
- CMDh Best Practice Guide on the use of eCTD in MRP and DCP

EU Harmonised eCTD Guidance

- The EU Harmonised technical eCTD guidance version 4.0
- The BPG for the use of eCTD in MRP/DCP version 4.0
- eCTD validation criteria v6.1 and Release notes - 12.7.2016.
- eCTD validation criteria v7.1 and Release notes - 02.03.2018 **New**. The updated validation criteria will enter into force on **1st of September 2018**.
- Variations in eCTD format Q&A document covering practical issues for variations in eCTD format
- Validation criteria Q&A 06.04.2017
- Q&A on Mandatory eCTD in MRP and how to manage changes to eCTD format during ongoing procedures **New**

EU Harmonised NeeS Guidance

- The TIGes Harmonised NeeS guidance document version 4.0 can be found here and Release notes here **(Note: The guidance is not applicable to centralised procedure)**
- NeeS Validation Criteria v4.1 and Release notes
- NeeS Validation Criteria v4.3 and Release notes - 02.03.2018 **New**. The updated validation criteria will enter into force on **1st of September 2018**.

Technical validation

Technical Validation Criteria were created and adopted. This has been crucial for the acceptance of eCTD format.

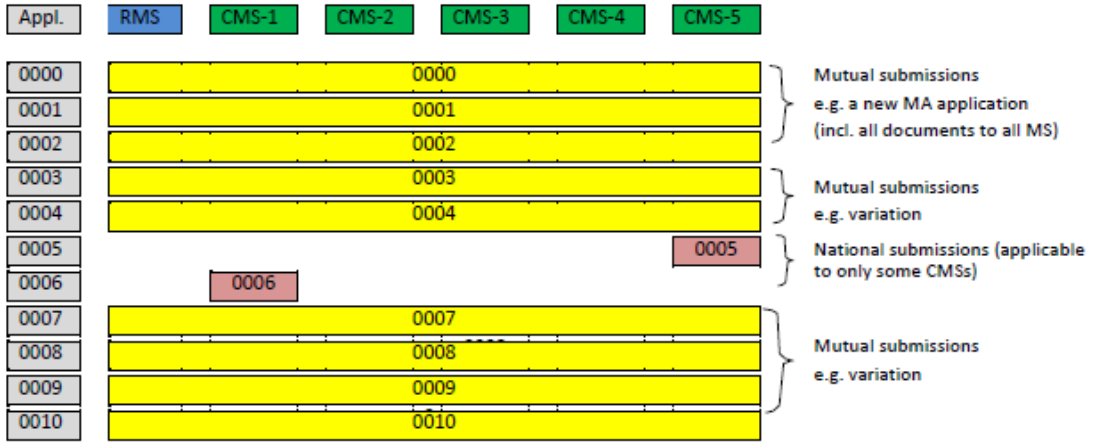
The member states agreed to validate according to these criteria using, for harmonisation reasons, one of two agreed tools.

In principle, the RMS is responsible for the technical validation, but CMS can validate too.

If the submission is technically invalid, a corrected sequence with the same number should be submitted to all RMS/CMSs.

CMDh Best Practice Guide on the use of eCTD in MRP and DCP

Figure 1: The Comprehensive Model for the Use of the eCTD format in MRP/DCP



It is important to agree on how to deal with submissions that do not concern all. In EU these are normally sent to the concerned member state only (e.g. OTC in only one member state).

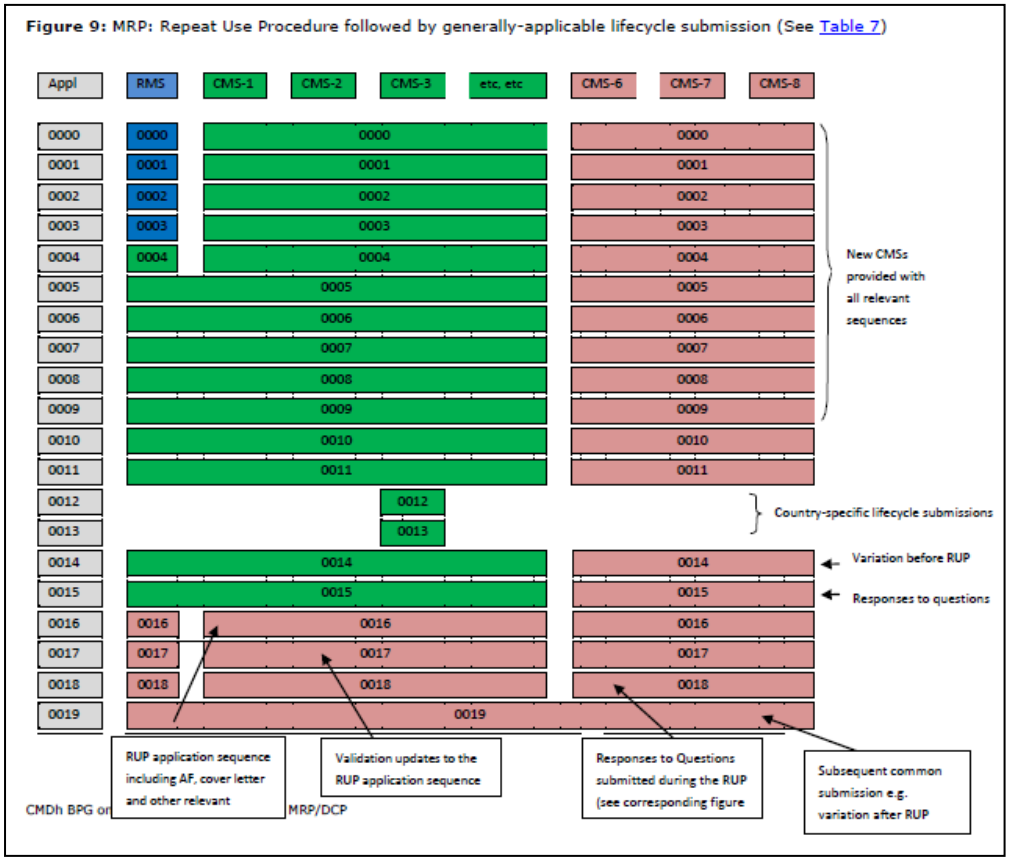
However, to minimise lifecycle problems, these sequences should be sent to all member states together with the next common sequence.

Sequence	Product Name: Wonderpill 200 / 400 mg capsules	RMS	CMSs–First Wave				
	Procedure Number: DE/H/0123/001-002	DE	AT	ES	FR	SE	SK
	Submission description		(CMS-1)	(CMS-2)	(CMS-3)	(CMS-4)	(CMS-5)
0013	Responses to Questions for 0012				Aug 10		
0012	Country-Specific Lifecycle Submission - France				Jul 10		
0011	Responses to Questions	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10
0010	Manufacturing change variation	Mar 10	Mar 10	Mar 10	Mar 10	Mar 10	Mar 10
0009	Day 90 – Final EN product information	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09
0008	Day 85-90 Responses	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09
0007	Day 60 Consolidated Response Document	Sep 09	Sep 09	Sep 09	Sep 09	Sep 09	Sep 09
0006	Validation update	Mar 09	Mar 09	Mar 09	Mar 09	Mar 09	Mar 09
0005	Country specific information (All)	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09
0004	MRP update sequence	Jan 09	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09
0003	Final agreed National product information	Dec 08	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09
0002	Responses to questions	Sep 08	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09
0001	Validation update	Dec 07	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09
0000	Initial MAA	Dec 07	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09

CMDh Best Practice Guide on the use of eCTD in MRP and DCP

It is also important to agree that any sequences that are formally submitted in eCTD format in a procedure (e.g. MRP first round) should not be validated again by the new member states in a Repeat use procedure.

The new member states need to accept the ”old” sequences as they are, since for example the specification or the validation criteria might have changed during the lifecycle.



Lessons learned

- NeeS was a successful step at that time to achieve harmonisisation for ”other formats” and getting well structured eSubmissions while moving towards e-only submissions.
- With the technology of today, I would however rather recommend against introducing this format, since eCTD, besides the lifecycle functionality, also has structured data for automatic processing.
- To really use the eCTD functionality in the assessment, an eCTD reader is necessary. Unfortunately, the tools available are not always accepted by users and some authorities struggle with financing.
- It takes time to communicate on invalidations, but nowadays most eCTDs are valid (99%).
  Not all applicants and not all authorities have enough knowledge, which is sometimes problematic.

Pieces of advice

- Use the already existing (EU) M1 specifications and guidance documents and just update to regional specifics where needed. Set up a regional eCTD group that is responsible for any document updates.
- Work on the guidance documents together with industry and use the combined knowledge. But in the end, the authorities adopt the documents trough a regional authority-only group.
- Organise regional authority training sessions both for administrative staff (eCTD basics and validation criteria) and assessors (eCTD lifecycle), preferably face-to-face with a train-the-trainers concept.
- Stick to guidances and send any disagreements to the ”eCTD guidance group” to discuss need for updates.