



**CMDh BEST PRACTICE GUIDE
ON THE USE OF THE ELECTRONIC COMMON TECHNICAL
DOCUMENT (eCTD)
IN THE MUTUAL RECOGNITION AND DECENTRALISED PROCEDURES**

*Doc. Ref.: CMDh/084/2008/Rev3
November 2011*

TABLE OF CONTENTS

	Page
1. INTRODUCTION.....	3
2. GENERAL CONCEPTS	3
2.1. Comprehensive Model.....	3
2.2 Tracking Table	4
2.3. Transition from Parallel National Model to Comprehensive Model	4
3. DECENTRALISED PROCEDURE (DCP).....	5
3.1 Validation and Assessment	5
3.2 Submission of National Translations of Product Information	6
3.3 Subsequent Lifecycle Submissions	6
4. MUTUAL RECOGNITION PROCEDURE (MRP).....	6
4.1 National Phase.....	6
4.2 Start of MRP	7
4.3 Validation and assessment	8
4.4 Submission of National Translations of Product Information	10
4.5 Variations and Other Procedures that Affect the RMS and all CMSs (Generally-Applicable Lifecycle Submissions).....	10
4.6 Procedures that Affect Only a Single CMS (Country-Specific Lifecycle Submissions)	11
4.7 Repeat Use Procedures	12
4.8 Change of RMS	13
4.9 Switch from paper or NeeS to eCTD	14
4.10 Use of the eCTD format for “Mixed Format Applications”	14
5. SUMMARY	14
TABLES.....	15

1. INTRODUCTION

Following experience gained both by industry and National Competent Authorities (NCAs), this best practice guidance has been developed in order to facilitate the use of the eCTD as a submission format in the Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP). The guidance shows the way for an applicant to meet their legal obligations within MRP and DCP in eCTD format. Some general principles apply to both procedures but there are some differences between the details for the MRP and DCP.

Applicants must still continue to comply with any national requirements to provide partial paper copies in addition to the eCTD if stated at the CMDh website [<http://www.hma.eu/277.html>]

Where this guidance recommends submitting documents outside the eCTD, it is recommended that they are submitted according to the file naming principles of the eCTD standard and on the same CD/DVD as the eCTD sequence where relevant.

2. GENERAL CONCEPTS

A key principle of this guidance is that the submissions made to the Reference Member State (RMS) and all Concerned Member States (CMSs) are managed as a single, comprehensive, eCTD. However at present, in the absence of a central repository for submission of MRP/DCP applications, it will be necessary to provide a copy of the eCTD to each NCA involved.

The content provided to each NCA will be identical for all the mutual stages of the procedures accept in case of MRP whereas activities such as transfers of ownership, and applications for change in legal status should normally be provided to the NCA concerned only. This means that it is allowable to submit submissions to NCAs in a non-sequential order e.g. CMS-1 may receive submission 0000, 0001 and 0002 while CMS-2 receives 0000 and 0002 but never 0001 if that sequence only concerned CMS-1. However, a sequence number should never be re-used except for resubmissions following a technical invalid submission, so the next submission (e.g. a variation) should utilise the next unused sequence number and so create a continuous numbering system.

2.1. Comprehensive Model

When submitting an eCTD in DCP or MRP, the so called ‘comprehensive’ model should be used, since it ensures that the same sequence number is used for all mutual submissions and therefore minimises any potential confusion between NCAs. The Applicant should maintain the full set of sequences as a comprehensive record.

Conceptually, this ‘comprehensive’ model is presented in Figure 1. More details of the model are presented in later sections of this best practice document.

3. DECENTRALISED PROCEDURE (DCP)

3.1. Validation and Assessment

See Figure 2, Table 1.

There are two separate kinds of validation – technical and content validation

The initial eCTD containing all common parts as well as any country-specific information should be submitted to the RMS and all CMSs. A separate Module 1 eCTD envelope should be used for each Member State included in the Procedure. Information for all countries will therefore be contained in this one submission. The organisation of the dossier and the use of the country attributes assigned to applicable documents will ensure that the CMSs will be easily able to find their country-specific information.

Technical validation is seen as a pre-step in the procedure. If a submission is found to be *technically* invalid, a corrected sequence should always be submitted immediately to all concerned member states, re-using the same sequence number. If during content-validation updates are to be made as a consequence of the regulatory validation process then it will depend upon the nature of the request as to whether the RMS and all CMSs or only a specific CMS receives an update by e-mail.

The content validation should be handled outside the eCTD (normally by e-mail) during the validation period and then at the end of the validation period all submitted documents should be resubmitted to the RMS and all CMS with the relevant operation attribute in one eCTD sequence. It should be clearly stated in the cover letter that all documentation has been previously provided outside the eCTD during the validation period. (Figure 2, Table 1).

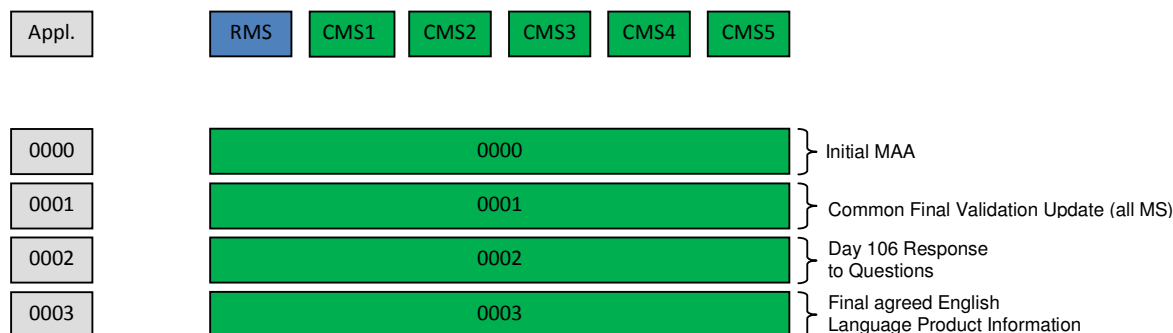
Any validation deficiencies that are not required until day 50, should preferably be sent together with the at day 50 response and be clearly stated in the cover letter.

During the **Assessment Steps**, any additional sequences, e.g. each Response to Questions, should also be submitted to the RMS and all CMSs. Regardless which MS raised a question it should be included in one common response document. No country specific answer should be provided. If, due to the tight time limits, the responses are sent outside the eCTD, a new sequence should always follow with any new or updated documents placed in the dossier with the correct operation attribute. Final agreed English language product information (Summary of Product Characteristics, Package Leaflet and Labelling) should always be submitted to the RMS and CMSs by the end of the procedure.

The common English product information texts communicated during the procedure should always be included in the eCTD as for all other relevant documents at the various key steps (e.g. in the initial application, responses to LoQ and final agreements). Word copies of the included PDFs, which are requested by some of the NCAs, should always be kept outside the eCTD as working documents.

Draft responses sent to the RMS during the ‘Clock-off Period’ should be handled outside the eCTD as they are not considered to be official submissions. Also procedural email correspondence should be exchanged outside the eCTD if not directly relating to the content of the dossier. Any other exemptions should be discussed with the RMS before submission.

Figure 2: DCP: Assessment Phase – including a validation update for common information submitted during the validation phase (See Table 1)



3.2. Submission of National Translations of Product Information

The national translations should be handled outside the eCTD in MRP and DCP, since the national phases are a responsibility of each NCA and normally handled by local affiliates of the applicants. Working documents for more than one NCA can however be submitted on the same CD. Sub-folders with the country code should then be used. eCTD file naming principles should be followed to facilitate for the assessors.

3.3. Subsequent Lifecycle Submissions

Once the DCP is finalised the procedure to be followed is an MRP. The envelope information for subsequent lifecycle submissions should have the <procedure_type> set to 'mutual-recognition'. The guidance in Section 4, Mutual Recognition Procedure should then be followed.

4. MUTUAL RECOGNITION PROCEDURE (MRP)

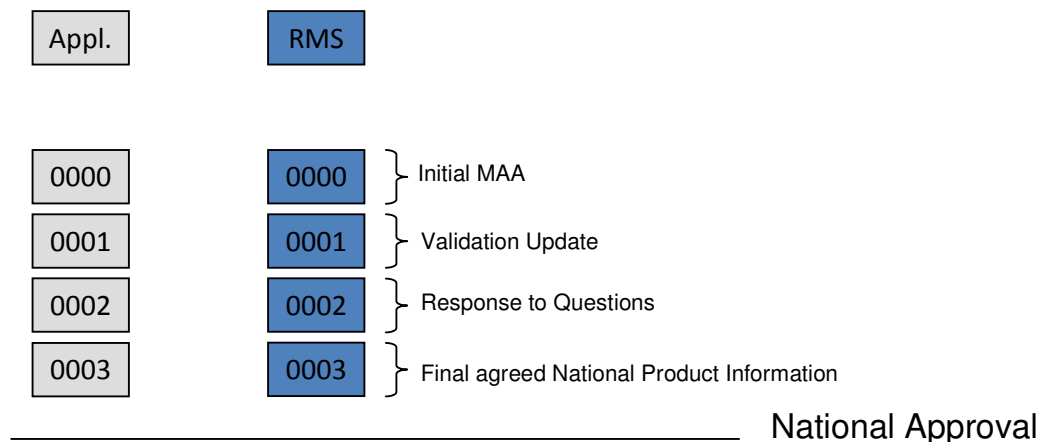
A number of differences exist between DCP and MRP and the best practices for the eCTD reflect these differences and are explained below.

4.1. National Phase

See Figure 3

An eCTD is submitted to the Member State that will become the Reference Member State (RMS). The envelope is specific to that NCA and the lifecycle is managed through from the initial submission to approval of the product nationally.

Figure 3: MRP: National Approval with NCA (intended future RMS)



4.2. Start of MRP

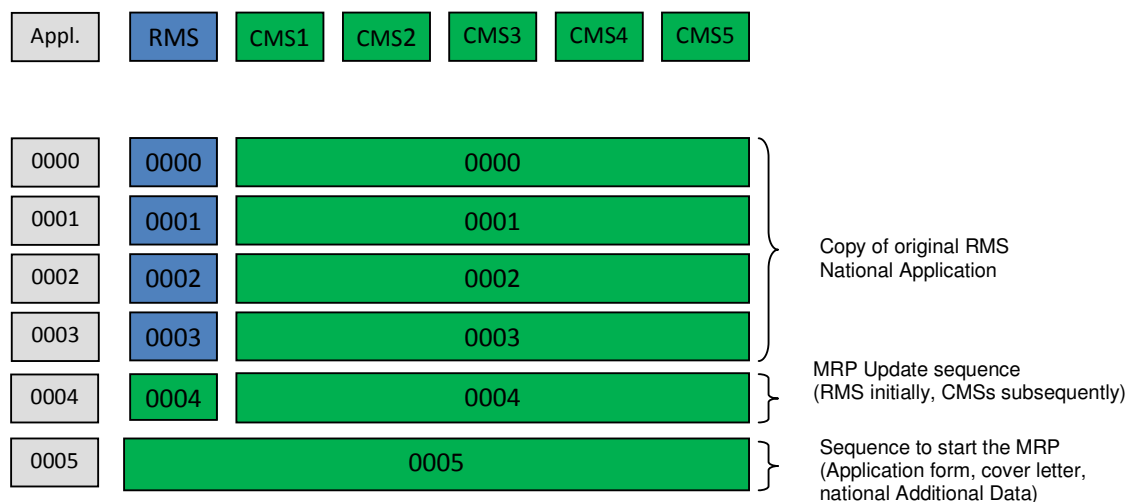
See Figure 4, Table 2

A key principle of this best practice is that for a submission managed as an eCTD it is not necessary to produce an updated dossier for provision to the Concerned Member States (CMSs). Within the eCTD review tools, the 'current view' of the set of sequences provided to the RMS as the initial filing and any further submissions will provide the equivalent of the updated dossier. It is noted that the 'current view' created from the RMS eCTD sequences that are all submitted to the CMSs will include the RMS specific documents submitted during the National Phase. However, the CMSs can easily identify these documents using the available metadata and disregard content not applicable to them.

When the application is submitted as an MRP, the submission type should be set to "initial maa" in the MRP initiation sequence (i.e. sequence 0004 in Figures 4).

The RMS continues with their national submission which evolves into the MRP submission. This allows the RMS to maintain their records and links to other systems. In advance of the initiation of the MRP, the RMS is provided with an updating sequence e.g. including the English product information documents (sequence 0004 in the figure below) and when the RMS is satisfied then the MRP can be initiated with provision of the initial RMS sequences (0000 – 0003), the update sequence (0004) and the documents to start the MRP, e.g. cover letter, application forms and additional nationally required documents included in a single sequence covering all CMSs (0005). The organisation of the dossier and the use of the country attributes assigned to country specific documents will ensure that the CMSs will be easily able to find their specific information.

Figure 4: MRP: Initial filing (See Table 2)



4.3. Validation and assessment

See Figures 5 & 6, Tables 3 & 4

There are two separate kinds of validation – technical and content validation.

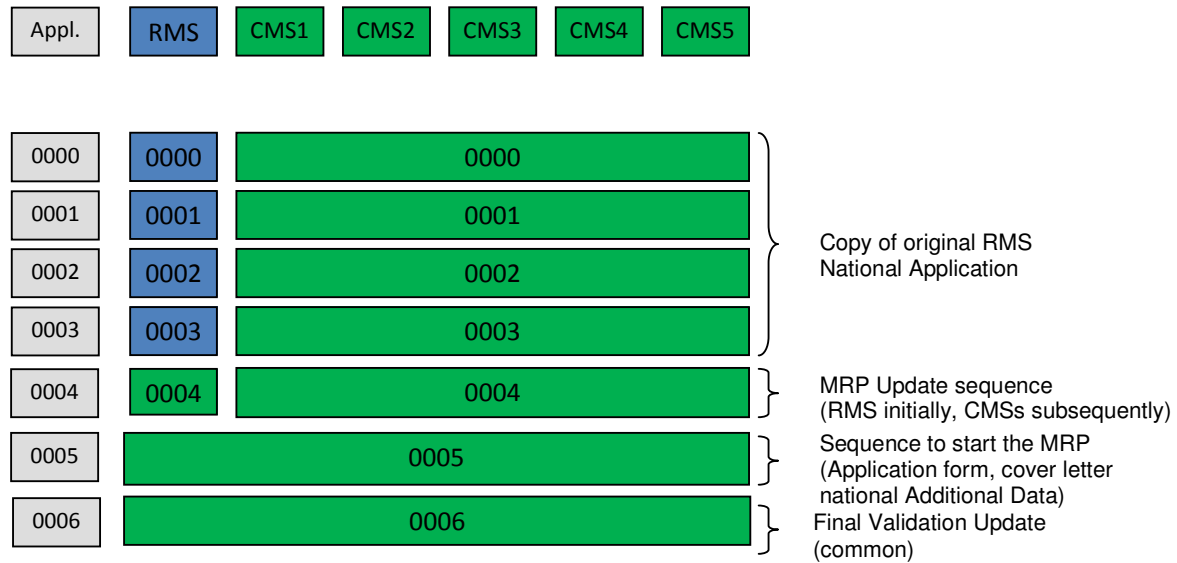
If a submission is found to be *technically* invalid, a corrected sequence should always be submitted immediately, re-using the original sequence number.

Technical validation of eCTD sequences submitted earlier within the national procedure (the current dossier) before the start of the MRP should not be performed. The technical validation is assumed to be already done by the RMS during the national phase. There is no need that new CMS are re-validating the dossier. Only the sequence to start up the MRP should be part of the MRP technical validation. This is regardless of technical validation being performed or not and use of validation tool. Only errors introduced because of poor copying and burning the CD/DVD that give problem in opening and reading the application or makes it impossible to import the eCTDs into a review system should need to be addressed and the applicant should make any possible effort to solve the problems.

The content validation should be handled outside the eCTD (normally be email) during the validation period and then at the end of the validation period all submitted documents should be resubmitted to the RMS and all CMSs with the relevant operation attribute in one eCTD sequence. It should be clearly stated in the cover letter that all documentation has been previously provided outside the eCTD during the validation period (Figure 5, Table 3).

Any validation deficiencies that are not required until day 50, should preferably be sent together with the at day 50 response and be clearly stated in the cover letter.

Figure 5: MRP: Validation update for documents submitted during the validation phase (See Table 3)



During the **Assessment Steps**, any additional sequences, e.g. each Response to Questions, should be submitted to the RMS and all CMSs. Regardless which MS raised a question it should be included in one common response document. No country specific answer should be provided. If, due to the tight time limits, the responses are sent outside the eCTD, a new sequence should always follow with any new or updated documents placed in the dossier with the correct operation attribute. Final agreed English language product information (Summary of Product Characteristics, Package Leaflet and Labelling) should always be submitted to the RMS and CMSs at the end of the procedure. (Figure 6, Table 4).

The common English product information texts communicated by email *during* the procedure should always be included in the eCTD as all other relevant documents at the different key steps (e.g. in the initial application, responses to LoQ and final agreements). Word copies of the included PDFs, which are requested by some of the NCAs, should always be kept outside the eCTD as working documents, preferably using the same naming conventions for these documents as when they are inside the eCTD.

Draft responses sent to the RMS should be handled outside the eCTD as they are not considered to be official submissions.

Figure 6: MRP: Review following provision of a single common validation sequence (i.e. based on Figure 5) (See Table 4)



4.4. Submission of National Translations of Product Information

The national translations should be handled outside the eCTD in MRP and DCP, since the national phases are a responsibility of each NCA and normally handled by local affiliates of the applicants. Working documents for more than one NCA can however be submitted on the same CD. Sub-folders with the country code should then be used. eCTD file naming principles should be followed to facilitate for the assessors.

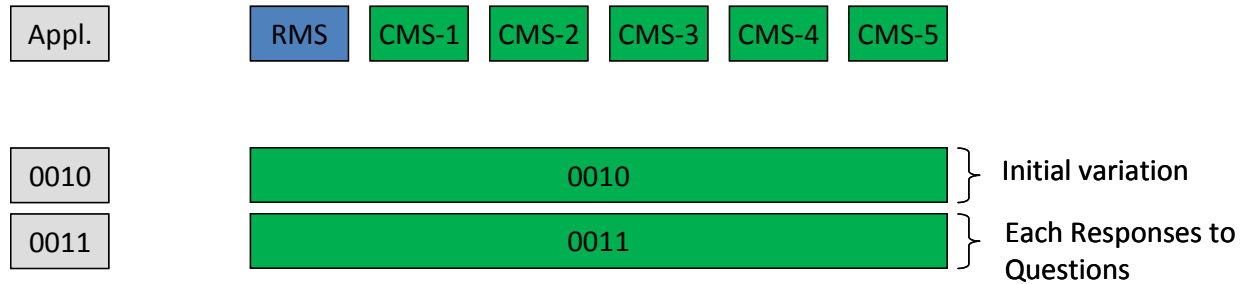
4.5. Variations and Other Procedures that Affect the RMS and all CMSs (Generally-Applicable Lifecycle Submissions)

See Figure 7, Table 5

Subsequent lifecycle submissions such as variations should be submitted to the RMS and all CMSs as a single sequence containing all documentation for all NCAs (including forms and letters) and any subsequent responses to questions should also be provided as one common sequence to the RMS and all CMSs. It is recommended to use one common application form for all NCAs.

When translations of the product information are required at the time of submission of a variation, these should be provided outside the eCTD but on the same CD/DVD in the separate working document folder in the respective country coded subfolder.

Figure 7: MRP: Generally-applicable lifecycle submissions (See Table 5)



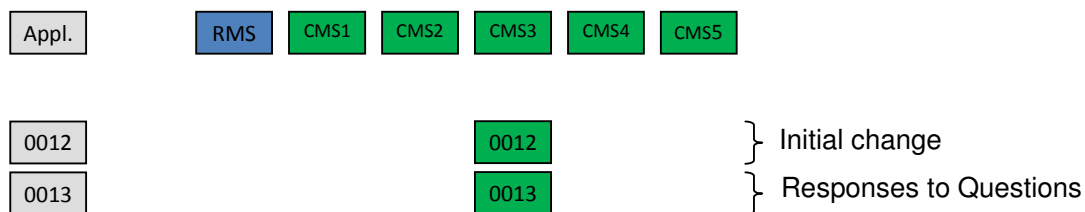
In the case where a variation is rejected, or partially rejected, by member states it is important that the authority maintains the rejected application within the eCTD to refer to. However, the continued inclusion of rejected information can cause confusion regarding what is 'current'. Applicants should refer to the “eCTD Variations Q&A document” at the EMA eSubmission website regarding the provision of a consolidation sequence.

4.6. Procedures that Affect Only a Single CMS (Country-Specific Lifecycle Submissions)

See Figure 8, Table 6

An MAH transfer or an application for change in legal status would be relevant to one CMS only and therefore the sequence should be provided to that CMS only and not to the RMS or any other CMSs. Subsequent submissions, e.g. Responses to Questions, associated with this activity should also only be submitted to that specific CMS. However, content provided in such country specific sequences should never be referred back to in lifecycle (e.g. replaced, deleted) in subsequent mutually applicable sequences, as this could result in failure of technical validation.

Figure 8: MRP: Country-specific lifecycle submissions (See Table 6)



4.7. Repeat Use Procedures

See Figure 9, Table 7

As the Repeat Use procedure is an MRP, a key principle of this best practice is that for a submission managed as an eCTD it is not necessary to produce an updated dossier for provision to the Concerned Member States (CMSs).

The rules for validation are identical as for an MRP and information about this can be found in section 4.3 of this guidance.

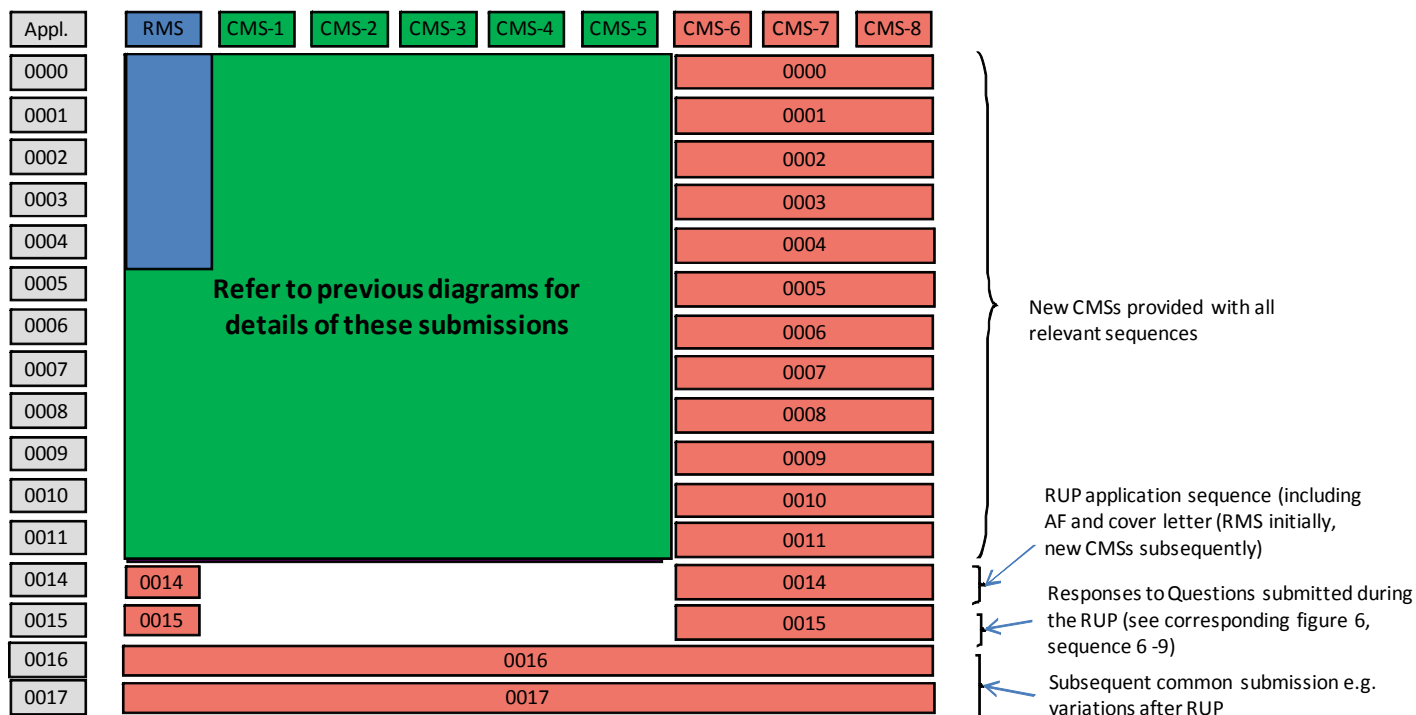
Technical validation of the “old” sequences is assumed to have been done by the RMS earlier and should not be repeated by the new CMS. Only the sequence to start up the RUP should be part of the RUP *technical* validation. However, errors introduced because of poor copying and burning of CD/DVDs that give problem in opening and reading the application or makes it impossible to import the eCTDs into a review system should need to be addressed and the applicant should make any possible effort to solve the problems..

The RUP is initiated with the new CMSs by submitting a new sequence (0014) including the cover letter, application forms and additional nationally required specific documents if any. Sequence 0015 in figure 9 is the placeholder for the MRP with the new MSs, which has to be finalised – specific sequences for RUP-MRP – see figure 5, sequence 6 -9.

After finalisation of the RUP and as no changes to the common dossier are possible during the RUP, there could be the necessity to update the common dossier in the RMS, existing CMSs and new CMSs to introduce changes agreed during the RUP. This has to be done via a variation, which is following the normal procedure e.g. submission of a generally-applicable lifecycle sequences (0016 & 0017) to all MS concerned by the MRP.

Subsequent RUPs should be managed in the same way as described for this first RUP.

Figure 9: MRP: Repeat Use Procedure followed by generally-applicable lifecycle submission (See Table 7)



4.8. Change of RMS

According to the CMDh procedural advice on changing the RMS, the MAH must notify the change of RMS to all CMS(s) before the change of the RMS takes effect.

The notification of the RMS transfer can take place in different ways (e-mail, telephone or letter). With regards to eCTD, the notification of RMS transfer is considered to be part of communication which is not relevant for the eCTD Life Cycle Management of the product and should therefore not be submitted as an eCTD sequence.

This means that it is not required to submit a new eCTD sequence to the involved Member States (RMS and CMS) for the notification of the RMS transfer.

For the submission of the next sequence in eCTD format (i.e. variation, renewal, etc), the applicant will change the procedure number in the envelope information and ensure that the RMS is changed from this point onwards in the tracking table. For examples on how to display changes to the RMS in the tracking table, see Tables 8 & Table 9.

In cases that the Marketing Authorisation (MA) of the country that previous acted as RMS is withdrawn, the withdrawal of the MA should be covered by submission of a sequence in eCTD format. The cover letter for the withdrawal of the MA should be submitted as an eCTD sequence. In this eCTD sequence, the procedure-MR-number from the new RMS will be displayed.

4.9. Switch from paper or NeeS to eCTD

When an applicant wants to switch from paper or NeeS to eCTD in a specific CMS and has already an up to date eCTD used elsewhere in the procedure for other countries, on agreement with the RMS, the lifecycle should continue and earlier sequences should be provided to the RMS and all CMSs. However, the “old” sequences should in these cases not be technically validated by this CMS, but accepted as they are. However, if there are problems with loading or reading the submitted files the applicant should be assisting in solving the problems. For further details, refer to the TIGes Harmonised Guidance for eCTD Submissions in the EU at the [EMA eSubmission website](#).

4.10. Use of the eCTD format for “Mixed Format Applications”

All applications have to be in CTD format in accordance with the Directive 2001/83/EC as amended. If an already existing paper dossier is only in the old NtA Part format, the structure has to be updated before going into an MRP or a RUP initial application as stated in the Notice to Applicant, CTD Q&A (Q4b). There it is stated that it is *acceptable* to have a mixed dossier with Module 1-3 in CTD format and Module 4-5 (Part III and IV) in the old NtA format.

In principle this would also be acceptable if the dossier is to be submitted in an electronic format. However, if submitted in eCTD format it is recommended to re-format the whole dossier into the eCTD format. Much of the documentation in Parts 1 and 2 would need to be re-worked into Modules 1-3 but most of the documents in Parts III and IV could be scanned and be put at the correct location in the eCTD structure.

If the applicant does not find it possible to place the document into the eCTD structure, the old Part documentation (IC, III and IV as relevant) should be handled outside the eCTD, either as paper (if preferred by the applicant and accepted by the RMS/CMS) or in a separate NtA Part folder structure for these documents submitted on the same CD/DVD. Relevant filenames should be used following the NtA Part structure and PDF TOCs with functional links should be included. The old Expert Reports should in that case also be handled outside the eCTD but a statement should be included in the eCTD Module 2 referring to these Reports (see NtA Q&A 4b).

5. SUMMARY

The approach outlined allows the applicant to maintain a single eCTD that covers all NCAs involved in the MRP/DCP throughout the life of the product. It also ensures that the RMS and each CMS has the complete set of sequences that are relevant to the mutual assessment phases and their country-specific information. Only purely national regulatory activities (MAH transfer and change in legal status) are handled as country specific sequences.

The principle of the updated dossier at the beginning of the MRP and Repeat Use Procedure is achieved by provision of a set of sequences of the generally-applicable information combined with the ability of the review tools to view the ‘current’ submission.

TABLES

Examples of the Sequence Tracking Table that should be included as an attachment to the Cover Letter for each sequence

Principles of Layout for the Tracking Table

- i) The Member State acting as the RMS should be identified and be the first Member States listed
- ii) The 'first wave' CMSs should be listed alphabetically and grouped under a heading 'CMSs - First Wave'
- iii) Subsequent waves should be grouped under a similar heading e.g. 'CMSs - Second Wave', 'CMSs - Second Wave' etc. and listed alphabetically
- iv) The RMS and CMSs should be identified by the two character country code
- v) When the RMS changes the new RMS should appear in the RMS column.
 - The typical scenario is that the old RMS no longer participates in the Procedure and no longer appears in the table moving forward but the historical record for that country remains.
 - An occasional scenario is that the old RMS continues within the Procedure as a CMS and is included within the CMS wave that is applicable and the countries re-ordered alphabetically. The historical record for that country remains.
- vi) The date presented should be month and year. This is defined by the applicant and should equate to the intended date of submission

Note: The inclusion of the identifier CMS-1, CMS-2 etc in the following tables is purely to allow cross-reference from the figures to the tables. The entries in the table should be consistent with the information in the envelope, namely that countries in the table should correspond to those included in the envelope and that the submission description used should be the same.

Table 1. DCP Assessment Phase – including a validation update for common information (See Figure 2)

Sequence	Submission description	RMS	CMSs – First Wave				
		DE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SE (CMS-4)	SK (CMS-5)
0003	Final agreed En product information	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10
0002	Day 106 Responses to questions	May 10	May 10	May 10	May 10	May 10	May 10
0001	Validation update	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09
0000	Initial MAA	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09	Dec 09

Table 2. MRP: Initial filing: (See Figure 4)

Sequence	Submission description	RMS	CMSs – First Wave				
		DE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SE (CMS-4)	SK (CMS-5)
0005	Country specific information (All)		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

Table 3. MRP: Validation update for common information submitted either during the validation phase or at the end of the validation phase (See Figure 5)

Sequence	Submission description	RMS	CMSs – First Wave				
		DE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SE (CMS-4)	SK (CMS-5)
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
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

Table 4. MRP: Review (See Figure 6)

Sequence	Submission description	RMS	CMSs – First Wave				
		DE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SE (CMS-4)	SK (CMS-5)
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

Table 5. MRP: Generally applicable lifecycle submissions (See Figure 7)

Sequence	Submission description	RMS	CMSs – First Wave				
		DE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SE (CMS-4)	SK (CMS-5)
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

Table 6. MRP: Country-specific lifecycle submissions (See Figure 8)

Sequence	Submission description	RMS	CMSs – First Wave				
		DE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SE (CMS-4)	SK (CMS-5)
0013	Responses to Questions – change in legal status (FR)				Aug 10		
0012	Change in legal status (FR)				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

Table 7. MRP: Repeat Use Procedure followed by generally-applicable lifecycle submission (See Figure 9)

Sequence	Submission description	RMS	CMSs – First Wave					CMSs – Second Wave		
		DE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SE (CMS-4)	SK (CMS-5)	FI (CMS-6)	LV (CMS-7)	NL (CMS-8)
0017	Responses to Questions	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11
0016	Manufacturing change variation	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11
0015	MRP with the new MSs has to be finalised – specific sequences for RUP-MRP – see figure 6, sequence 6 - 9	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11
0014	RUP initiation sequence	Dec 10	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11
0013	Responses to Questions – change in legal status (FR)				Aug 10					
0012	Change in legal status (FR)				Jul 10					
0011	Responses to Questions	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10	Jan 11	Jan 11	Jan 11
0010	Manufacturing change variation	Mar 10	Mar 10	Mar 10	Mar 10	Mar 10	Mar 10	Jan 11	Jan 11	Jan 11
0009	Day 90 – Final En product information	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Jan 11	Jan 11	Jan 11
0008	Day 85-90 Responses	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Jan 11	Jan 11	Jan 11
0007	Day 60 Consolidated Response Document	Sep 09	Sep 09	Sep 09	Sep 09	Sep 09	Sep 09	Jan 11	Jan 11	Jan 11
0006	Validation update	Mar 09	Mar 09	Mar 09	Mar 09	Mar 09	Mar 09	Jan 11	Jan 11	Jan 11
0005	Country specific information (All)	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0004	MRP update sequence	Jan 09	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0003	Final agreed National product information	Dec 08	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0002	Responses to questions	Sep 08	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0001	Validation update	Dec 07	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0000	Initial MAA	Dec 07	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11

Table 8: MRP: Change of RMS with old RMS no longer continuing in the Procedure

Sequence	Submission description	RMS (2)	CMSs – First Wave				CMSs – Second Wave		
		SE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SK (CMS-4)	FI (CMS-6)	LV (CMS-7)	NL (CMS-8)
0020	Responses to questions	Jul 11	Jul 11	Jul 11	Jul 11	Jul 11	Jul 11	Jul 11	Jul 11
0019	New indication variation (including change of RMS)	May 11	May 11	May 11	May 11	May 11	May 11	May 11	May 11

Sequence	Submission description	RMS (1)	CMSs – First Wave					CMSs – Second Wave		
		DE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SE (CMS-4)	SK (CMS-5)	FI (CMS-6)	LV (CMS-7)	NL (CMS-8)
0018	Withdrawal of product from German market	May 11								
0017	Responses to Questions	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11
0016	Manufacturing change variation	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11
0015	Country specific information	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11
0014	RUP initiation sequence	Dec 10	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11
0013	Responses to Questions – change in legal status (FR)				Aug 10					
0012	Change in legal status (FR)				Jul 10					
0011	Responses to Questions	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10	Jan 11	Jan 11	Jan 11
0010	Manufacturing change variation	Mar 10	Mar 10	Mar 10	Mar 10	Mar 10	Mar 10	Jan 11	Jan 11	Jan 11
0009	Day 90 – Final En product information	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Jan 11	Jan 11	Jan 11
0008	Day 85-90 Responses	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Jan 11	Jan 11	Jan 11
0007	Day 60 Consolidated Response Document	Sep 09	Sep 09	Sep 09	Sep 09	Sep 09	Sep 09	Jan 11	Jan 11	Jan 11
0006	Validation update	Mar 09	Mar 09	Mar 09	Mar 09	Mar 09	Mar 09	Jan 11	Jan 11	Jan 11
0005	Country specific information (All)	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0004	MRP update sequence	Jan 09	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0003	Final agreed National product information	Dec 08	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0002	Responses to questions	Sep 08	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0001	Validation update	Dec 07	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0000	Initial MAA	Dec 07	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11

Table 9: MRP: Change of RMS with old RMS continuing as a CMS in the Procedure

Sequence	Submission description	RMS (2)	CMSs – First Wave					CMSs – Second Wave		
		SE	AT (CMS-1)	DE (CMS-4)	ES (CMS-2)	FR (CMS-3)	SK (CMS-5)	FI (CMS-6)	LV (CMS-7)	NL (CMS-8)
0019	Responses to questions	Jul 11	Jul 11	Jul 11	Jul 11	Jul 11	Jul 11	Jul 11	Jul 11	Jul 11
0018	New indication variation (including change of RMS)	May 11	May 11	May 11	May 11	May 11	May 11	May 11	May 11	May 11

Sequence	Submission description	RMS (1)	CMSs – First Wave					CMSs – Second Wave		
		DE	AT (CMS-1)	ES (CMS-2)	FR (CMS-3)	SE (CMS-4)	SK (CMS-5)	FI (CMS-6)	LV (CMS-7)	NL (CMS-8)
0017	Responses to Questions	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11
0016	Manufacturing change variation	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11
0015	Country specific information	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11
0014	RUP initiation sequence	Dec 10	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11	Jan 11
0013	Responses to Questions – change in legal status (FR)				Aug 10					
0012	Change in legal status (FR)				Jul 10					
0011	Responses to Questions	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10	Jun 10	Jan 11	Jan 11	Jan 11
0010	Manufacturing change variation	Mar 10	Mar 10	Mar 10	Mar 10	Mar 10	Mar 10	Jan 11	Jan 11	Jan 11
0009	Day 90 – Final En product information	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Nov 09	Jan 11	Jan 11	Jan 11
0008	Day 85-90 Responses	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Oct 09	Jan 11	Jan 11	Jan 11
0007	Day 60 Consolidated Response Document	Sep 09	Sep 09	Sep 09	Sep 09	Sep 09	Sep 09	Jan 11	Jan 11	Jan 11
0006	Validation update	Mar 09	Mar 09	Mar 09	Mar 09	Mar 09	Mar 09	Jan 11	Jan 11	Jan 11
0005	Country specific information (All)	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0004	MRP update sequence	Jan 09	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0003	Final agreed National product information	Dec 08	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0002	Responses to questions	Sep 08	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0001	Validation update	Dec 07	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11
0000	Initial MAA	Dec 07	Feb 09	Feb 09	Feb 09	Feb 09	Feb 09	Jan 11	Jan 11	Jan 11