Annex 2 to the HMA eSubmission Roadmap: Implementation of mandatory use of eCTD format for regulatory submissions

(Adopted by the eSubmission expert group on 30.11.2018)

Scope

This annex is intended for both applicants and national authorities and describes details:

- to be monitored during implementation;
- for additional guidance to support a smooth processing of eCTD submissions and to avoid uncertainties on how to handle eCTD correctly;
- on aspects to be mitigated to cover concerns and identified hurdles.

This annex refers to the implementation of the current eCTD specification as per the HMA eSubmission Roadmap and only applies for products for human use[1] including ASMF, since veterinary products are handled in another stream. The outline of stream II defines different steps for implementation:

- **Use of eCTD for centrally authorised products**

This step can be considered completed since all dossiers in the Centralised Procedure (CP) are handled in eCTD format.

- **Use of eCTD for new MAA in DCP by 1 July 2015**

This step can be considered completed since applications for marketing authorisation within the Decentralised Procedure (DCP) are submitted in eCTD format since 1 July 2015. No major problems with this step have been identified.

- **Use of eCTD for new MAA in MRP by 1 January 2017**

This step can be considered completed since applications for marketing authorisation within the Mutual Recognition Procedure (MRP) are submitted in eCTD format since 1 January 2017. No major problems with this step have been identified.
There is clear guidance how to move from paper or NeeS to eCTD[2] and how to handle eCTD in MRP[3] to facilitate this step. It should be noted that this requirement on eCTD format from 1

[1] *As for registrations according to article 14 or 16a of Directive 2001/83/EC (simplified registration procedure either for homeopathic medicinal products or traditional herbal medicinal products), the time lines of the eSubmission Roadmap are considered optional. Please refer to regional guidance of the member states.*
[2] *The EU Harmonised technical eCTD guidance,*
[3] *The BPG for the use of eCTD in MRP/DCP,*

January 2017 also includes Repeat Use Procedures (RUP) and so-called duplicates of new or previously submitted DCP or MRP applications.

- **Use of eCTD for <u>all</u> regulatory activities in European procedures (DCP/MRP) by 1 January 2018**

This refers to all submission types for a dossier such as variations, renewals, PSURs, ASMFs and so on. To allow sufficient time for all stakeholders to amend relevant processes, stepwise implementation timelines have been given for full implementation in MRP. The requirement is applicable for *all* MRP submissions from that date whatever current format of the concerned dossier. Clear guidance is given on different submission types[4] to facilitate this step. No baseline submissions are required. However, it is recommended to consider a submission of baseline for module 3 in which case the relevant guidance[5] should be followed.
The timeline for implementation for MRP is still kept as no major concerns have been raised by industry or NCAs.

- **Use of eCTD for new MAA in NP by 1 July 2018**

This step has been added to the updated version of the eSubmission Roadmap to strive for a harmonised approached within the EU and in consultation with all NCAs. At the time of the revision of the Roadmap, on an average, approximately half of all National Procedures (NP) were submitted in eCTD format in EU, in some NCAs even 100%. Some NCAs have already announced their intentions to require eCTD format submissions for purely Nationally Authorised Products (NAPs) to achieve simplifications of processing and working with dossiers regardless of the procedure type and regulatory activity at any level. In addition, similar benefits at industry side should be gained by keeping processes and formats for all products as harmonised as possible.
To ensure harmonisation, all types of national deviations to the eCTD format must be avoided and EU specifications and guidelines should be adhered to. Otherwise, benefits of using eCTD in regard to harmonised processing and simplification of dossier management and quality improvement, aside from any legal requirement and compliance with European or international standards, cannot be achieved. The decision on the implementation of mandatory eCTD submissions for National Procedures was discussed widely in relevant telematics bodies and a phased implementation timeline was agreed. Information about national plans for implementation should be transparent at the level of the IT Directors Group with an effort to publish the information. Any timelines set for implementation of mandatory use of eCTD in National Procedures (NP) should take into consideration a transitional period of at least 12 months and need to be communicated to allow this period. The harmonised date set in the Roadmap should be strived for by all NCAs.

- **Use eCTD for <u>all</u> regulatory activities in National Procedures (NP) by 1 January 2019**

This step has been added to the updated version of the eSubmission Roadmap to have the same stepwise approach as for MRP submissions.
This step refers to all submission types for a dossier such as variations, renewals, PSURs, ASMFs and so on. To allow sufficient time for all stakeholders to amend relevant processes, stepwise implementation timelines have been given for full implementation for NP. The requirement is applicable for *all* submissions from that date whatever current format of the concerned dossier. Clear guidance is given on different submission types[6] to facilitate this step. No baseline submissions are required, however, it is recommended to consider a

[4] *see footnote 2 and 3*
[5] *see footnote 2 and 3*
[6] *see footnote 2 and 3*

submission of baseline for module 3 in which case the relevant guidance[7] should be followed.

Key Performance Indicators

To allow a follow-up of the implementation, some statistical key performance indicators should be defined and being monitored by the Human Harmonisation Maintenance Group (HHMG).
The roadmap has very strict milestones for the mandatory use. To monitor the progress towards each date of the implementation plan, a survey will be initiated periodically by the **eSubmission CMB** asking **the NCAs** to track and confirm the formats received for each procedure.

Mandatory use of eCTD for all submissions in MRP (periods covering Q3-4 2017 and Q1-2 2018)
Total number of variations in MRP acting as RMS:_____
- Number of these in eCTD:_____
- Number of these in NeeS:_____

Total number of renewals in MRP acting as RMS:_____
- Number of these in eCTD:_____
- Number of these in NeeS:_____

Mandatory use of eCTD for purely national submissions (periods covering Q3-4 2017 and Q1-2 2018 and Q3-4 2018)
- Planned date of making eCTD mandatory:_____
- Number of NP MAA applications in eCTD:_____
- Number of NP Variations in eCTD:_____
- Number of NP MAA applications in NeeS:_____
- Number of NP Variations in NeeS:_____
- Number of NP MAA applications and Variations in other formats:_____
- Number of NP MAA applications in other formats:_____

General Concerns

Depending on the size and the **business model of a pharmaceutical company** there are major differences how regulatory affairs activities are organised. A more centralised approach can be followed in case eCTD capabilities are associated with a European headquarter. When eCTD capabilities are available at affiliates a more decentralised approach is usually implemented.
The main changes required to support the use of eCTD in case of centralised capabilities are:

- a single common application form for all MS is accepted;
- a single common cover letter for all MS can be submitted;
- no national requirements are set.

A common cover letter and a common application form (eAF) for all concerned member states can normally be submitted with each application. (Please note, for new MAA in MRP/DCP one eAF is needed for each pharmaceutical form or strength.)

Some countries are currently still requesting **wet signature** application forms, cover letters and/or declarations, which prevents electronic only working. In this regard, a clear statement of the strategy of NCAs is required towards an improved situation. A common approach is

[7] *see footnote 2 and 3*

necessary with an aim to avoid the need for wet signatures without the need to implement qualified electronic signatures.
Since signatures have not been certified in the past (as wet signatures) it should not be necessary to establish a higher level of validity of signatures than previously accepted for paper submissions. Acceptance of submissions through CESP without any parallel wet signatures should preferably be the most effective way to reach an electronic-only way of working[8] and is already implemented by most NCAs.
There is no need to provide wet signed papers for any types of submissions to EMA when submitting via the eSubmission Gateway.

Mandatory use of eCTD format in MRP/DCP is also applicable to **ongoing regulatory activities**. However, in National Procedures (NP), the change to eCTD format is recommended at the start of a new regulatory activity and hence not for ongoing regulatory activities until that first switch is made for the product dossier. More details can be found in the *Q&A on how to handle ongoing procedures in relation to mandatory eCTD format*.
As previously agreed for European procedures (MRP/DCP/national), it is not required to provide a so called **baseline**, meaning a re-submission of previously submitted files, in case of a switch to eCTD. Normally, a switch should be avoided during an ongoing regulatory activity. To meet the mandatory use of eCTD also in long-running ongoing regulatory activities in MRP, it is recommended to submit the next submission unit in eCTD format regardless of the status of the ongoing MRP.
The guidance also outlines different options for baselines which should be taken into account.

A submission of a **consolidation sequence** at the end of a procedure will improve the life cycle of a product. In case of partially or completely rejected Variations, documents that are no longer relevant should be deleted. All documents should be replaced by the most recent version as agreed at the end of the procedure. These principles should also be applied in case extensive information exchange has taken place during finalisation of the procedure.

In general, **national requirements** as outlined on CMDh website have been indicated as painful hurdles and these should be revisited at each NCA to carefully assess whether they are still needed or if a workaround can be established to ease publishing of eCTD sequences. Preferably, the requirements should be better harmonised. Even though an NCA might accept a scan of a solely nationally required document, in most cases this document will be prepared locally, provided to the HQ to be added to the eCTD sequence. Alternatively, this document is added to the eCTD at the national level which requires additional local software licenses and staff training. In both cases additional costs can be avoided in case those local documents are not necessary or are allowed to be exchanged separately. Therefore, all NCAs should review whether such documents are still required.
If national documents are still required, they should preferably be handled separately and not required to be included in the common eCTD dossier.

Today NCAs are supplied only with the information that is applicable for the specific country. Most applicants have MAA dossiers in MRPs/DCPs in **one eCTD with all** the dosage forms and strengths included. This means that all NCAs will receive all information, also for not applicable strengths. This approach should be accepted by all NCAs.

It is recommended to handle the **national translation phase** outside of eCTD. Some NCAs require NeeS format for these submissions.

[8] Details on future portal solutions will be provided in the Best Practice Guide on eCTD prepared by CMDh (refer to footnote 2) and may be outlined in another Annex to the Roadmap.

Most NCAs are using eCTD life cycle features supported by appropriate tools that allow for the benefit of eCTD to be realised. Based in current experience, NCAs and industry are using eCTD according to the published specifications and business rules. To avoid inappropriate workload, one dossier per product regardless of strengths or pharmaceutical forms is recommended. In exceptional cases separated dossiers per form or strength might be more appropriate. However, the necessity for this needs careful considerations in the view of the additional workload during lifecycle of the product.

Investments for an eCTD publishing tool have been a concern for a number of applicants. However, the cost of eCTD compiling/building technology has been lowered and several models how to use eCTD technology and support are established to avoid high investments.

Concerns whether **eCTD v4.0 can be used seamlessly** having eCTD v3.2.2 in place will be tackled by the forward compatibility topic of ICH M8 for eCTD v4.0. For details refer to Annex 1. The approach documented in the ICH Implementation Package will use some technical rules of mapping previously submitted leafs in eCTD v3.2.2 with future context of use elements as defined in eCTD v4.0:
The applicant needs to submit a “Current View” message that will transition all current content to v4.0 in one message. The forward compatibility transition mapping message will be based on the Current View, which is defined as follows:

1. Only submission content that has been submitted to the Regulator should be included in the transition mapping
2. All current submission contents (excludes any leaf elements that were deleted or replaced) should be transitioned regardless of whether or not the content will undergo life cycle
3. Any sequences under development should be submitted after the transition mapping submission.

Although the transition mapping message will not recreate the presentation of submission content, the data elements sent forward will be used to enable the following two objectives:

- To maintain Context of Use life cycle in new submissions/regulatory activities
- To enable the reuse of documents within and across applications.

There is also a desire to have the ability to disconnect completely from v3.2.2 in the future, so the approach should support the eventual retirement of v3.2.2 – i.e., there will be a point in time that all applications with activity must be transitioned.
Furthermore, eCTD v4.0 will ease the update of keywords replacing the current functionality of attributes on leafs which cannot be changed in eCTD v3.2.2.
The current complex processing in case of an update of the DTD for eCTD v3.2.2 will be replaced by just updating controlled vocabularies without any further software changes and complex roll-out plans.

For **ASMF submissions in eCTD** a guidance document is available at http://esubmission.ema.europa.eu/eASMF/index.htm. For ASMF in centralised procedure, the eCTD format has become mandatory on 1 July 2016. For MRP/DCP it has become the mandatory format as of 1 January 2018.
Although the prescribed eCTD structure can accommodate the submission of data required for the ASMF, it should be clarified that the eCTD ASMF dossier remains, from a technical perspective, a standalone dossier and is distinct from the marketing authorisation dossier and lifecycle. The eCTD ASMF dossier will be submitted with its applicant part and restricted part by the ASMF holder and will have its own lifecycle.

In case an ASMF dossier in eCTD format is to be used for a veterinary submission, please refer to the document Exceptions to the VNeeS format.