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

(Status: updated version adopted by the eSubmission CMB. Dated 30.1.2015)

Scope

This annex describes the 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.

Stream II, which refers to the implementation of eCTD as per the HMA eSubmission Roadmap only applies for products for human use, 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 as completed since all dossiers in the Centralised Procedure (CP) are handled in eCTD format.

- **Use of eCTD for new MAA in DCP by Q3 2015**

This will include so called Duplicates in DCP. The vast majority of applications for marketing authorisation within the Decentralised Procedure (DCP) are already submitted in eCTD format and no specific problems are foreseen in reaching full implementation by date set for mandatory use.

- **Use of eCTD for new MAA in MRP by Q1 2017**

This will include so called Duplicates in MRP and all Repeat Use Procedures as well as all kinds of Extensions regardless whether submitted as a DCP or MRP application. About 50% of the applications for Mutual Recognition Procedure (MRP) were submitted in eCTD format at end of 2013[1]. The date for full implementation is therefore set for a later date. In some cases, the national dossiers intended for the MRP could still be in paper, however, usually they are handled in electronic format, mainly in Non eCTD electronic Submission (NeeS) format, if not already as eCTD. There is a clear guidance how to move from paper or NeeS to eCTD[2] and how to handle eCTD in DCP and MRP[3]. It should be noted that this also includes Repeat Use Procedures (RUP) and so called duplicate submissions.

- **Use of eCTD for all regulatory activities in European procedures (DCP/MRP) by Q1 2018**

This refers to all submission types for a dossier such as variations, renewals, PSURs and so on. Overall, approximately half of these submissions are currently received in eCTD format, and based on this more than three years are given for full implementation. The requirement is applicable for *all* submissions from that date whatever format of the concerned dossier. Clear guidance is given on different submission types[4]. No baseline submissions are

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[1] Survey at NCA and Industry in relation to preparing the HMA eSubmission Roadmap, http://www.bfarm.de/SharedDocs/Downloads/DE/Service/Termine-und-Veranstaltungen/veranstalt/2014/140513-Anlage.pdf?__blob=publicationFile&v=1

[2] The EU Harmonised technical eCTD guidance version 3.0 http://esubmission.ema.europa.eu/tiges/docs/eCTD%20Guidance%20v3.0%20final%20Aug13.pdf

[3] The BPG for the use of eCTD in MRP/DCP version 3.0, http://www.hma.eu/277.html

[4] see footnote 2 and 3

required, however, it is recommended to consider a submission of baseline for module 3 in which case the relevant guidance[2] should be followed.

- **eCTD for purely national procedures**

This step has been excluded from the eSubmission Roadmap as any decision taken in this area is the responsibility of National Competent Authorities (NCAs). However, there is an expectation that many NCAs will require, for purely Nationally Authorised Products (NAPs), eCTD format 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. Industry, as well as all NCAs, needs to work towards the same goal in a harmonised way. 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. This is not expected being implemented in conflict with, or at earlier date as for European procedures.

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 new MAA in DCP (periods covering Q3-4 2014 and Q1-2 2015)

- Total number of new MAA in DCP acting as RMS:_____
- Number of these in eCTD:_____
- Number of these in NeeS: _____

Mandatory use of eCTD for new MAA in MRP (periods covering Q3-4 2015, Q1-2 2016 and Q3-4 2016)

- Total number of new MAA in MRP* acting as RMS:_____
- Number of these in eCTD:_____
- Number of these in NeeS:_____

(including RUP)*

Mandatory use of eCTD for all submissions in MRP (periods covering Q1-2 2017 and Q3-4 2017)

- 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:_____

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 head quarter. 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.

However, also in case of a decentralised approach, the acceptance of just one cover letter and a single application form will reduce the workload. This needs therefore to be agreed on an EU level as soon as possible.

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 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[5].

As previously agreed for European procedures, it should not be required to provide a so called **baseline**, meaning a re-submission of previously submitted files, in case of a switch to eCTD. All NCAs should confirm that the switch to eCTD will be possible at any point of the life cycle of a product in line with previously agreed TIGes guidance document[2]. Normally, a switch should be avoided during an ongoing regulatory activity.
The guidance also outlines different options for baselines which should be taken into account.

Improving the life cycle of a product by providing a consolidation sequence at the end of a procedure is highly appreciated. The existing Guidance documents should be revised to introduce clarifications and possible improvements. In any case, these documents may have been submitted already and in those cases should not be re-sent.

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 a 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.

[5] Details on future portal solutions will be provided in the Best Practice Guide on eCTD prepared by CMDh and may be outlined in another Annex to the Roadmap.

If national documents are still required, they should preferably be handled separately and not required to be included in the common eCTD dossier.
A common rule should be established allowing only the MS-Word working documents in the "workingdocuments" folder. If it is confirmed that certain national documents are still necessary; a common way of providing these documents, outside the 'workingdocuments' folder; should be established.

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 standard to submit these submissions. However, guidance on how submissions of national translations should be handled in a harmonised way across EU would be preferred.

Another serious remark was made in regard to the **readiness of NCAs** using eCTD life cycle features supported by appropriate tools. The benefit of eCTD can be achieved only in case of consequent upload of all submitted sequences of a dossier. NCAs and industry are obliged to use 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 can be 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. The approach under consideration 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.

ASMF submissions in eCTD format needs to be considered. The current version of the ASMF guidance (v1.0 from 2010) document is not fully compliant with the validation criteria (as is clarified in the criteria) however; this should not prevent ASMF submissions in eCTD format. The ASMF guidance should be revised as soon as possible. Recommendations of the EMA how to use ASMF in centralised procedures should be considered. For the documents of the open part of an ASMF, it is clear that the requirement for mandatory eCTD format of the MAA dossier is applicable since it is included in the MAA dossier. Therefore, it needs to be noted:

- The open part of the ASMF should always follow the dossier format. The same dates apply as for the MAA dossier as outlined above.
- Full ASMFs (open and restricted part) submitted by the ASMF holders are foreseen in eCTD format from 1January 2018. Further details will be available from the updated eCTD ASMF guidance once it becomes available.

Actions prior to step 1 and beyond

1. To monitor the real time usage and success of the implementation plan a survey should be initiated by the eSubmission CMB periodically requesting the NCAs to provide information on the formats they received for the each procedure when acting as RMS. This should be done by a very simple form to be filled out by NCAs:
   - Mandatory use of eCTD for new MAA in DCP (periods covering Q3-4 2014 and Q1-2 2015)
   - Mandatory use of eCTD for new MAA in MRP (periods covering Q3-4 2015, Q1-2 2016 and Q3-4 2016)
   - Mandatory use of eCTD for all submissions in MRP (periods covering Q1-2 2017 and Q3-4 2017)

2. Ask NCAs (via CMDh) whether a simplification can be supported by accepting;
   - a single application form for all MS
   - a single cover letter for all MS
   - avoiding the requirements of signatures as far as possible and
   - avoiding replacement of wet/scanned signatures by qualified digital signatures (involvement EMACOLEX may be considered)
   - maintaining the decision not to mandate applicants to provide a so called baseline, and thus avoiding a resubmission of previously submitted files, in case of a switch to eCTD
   - avoiding purely nationally required documents; if this is not possible provide them outside the common eCTD in a harmonised way

3. Update of CMDh Best Practice Guide on the use of eCTD in the MRP/DCP and the EU Harmonised eCTD technical guidance

4. NCAs to agree on (via CMDh)
   - a common rule having only the MS-Word working documents in the “workingdocuments” folder.
   - accepting receiving all information in case applicants have the MRPs/DCPs in one eCTD with all the dosage forms and strengths included even if not applicable to all CMSs
   - to investigate the possibility to provide a Guidance on how national translations and other national submissions for MRP products should be handled in an harmonised way across EU

5. NCAs to confirm that the switch to eCTD will be possible at any point of the life cycle of a product, but normally not within an ongoing regulatory activity

6. NCAs and industry to be obliged to use eCTD according to the published specifications and business rules

7. Revision of the ASMF eCTD guidance as soon as possible

8. Decision needs to be taken
   - whether ASMF submissions for new MAA are required to be in eCTD format by the same implementation timeline as for new MAA submissions (2015/2017) or whether this requirement can be postponed until eCTD format is mandatory for all submission types (2018)
   - whether duplicates of MAAs not yet in eCTD must be transformed in case they will be submitted as new DCP after July 1, 2015
   - whether repeat use procedures not yet in eCTD must be transformed in case they will be submitted as new MRP after January 1, 2017

9. Make plans for implementation of mandatory eCTD for purely national procedures transparent at the level of IT Directors Group, including plans for legal basis changes, and promote the communication well in advance of implementation