Annex 1 to the HMA eSubmission Roadmap: Implementation of eCTD version 4.0

Adopted by the eSubmission expert group on 15.06.2018

1. Scope

The HMA eSubmission Roadmap published on the EMA website describes the current situation of eSubmission procedures for human and veterinary medicines in the European Medicines Regulatory Network (EMRN) and the initiatives that will be addressed in the near future. The roadmap includes many schemes concerning dossier formats, integrated portal solutions, electronic application forms, common repositories and use of master data (SPOR).

This annex describes applicable details of these regarding the future implementation of eCTD version 4.0:

- what pre-requisites have already been identified and what they could be,
- when an optional use within the different European Procedures might be possible,
- how and when regular use might be mandated (although the time scope of the roadmap extends to just beyond the end of 2021),
- how the transition from v.3.2.2 to v.4.0 might be organised and managed; and what this transition is anticipated to include.

The outline of Stream I describes the optional use of eCTD v4.0 from Q3 2020 onwards and visualises the expected migration from eCTD v3.2.2 to v4.0. This outline implies already that the specification will be ready for use at that time and testing of tools has taken place. However, a number of additional conditions are necessary to be realised before optional use can be allowed and therefore a long planning period is expected.

2. Pre-requisites

This section summarises the major necessary pre-requisites for the usage of eCTD v4.0 in Europe.

2.1. ICH Implementation Guide

Three major milestones have been achieved:

- In September 2014 the under-lying standard on Regulated Product Submission (RPS) based on HL7 Version 3 became normative. This finalised standard was published by the end of 2014[1]and serves as the technical basis for the improved specification of eCTD. eCTD v4.0 will cover relevant requirements collected so far for version 3.2.2 including a number of improvements compared to version 3.2.2.
- At the ICH meeting in November 2014 the package described above with all relevant documents for this new version reached Step 2 and was published for public consultation at the end of 2014.
- At the ICH meeting in December 2015 the final version (Step 4 [2]) of the ICH Implementation Guide was signed off by the Assembly and was published after minor editorial updates as version 1.1. Covering requested changes, a further update was decided in December 2016. The currently valid version is 1.2.

[1] The documentation on the standard is published at: http://www.hl7.org/implement/standards/product_brief.cfm?product_id=362 (user account required)
[2] For details see at http://www.ich.org/about/process-of-harmonisation.html

The ICH package (Step 4) for implementation includes[3]:

Document	Description
ICH eCTD v4.0 Implementation Guide v1.2	Instructions for the harmonised portions of the eCTD v4.0 message specification
ICH Code List v2.0	Harmonised controlled vocabularies
Specification for Submission Formats	Describes the way the files should be constructed for inclusion in eCTD v4.0.
M8 Genericode Schema and Files	Computable list of controlled vocabularies for eCTD v4.0

This package will be presumably updated to version 1.3 to address some further clarifications in regard to presentation of content. Publication is planned on Q3 2018.This will be used for the regional implementation and is therefore one of the major pre-requisites for the usage of v4.0.

2.2. EU Implementation

The regional EU Implementation Guide (EU IG) is expected to be released during Q3 2018 once comments and proposals for correction submitted during the public consultation have been evaluated. The EU IG includes necessary technical guidance on how to create a message and technical validation criteria (needs to be used together with the ICH Implementation Guide).

The message, meaning an XML file in line with the eCTD specification v4.0, will only be complete if the common part (ICH) and the regional part (EU) are created as one single message (i.e. submissionunit.xml file).

The proposal for the final version of the EU IG developed by the eCTD Maintenance Group will be confirmed by the eSubmission expert group and acknowledged by the Telematics CMB, IT Directors Executive Committee, the IT Directors Group and the EU Telematics Management Board. Although this specification will neither interfere with architectural aspects of the EMRN nor establish new metadata sets not yet in use, the Telematics Enterprise Architecture (EA) Board and the EU Data Network Board will also be informed accordingly. This process is planned to be managed prior to publication of the final version of the EU IG. This will likely lead to addition of new European controlled terms as necessary.

2.3. Viewing tool

In parallel to the formal aspects, it is necessary that all stake-holders become familiar with the changes introduced by v4.0. One of the major differences will be that a dedicated viewing tool (i.e. not a standard Internet Browser) is required in all cases as eCTD v4.0 does not include a style sheet like in v3.2.2 and all elements are referenced by their identifiers. A display of content will be possible only if the full access to controlled vocabularies provided by ICH or SPOR-RMS is guaranteed as far as relevant for display purposes. It is anticipated that in a second step, additional tool capabilities and additional capabilities of the under-lying systems, i. e. Single submission portal and Common repository, will be needed for regulatory authorities to create messages and implement the 2-way-communication capability.

[3] http://estri.ich.org/new-eCTD/index.htm

As soon as these pre-requisites are fulfilled, the new specification would be used by industry and regulators for practical testing. However, in order for these submissions to be tested, the receiving regulatory authorities will need to have viewing or review tools. It should be noted that all regulatory authorities need to implement a viewing tool as a pre-requisite; and for cost-efficiency the EMNR should implement a common solution. Due to difficulties one can expect in developing such a solution, negotiations should be started as soon as possible. In any case, it will be necessary that the implementation is harmonised across Europe to ensure timely adoption of eCTD v4.0 to align with other regions. To facilitate the implementation, a stepwise approach is foreseen, starting with submissions within the centralised procedure.

The upgrade to the eCTD 4.0 standard is so significant that change management process for its adoption needs to be considered in advance. This includes the training of staff (both authorities and industry), availability of additional technical and practical business guidance on regional level, migration guidance from version 3.2 to version 4.0 and learning from the initial experience gained with the standard. All of this needs to be planned carefully in advance. The HMA eSubmission Roadmap, including this annex should create the awareness for all parties involved in the upgrade process for agencies as well as for applicants and vendors of eCTD tools.

3. Principles and Expected Advantages of eCTD v4.0

The flatter and lighter folder structure of eCTD v4.0 is made possible by the governing of contents by so called ***contextOfUse*** elements, which replace the folder hierarchy and folder naming conventions of eCTD 3.2.2 and all prior versions. Also for EU Module 1, the first sub-level of structure of the current folder structure (i.e. version 3.0.2) is recommended to be removed.

The ***contextOfUse*** element will reference a document element and provides a combination of keywords to order the content and to describe the functional purpose of the file. The ***document*** element will reference one specific file (except in case of deleting the file from the current view). All lifecycle activities will be executed via the ***contextOfUse*** element.

To keep the intended order of ***contextOfUse*** elements with the same set of keywords a priority number will be assigned. The ***keyword*** element will indicate keywords defined by the ICH Implementation Guide and the EU IG and will become publicly available. In addition, the keyword element will indicate keywords defined by the sender as part of the message and apply to all elements of all submission units assigned to an application by the applicable applicant.
All elements will be described together in the submissionunit.xml file (containing common and regional information).

The HL7 RPS standard[4] offers the options to;

- accommodate regulatory changes without delay (which will mean that laborious and expensive updates are no longer required)
- accommodate major technical changes
- allow simplification of lifecycle
- allow more flexibility of dossier granularity
- allow grouping of documents
- assign submission units to different applications by only referencing a sequence number and application ID
- allow referencing and re-use of documents across applications of the same MAH and among MAHs (in the best case if a common repository is provided[5]) and applicability in general to all kind of products without changes of the tools.

[4] see footnote 1

A theoretical example of the last bullet point is that the standard could be implemented for veterinary products by simply changing the ***contextOfUse*** code list and defining some specific keywords relevant for veterinary products. Accordingly, steps towards moving from the current electronic submission format VNeeS to eCTD 4.0 format for veterinary applications maintaining the current NtA structure within the identical technology should be reviewed to assess the feasibility and added value as a future project.

Should the option of 2-way-communication be implemented in the future, all responses from regulators as well as dossier relevant documents exchanged between regulatory authorities can be included into the dossier structure using the same message standard.

4. Timings for Implementation

If the above-mentioned pre-requisites have been achieved as planned, the use of eCTD v4.0 messages may be feasible from 2019 onwards for practical (training) use in a testing environment. In Centralised Procedures viewing capabilities would need to be provided for the Common repository in case not all national agencies will have a viewing tool installed or an updated version of their current viewing tool available to support eCTD 4.0. Decentralised and Mutual Recognition Procedures would also only be viable if all NCAs in the concerned member states have installed at least a simple viewing tool, but the full functionality of eCTD 4.0, referring the same document from different dossiers, would not be possible without a common European repository for DCP/MRP dossiers.
The tool availability across the EMRN could possibly become a road block to implementation. Therefore as discussed above, an early involvement of tool developers (vendors) in the process seems advisable.

Assuming the development and implementation of appropriate tools has happened, the optional use of eCTD v4.0 messages could be started end of 2020. It is considered that a stepwise approach, as realised for mandatory use of eCTD v3.2.2, could be repeated to implement mandatory use of eCTD 4.0 over a period in time.

Timelines for these steps need to be confirmed by all NCAs and EMA in a revised eSubmission Roadmap to allow a considerable planning for all stakeholders.

5. Transition from Version 3.2.2 towards Version 4.0

For all stakeholders the evaluation of the expected workload and costs (i.e. upgrading of viewing tools and submission repositories) for transitioning from v3.2.2 to v4.0 is very important. The ICH IG describes a onetime transition mapping message (TMM) based on the current regulatory view of a dossier. This means that all valid content of a dossier in eCTD format v3.2.2 will be mapped in a way that document elements can be referenced in the future according to the eCTD specification v4.0. Transitioning to eCTD v4.0 will work whether the dossier in eCTD v3.2.2 format has been baselined or not but can be executed only on content submitted in eCTD format. The transition sequence must be built by the applicant and agreed with the responsible Competent Authority. Any advantage of version 4.0 can be achieved only after transition.

Once version 4.0 had become mandatory– as backward compatibility is technically not possible – guidance needs to be established on how dossiers in v3.2.2 format can be handled further on.

[5] The access to referenced documents (PDF files) for re-use is essential to avoid technical validation errors. To that regard a common European repository will assure that all documents are stored in a way that accessibility is guaranteed. Any other technical option might become complex or difficult to handle.

6. Next steps to do

Action	Due
Resolution of all comments received during public consultation of the draft EU Regional IG	Jan to Aug 2018
Consulting the final version of the EU Regional IG within EU IT Governance	Sept 2018
EU Regional IG published on eSubmission web page	30 Sept 2018