European Medicines Agency
Evaluation of Medicines for Human Use

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EMEA IMPLEMENTATION OF ELECTRONIC SUBMISSIONS AND eCTD SUBMISSIONS: STATEMENT OF INTENT

QUESTIONS AND ANSWERS RELATING TO STRATEGIC AND GENERAL ASPECTS OF THE IMPLEMENTATION

This question-and-answer document aims to address commonly asked questions and provide guidance regarding strategic aspects of the EMEA's plans to implement electronic, and specifically eCTD, submission of applications within the centralised procedure.

The document is a representation of EMEA's position and thoughts at the current point in time and in light of current experience with eCTD submissions. Further input to this document by way of additional questions that EMEA may answer is sought and encouraged, in order to increase the quantity and quality of guidance available prior to full implementation of electronic working and the eCTD.

Questions relating to:

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eCTD and non-eCTD

Q1: What is the difference between an eCTD and a non-eCTD electronic submission?

A *non-eCTD electronic submission* is any submission of electronic information sent by an applicant to an agency in support of a marketing authorisation application procedure. This might be information relating to the initial application or to post-authorisation activity. A non-eCTD electronic submission is formatted as a simple set of electronic files and folders, usually now broadly organised into module folders as per the paper CTD guidance. The files contained are usually PDF or proprietary MS Word files, with other file formats as appropriate. Each non-eCTD electronic submission is a standalone submission, a reproduction as far as possible of the paper dossier. There is no ability to see relationship between the original submission and subsequent updates – the user has thus to navigate in and out of individual folders. There is no easy way with a non-eCTD electronic submission to ascertain what the 'current status' of the application is, pre- or post-authorisation (i.e. which are the current files and approved changes).

Agencies have been accepting and processing non-eCTD electronic submissions, usually in addition to paper copies, for many years.

The *eCTD* as a specific format is, quite simply, an electronic version of the Common Technical Document (CTD). The structure, folder and file names correspond to those of the CTD. As a submission format, however, it contains additional technical components which enable the lifecycle of individual files in the application, and the lifecycle of the product itself, to be managed.

The CTD was developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as a standard format for regulatory submissions in the USA, Europe and Japan. The specification for the eCTD was developed in parallel with the guideline for the CTD (ICH Topic M4).

An eCTD has the following components:

- Folder structure
- Contents
- XML backbone.

The folder structure has a hierarchical organisation reflecting that of the CTD, and it holds the scientific and technical contents of the eCTD (divided into many files which are the same as those in non-eCTDs, usually in PDF format).

The XML backbone (recognisable as 'index.xml' at the root level of the submission folder) of the eCTD provides two useful functions:

- It provides a hyperlinked table of contents to the entire submission when viewed in web browser with a suitable stylesheet
- It provides descriptive information ('meta-data') on the files that make up the actual content of the eCTD.

An important feature of the eCTD is that amendments/supplements are never incorporated directly into the original submission but remain entirely separate.

Each amendment/supplement is a discrete submission with its own XML backbone ('index.xml') which contains information on how each file contained in it relates to files submitted previously.

Although an eCTD *can* be viewed without the aid of specific tools (a web browser and Acrobat reader are sufficient), the technical components of the eCTD can be utilised to their full extent by the use of dedicated viewing tools which provide powerful functionality relating to lifecycle management of the application.

Whilst a web browser and Acrobat reader are suitable tools for reviewing an initial submission, specialist reviewing tools will be needed to help reviewers keep track of subsequent changes.

Specialist reviewing tools can use the XML backbone files to determine which of the files in the original submission and subsequent amendments/supplements represent current versions (i.e. not replaced or deleted subsequently), thus allowing a 'virtual' table of contents to be displayed that lists the current version of every file in the complete eCTD.[1]

Business case

Q2: Why does the EMEA wish to implement the electronic eCTD for the centralised procedure?

In the context of the EU Telematics Strategy, the promotion of paperless operation and promotion of eSubmission will facilitate the operation of the procedures.
The EMEA has accepted electronic submissions alongside paper for some time. While the electronic dossier is used for ease of management of information and review, the burden of processing the paper dossiers in tandem currently remains. There is also some variation in the presentation of electronic submissions received.

The management of electronic-only dossiers using appropriate tools brings several advantages over paper:

- Automation and standardisation of some administrative tasks
- Dossier evaluation and management improvement via appropriate tools
- Reduction of handling and printing of paper
- Reduction in management and archiving costs
- Improvements in ease of access and assessment of data
- Facilitation of the automatic transfer of data to external EU sources
- Greater transparency of dossiers and medicinal products concerned.

The eCTD itself, as the proposed format, offers additional practical advantages, including navigation and lifecycle management (LCM) capabilities:

- Ability to show relationships between dossiers and manage complex lifecycle
- Ability to see at any time the current documentation for a product
- Standardisation and harmonisation of information provided
- Electronic workflow
- Ease of access to correct information for evaluation
- Harmonisation of the regulatory process
- Consistency of format.

Paper/non-eCTD electronic submissions

Q3: Will the EMEA continue to accept paper submissions after 1 January 2009?

The EMEA is committed to working with electronic-only submissions after 1 January 2009, and appropriate hardware and systems are being put in place to facilitate this change. Paper submissions received after 1 January 2009 will be accepted but it is strongly recommend using the electronic-only submissions. Paper and other electronic formats will be an exception to the general e-CTD format recommended for any application.

Q4: Will the EMEA continue to accept non-eCTD electronic submissions after 1 July 2009?

The EMEA is committed to the eCTD as the preferred format for submissions via the centralised procedure from 1 July 2009, and appropriate hardware and software (an eCTD technical validation and

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review tool) is being put in place to facilitate the implementation. Any electronic submission received after 1 July 2009 that is not in eCTD format may require different handling, and will not be subject to the same technical validation and comparative checks as eCTD submissions, which may in turn affect the quality and speed of the procedure and the feedback received.

Context: national competent authorities and eCTD

Q5: How are the Member States' paper and electronic requirements affected by the EMEA's strategy?

The EMEA's strategy for implementation of the eCTD pertains to the centralised procedure only, and the principles contained in this strategy extend to Member States only in so far as they are involved in the centralised procedure. National competent authorities (NCAs), although no longer receiving paper submissions from 1 January 2009 and no longer receiving non-eCTD electronic submissions from 1 July 2009 for the centralised procedure, may continue to require paper submissions and/or accept other electronic formats after these milestone dates in the context of national procedures and mutual recognition / decentralised procedures (MRP/DCP). NCAs should be consulted individually for details of these other requirements.

Q6: What should my company do if requested to provide paper by a Rapporteur or CHMP member for a centralised application after the 1 January 2009 milestone when I have filed an eCTD application to the EMEA?

You should refer to the EMEA Product Team Leader for your application, who will liaise with the national competent authority or individual in question as appropriate to ensure that the principle of non-compulsory paper submission is upheld for an application filed as eCTD.

Q7: Do all Member States have experience of working with eCTD?

All national competent authorities in the EU and EEA are able to receive and review eCTD submissions, even if no dedicated eCTD review tool is in place in the NCA. No European NCA should refuse an eCTD submission.

If no dedicated eCTD review tool is in place within a particular NCA, the submission can be accessed and used for assessment, but no additional benefit can be gained from the lifecycle management functionality inherent in the eCTD – this is no different from handling a non-eCTD electronic submission, however. Currently, as part of the European Review System (EURS) project, more than 20 NCAs have an eCTD review system installed, and the requirements and issues associated with implementation of review tools and the eCTD are being handled by a pan-European EURS Implementation Group, and also by the Telematics Implementation Group for eSubmission (TIGes). Although experience with eCTDs is growing in many NCAs, some do not have significant experience with handling eCTD submissions as part of national or joint procedures. This should not be seen as a barrier to implementation, however, as NCAs are keen to work with eCTD submissions in order to refine requirements and realise the benefits of the format.

Q8: What is the place of the EMEA announcement within the context of the '2009 deadline' for eCTDs in the EU?

By an HMA-agreed end-2009 deadline, the European Regulatory Network must have the infrastructure and processes in place to handle electronic-only eCTD to successfully support the related decision-making processes for medicinal products within the European Union. All national competent authorities must, by this deadline, accept electronic-only submissions, the format for these submissions being eCTD. (It must be made clear that this does *not* mean that eCTD submission must be mandatory in each Member State by the deadline; merely accepted without paper.)

Full adoption of eCTD entails the following:

- No requirement for any accompanying paper submission or paper archive copies
- The eCTD is valid for all European procedures (centralised procedure, decentralised / mutual recognition procedures, national procedures)
- The eCTD is valid for all types of submissions (marketing authorisation applications and renewals, type-I and type-II variations, responses to the LoQ, other MA-related follow-up measures, etc.).

Implementation of the eCTD is being handled at various levels in the EU:

- A pan-European level, coordinated by the Telematics Implementation Group for eSubmission (TIGes), where common issues, requirements and guidance relating to eSubmission and eCTD are discussed and agreed
- A centralised level, which relates to the centralised procedure in particular, involving all Member States, coordinated by the EMEA
- A national level, where national legal, technical, procedural and practical issues and requirements for eSubmission and eCTD are agreed.

The EMEA's strategy covers the centralised level of implementation, and although the EMEA's plans for the centralised procedure do not necessarily affect pan-European and national implementation efforts, there is a desire to ensure a common implementation approach as far as possible for all procedures and agencies, and the publication of harmonised guidance for eCTD submission.

Submission types

Q9: What submission types are covered by the EMEA's strategy to implement electronic submission and eCTD?

All submission types are covered by this strategy, i.e. any submission of updated documents/information made in the context of any centralised application procedure. Such submission types would then include (this list is not exhaustive):

- Initial applications
- Supplementary information following validation
- Responses to questions
- Variation submissions
- Renewal submissions.

In this context, the eCTD format should also be used for submission types for which formal CTD/eCTD guidance has not historically been in place, e.g. periodic safety update reports (PSURs) and follow-up measures (FUMs). Guidance on placement of documents within the eCTD structure for particular submission types can be found in the EU-CTD Notice To Applicants (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2b) and/or in the EMEA Post-Authorisation Guidance (http://www.emea.europa.eu/htms/human/postguidance/ index.htm).

Q10: Are any submission types exceptionally out of scope of eCTD for EMEA?

Referrals, (except Article 20 procedures concerning centrally authorised products) are in principle excluded, but could be submitted in eCTD on a voluntary basis.

eCTD review tools

Q11: Is it possible to work with eCTD submissions without specific hardware or software, i.e. will all competent authorities be able to work with eCTD submitted via the centralised procedure before the end-2009 HMA deadline?

There is no requirement for a dedicated review tool in order to access the eCTD submission. The eCTD is a self-contained standard – a stylesheet submitted with the eCTD means that an internet browser and Acrobat reader for PDF files are the only requirements to navigate through the eCTD dossier and view information.

However, without a dedicated review tool, no use can be made of the powerful lifecycle management (LCM) capabilities inherent in the eCTD, and whilst a web browser and Acrobat reader are suitable tools for reviewing an initial submission, specialist reviewing tools may be needed to help reviewers keep track of subsequent changes.

Specialist reviewing tools can use the XML backbone files to determine which of the files in the original submission and subsequent amendments/supplements represent current versions (i.e. not replaced or deleted subsequently), thus allowing a 'virtual' table of contents to be displayed that lists the current version of every file in the complete eCTD. Review tools provide lifecycle views by using the operation attributes of individual files, and other 'meta data' of the submission itself. An eCTD review tool must exploit the knowledge of the lifecycle to its full extent, meaning relations between sequences must be visualised in an intelligent and comprehensible manner.

Without the use of a dedicated tool, assessors have to navigate in and out of eCTD submission folders to access the current information and infer relationships between files (as is the case for non-eCTD electronic submissions and, similarly, for paper submissions).

All competent authorities are therefore, in principle, able to work without dedicated hardware and software with eCTDs submitted via the centralised procedure before the end-2009 HMA deadline.

Future developments: central repository/EURS

Q12: What are the EMEA's plans for implementation of a central repository for the centralised procedure, and how do these plans correspond to the implementation strategy for electronic eCTD?

EMEA is currently working on the implementation of a central repository for use by national competent authorities in the context of the centralised procedure. A central repository, hosted by EMEA and accessed by NCAs, is a key element in the facilitation of joint procedures.

The EMEA chose a review tool that it would use for the review of eCTDs ('EURS is Yours' from Extedo) at the end of 2006, and this tool is to be provided to NCAs that choose to also implement it. The tool is currently installed and in use at the EMEA, and installed in more than 20 NCAs. The architecture of the central repository is based on use of the EURS tool, although the technical details of the repository must be made publicly available to such an extent as to enable an NCA not wishing to use the chosen EURS tool to access the submissions in the central repository using a different eCTD review tool.

An EURS and Central Repository Implementation Group, representing the EMEA and 14 Member States, has also been formed. The objectives of this group are to monitor the installations of the EURS and other review tools, discuss and resolve process and technical issues related to the use of the review tools, develop further EURS requirements, and handle all aspects of implementation of the central repository for the centralised procedure. This group reports to the wider Telematics Implementation Group for eSubmission (TIGes), where all Member States are represented.

Once the central repository has been fully tested and all success criteria are met, it is the intention that with full implementation, only one copy of each eCTD submission would be sent, to the EMEA, in the

context of a centralised procedure, rather than the current decentralised distribution model. The eCTD submission would need to be loaded into the central repository, and technical validation on the eCTD carried out by the EMEA. The submission would then be registered for access by all Member States by the EMEA.

The central repository is currently being tested; issues are being identified and resolved, and requirements are being gathered. Testing is being carried out with a limited number of Member States in the first instance, and the testing will be extended in phases to include all Member States. A date for completion of the test phases is not currently set.

The implementation of electronic and eCTD submission for the Centralised Procedure is not dependent on the implementation of the central repository, and vice-versa. The two implementation projects will continue in parallel. It is hoped that the full implementation of the central repository may coincide with the July 2009 deadline for recommended eCTD submission for the Centralised Procedure, as this would bring about a harmonised policy change.

Implementation of eCTD at sponsor level

Q13: If my company has no prior experience of building an eCTD, is there any advice that the EMEA can give on implementation for the EU at a sponsor level?

It is advised that a company embarking on eCTD submission for the first time first refers to the eCTD background, specification and guidance published by ICH: http://www.ich.org. The eCTD EU Module 1 specification should then be consulted: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm.

Further guidance will be provided soon in the EMEA's practical and technical.

The vendor market in eCTD builder tools and consultancy on all aspects of eCTD preparation and submission is mature, and companies should research these options, if applicable, for engaging external expertise. The EMEA is unable to list or recommend specific vendors. However, companies interested in gaining more information relating to software should contact pharmaceutical trade associations active in the EU for details of existing eCTD Topic Groups.

In addition, there are certain steps that can be taken that can provide tangible benefits when it comes to generating paper CTD submissions. The following steps should be considered:

- Review internal processes for electronic authoring of documents

  The way that documents are authored can significantly affect the amount of work that is needed at the time of publishing. If documents are authored in MS Word using templates with styles, bookmarks and electronic cross-referencing, then PDF files generated from these files will be automatically bookmarked and hyperlinked internally. This saves on the amount of manual hyperlinking that has to be done at the time of publishing. The use of suitable electronic templates guarantees a consistent typographical style and improves the accuracy and quality of cross-referencing. It also allows cross-referencing to be inserted at the time of writing and not left until the end of the process.

- Review internal arrangements for electronic archiving of documents

  A secure electronic repository such as an electronic document management system for electronic source information is recommended (together with appropriate internal processes, procedures and workflow), in order to ensure that this information is readily available and that documents can be verified as being authentic electronic versions of the corresponding documents stored in the paper archive.

- Ensure that electronic source documentation will be available from third parties, e.g. licensing partners and CROs

  The availability of electronic source documentation is important for assembly of an eCTD. It is recommended that negotiations with licensing partners and CROs should include discussion of

availability of electronic source documentation in a suitable format for future electronic regulatory submissions.

Small and medium-sized enterprises

Q14: Is there any special assistance offered to SMEs in preparation for required eCTD submission?

Assigned SMEs can address queries related to the preparation and implementation of eCTDs to the EMEA's SME Office (e-mail: smeoffice@emea.europa.eu).

Veterinary submissions

Q15: What is the status of implementation of the eCTD and eSubmission for veterinary medicines in the EU, and how does the EMEA strategy encompass veterinary applications?

The EMEA strategy for electronic submission and eCTD submission pertains to human medicines only.

ICH standards for CTD and eCTD are currently developed for human medicinal products and a veterinary parallel has not been elaborated. In its absence, the Notice to Applicants format applies to veterinary submissions.

The work of the Telematics Implementation Group (TIGes) is focused on the continuing development and implementation of the eCTD and associated structured data formats (electronic application form, PIM) for the human sector. It is felt that the work of the TIGes with regard to the implementation of electronic submission formats for the veterinary sector should be appropriately scaled to the EU animal health market, which reaches a small percentage of the size of the human pharmaceutical market. Whilst respecting and harnessing the extensive work already carried out in the implementation of electronic standards for human medicines, a pragmatic and appropriate solution for the veterinary sector is sought that takes into account the scale of the industry, adherence to current standards for harmonisation, amount of non-electronic legacy information, and available financial, technical and human resources.

It is with the objective of developing these veterinary standards and associated implementation guidance that the TIGes Vet Group for eSubmission in the veterinary sector was formed, and its creation is endorsed by the Telematics Steering Committee with endorsement from NtA and HMA. This group has finalised eSubmission guidelines for veterinary applications for all procedures, and is currently working on the development of electronic application form standards for veterinary applications. There are currently no plans to require electronic-only applications in the near future for any procedure for veterinary applications.

The EMEA will continue to receive paper submissions alongside electronic submissions for veterinary applications in the centralised procedure, and national competent authorities should be consulted for individual requirements for MRP/DCP and national procedures.

If your questions are not adequately addressed by this document, or if you have any comments, please forward your query or comments to: eCTD@emea.europa.eu.