European Medicines Agency
Evaluation of Medicines for Human Use

London, December 2008
EMEA/596881/2007
v0.5

EMEA IMPLEMENTATION OF ELECTRONIC-ONLY SUBMISSION AND eCTD SUBMISSION:

QUESTIONS AND ANSWERS RELATING TO PRACTICAL AND TECHNICAL ASPECTS OF THE IMPLEMENTATION

This question and answer document aims to address the commonly-asked questions and provide guidance regarding technical and practical aspects of the EMEA's plans to implement electronic-only, and specifically eCTD-only, submission for the Centralised Procedure.

The document is not definitive at this point in time, but is a representation of EMEA's current view and in light of current experience with eCTD submissions. It is intended to be a 'living' and dynamic document, on which feedback from applicants, other regulators, consultants and vendors impacted by the EMEA's plans for eCTD is actively encouraged. Guidance contained in this document is thereby open to discussion and amendment where considered necessary, and additional points of relevance may be included at any time.

The document is considered a basis for discussion and collaborative development of guidance, to be completed and formalised in line with the implementation strategy.

In addition to this document, further eCTD Q&A issued by ICH and relating to all regions can be found at http://estri.ich.org/eCTD/index.htm.

All other submissions provided to EMEA in non-eCTD format should follow the separate guidelines for such non-eCTD submissions published by EMEA.

A brief glossary of terms (for the purpose of this document only) is indicated below:

Term	***Definition***
Applicant	A pharmaceutical company or its agent that is submitting information in support of an ***application***.
Applicant's information	Regulatory information submitted by an ***applicant*** for or to maintain a marketing authorisation that falls within the scope of this guidance document
Application	A collection of documents compiled by a pharmaceutical company or its agent in compliance with European legislation and guidelines in order to seek a marketing authorisation or any amendments thereof. An **application** may comprise a number of **submissions**.
Procedure	A Community registration procedure for the authorisation of medicinal products in the European Community. There are 4 types of procedures that operate within the EC – the Centralised, Decentralised, Mutual Recognition and National Procedures.
Submission	A single set of information and/or documents supplied by the applicant as a part of, or the complete, Application. In the context of eCTD, this is equivalent to '**sequence**'.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Questions Relating To:

SUBMISSION TYPES

Q1. Is the 1st July 2008 deadline for electronic-only submissions to EMEA flexible in any way? Will EMEA accept electronic-only submissions provided *just prior* to the July 1st milestone?

No. The deadline is not flexible. Even though applicants may be ready to submit electronic-only submissions to EMEA before 1st July, this milestone for electronic-only submissions should be respected by all. Exceptions will not be made for any application, since any such exceptions could not be supported in a consistent and fair manner.

Q2. What sort of information submitted is covered by the requirement to use the eCTD format for the Centralised Procedure?

As indicated in the associated document 'Q&A on Strategic Aspects of EMEA eCTD Implementation for the Centralised Procedure', any submission of information made in the context of a Centralised Application Procedure and the subsequent maintenance of the lifecycle of the application (e.g. initial application, supplementary information, variations, renewals, Follow-Up Measures (FUMs), Periodic Safety Update Reports (PSURs), Notifications etc) may be made in eCTD format.
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/vol2_en.htm;
The CTD question and answer document published by the Notice to Applicants
- http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/ctd_qa_05_2006.pdf;
The ICH CTD Q&A
- http://www.ich.org/LOB/media/MEDIA1189.pdf;
The EMEA post-authorisation guidance
- http://www.emea.europa.eu/htms/human/postguidance/index.htm.

However, it should be clarified that the recommended use of the eCTD format for submission does not extend to information submitted prior to the initial application, (e.g. scientific advice application) and certain information relating to pharmacovigilance and clinical trials.

It should then be noted that the following types of information submitted to EMEA and Regulatory Authorities are not covered by the eCTD guidance:

- **Individual Case Safety Reports** ("ICSRs"): This information is submitted to the National Competent Authorities (NCAs) and the EMEA in the context of the EudraVigilance system.
- **Clinical trials registration information**: This information is to be submitted to the NCAs in the format and manner prescribed by such Authorities for the territory in which the trial is conducted. A central, European database to support the implementation of Directive 2001/20/EC is to be established. The timing of the implementation of such a database will be announced once it has been decided.
- **Suspected Unexpected Serious Adverse Reactions** ("SUSARs") encountered during clinical trials are reported to the central, Eudra Clinical Trials (EudraCT) database in support of the implementation of Directive 2001/20/EC.
- **Scientific Advice (formal), Protocol Assistance**
- **Orphan Drug Designations**
- **Other Processes (e.g. referrals)**

Q3. Should correspondence be included in the eCTD?

The term 'correspondence' applies to all communications (emails, Eudralink mails, documents) that are exchanged between Applicant and regulator in the context of an authorisation procedure but which do not have a formal designated placeholder within the eCTD structure. For example, responses to authority questions are not classified as 'correspondence' since the EU M1 eCTD DTD includes a designated section for such information. Not all correspondence should be included in the eCTD. This is because the eCTD exchange is currently one way only (from applicant to Agency), and not all correspondence is directly relevant to the application dossier. Accordingly, only the minimum amount of correspondence that relates directly to the content of the dossier should be included in submissions to the EMEA (e.g. scientific advice letter).
All other correspondence should be exchanged outside the eCTD via the usual electronic means (email, Eudralink etc). Such documentation will be held in the electronic document management system of EMEA and will be linked to the eCTD repository as appropriate.

Where correspondence acknowledges the final change to details submitted in the body of the dossier, the agreement cannot be documented by that correspondence alone. The revised information should be provided in an accompanying replacement document situated in the appropriate place in the body of the dossier, with the relevant information contained in a covering letter.

The eCTD is designed to ensure that one has a current view of the information submitted in the appropriate place in the dossier at all times.

Q4. Is the Centralised Procedure electronic-only from January 1st 2009, or should paper still be sent on specific request to National Competent Authorities?

No paper should be submitted to any agency after 1st January for the Centralised Procedure. This includes EMEA, Rapporteurs and all CHMP members. National requirements for numbers of electronic copies of the dossier should still be met, however. Any request made by a National Competent Authority for paper copies after January 1st 2009 should be forwarded to EMEA. See EMEA pre- and post-authorisation guidance for further information.

FILE FORMATS

Q1. What file formats are accepted or required within the eCTD for the Centralised Procedure by EMEA?

The EMEA accepts file formats in compliance with the ICH eCTD specification document v3.2(.1) http://estri.ich.org/eCTD/index.htm and the EU Module 1 v1.3 specification document http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm.

The eCTD specification further indicates that: "Regulatory authorities and applicants could agree to use other formats regionally (i.e., non-common formats or uses of the common formats in a different way from above). The use of other formats is discouraged and the intention is to use as much as possible the common formats. The intention of the use of other formats is for transition."

There are also initiatives within the European Union to enable the submission of structured data using XML. These initiatives relate to the Application Form, and Product Information (i.e. PIM). Both initiatives are under development, and therefore the EMEA currently accepts the formats as set out in the table below.

Document	***File format***	***Remark***
Module 1		
Cover Letter	XML, PDF, RTF	PDF, preferably generated from an electronic source (Note EMEA also requires a signed original hard copy of the Cover Letter with the eCTD).
Administrative forms: • Application form and its annexes • Variation application form inc. background for the variation • Renewal form and its annexes	XML, PDF, RTF PDF, RTF PDF, RTF	Documents should be generated from electronic source documents, any signature may be embedded as graphic file in the PDF text if desired, or a digital signature may be used.
Product Information: • Product Information text* • Packaging mock-ups • Reference to Specimens • User Testing	ZIP, TGZ, XML[1], PDF, RTF PDF PDF PDF	Product information texts can be submitted in ZIP or TGZ format according to the PIM Data Exchange Standard. In that context, images can be transmitted in JPEG, GIF, PNG, TIF, SVG, or MathML and PIM information is exchanged in XML. If a higher resolution is necessary for the mock-ups, use JPEG, GIF, PNG or SVG on a case-by-case basis Include Word (97 or higher) or RTF in addition to the PDF, for ease of review – note that Word files should be sent in a separate folder to EMEA and should not be included in the eCTD backbone. Provision of Word files as opposed to RTF is preferred. Insert all Product Information as one merged file, per language (as per QRD guidelines). Product Information documents referenced in the backbone should be presented as clean and track changes documents as appropriate, with blue strikethrough used for deleted text and red italic for added text.
Other	PDF, RTF	PDF preferably generated from electronic source

[1] Product Information submitted in XML format should be prepared in accordance with the PIM Data Exchange Standard Specification. Please see http://pim.emea.europa.eu for further details. The EMEA is currently in a pilot phase of PIM implementation for the Centralised Procedure where limited PIM submissions are accepted, and PIM submissions will only be accepted following discussion and prior agreement with EMEA.

• **Modules 2, 3, 4 and 5**		
Narrative	PDF, RTF	Modules 2.2 – 2.5 should be provided in Word/RTF in addition to PDF, for ease of review
Structured	XML	
Graphic	PDF, JPEG, GIF, PNG, SVG	Whenever possible, use PDF. Special formats for very high resolutions may be appropriate on a case-by-case basis.

*= SPC, Labelling and Package Leaflet

Q2. As the EMEA requires the submission of RTF/Word documents for the Product Information (SPC, Labelling and Package Leaflet) and for some Module 2 documents, in addition to PDF, how should these Word documents be handled?

The EMEA requires RTF/Word documents (Word being the preferred format) for Product Information (SPC, Package Leaflet and labelling documents) and M2.2 – 2.5 in addition to the PDF for the purposes of review and document manipulation, whilst in a transition period to exclusive use of PDF. The Module 2 summaries (2.6, 2.7) are **not** required in RTF/Word format. Whilst RTF is an accepted eCTD format, Word documents are considered, as an aid to review and are not a formal part of the eCTD submission. The following principles apply to the submission of Word documents with the eCTD:

- PDFs (and other accepted file formats, see table above) only are to be referenced in the eCTD XML backbone. Word documents should *not* be included in the eCTD backbone, as they are provided merely as an aid to review and inclusion within the eCTD would require unnecessary management of the lifecycle of these documents in addition to the formal PDF documents.
- Word documents required for review in Modules 1 and 2 should be located in a separate folder to the eCTD and not referenced in the XML backbone, but made available on the same hard media. For submissions made in support of the product lifecycle, both 'clean' and 'track changes' copies of Product Information documents should be provided where applicable.
- All Product Information Word/RTF files submitted to the EMEA (outside the eCTD backbone and therefore it is not necessary to observe eCTD file naming conventions) should be named using the following convention, including the full application number/procedure application number only if this is known at the time of submission:
    - ProductName-H-ApplicationNumber-ProcedureType-ProcedureNumber-PI-language code
    - Example: **WonderPil-H-640-S-15-PI-en**
- An indication should also be given in the filename as to whether the document is 'clean' or 'highlighted', if applicable. (This indication should also be given for PDF files in the eCTD leaf title).
- The filenames for M2 documents should be succinct and meaningful, and should match as far as possible the corresponding leaf titles for the PDF documents submitted in the eCTD.

Q3. Is RTF accepted for the Centralised Procedure within eCTD?

Rich Text Format (RTF) is accepted for Centralised electronic applications for certain documents in addition to PDF as indicated in the table in Q1. Although RTF documents can be included in the eCTD XML backbone, however, as specified in Q2 above, they are considered, if submitted in addition to PDF, as electronic 'working' documents and so it is recommended that, if submitted, they are included in a separate folder. Note that Word is a preferred format to RTF for working copies of the documents. The RTF Specification[2] details a method of encoding formatted text and graphics for easy transfer between computer applications. RTF uses the American National Standards Institute (ANSI), PC-8, Macintosh, or

[2] Rich Text Format (RTF) Specification, version 1.6: See http://msdn.microsoft.com/library/specs/rtfspec.htm

IBM PC character set to control the representation and formatting of a document, both on the screen and in print. With the RTF Specification, documents created under different operating systems and with different software applications can be transferred between those operating systems and applications.

Q4. Are there any particular requirements for PDF documents submitted within the eCTD?

Portable Document Format (PDF) is an electronic format that is open, de facto, and published and created by Adobe Systems Incorporated (http://www.adobe.com). No specific products from Adobe or any other company are necessary to produce PDF documents.

The following points can be made in relation to PDF files:

- files should be PDF v1.4 (except for documents that must be submitted in another PDF version (e.g. Paediatric Investigation Plan), and should be legible with the Acrobat Reader search plug in or any other freeware viewer;
- PDF files should be saved as 'Optimized' to reduce the size and allow faster opening when viewed via an internet connection
- the use of additional software to navigate and work with the files is not acceptable, unless agreed upon with the Agency;
- PDF files produced from an electronic source document are much preferred to PDF files generated from scanned paper since those 'electronic' PDF files provide the maximum functionality to the reviewers in terms of search capabilities and copy & paste functionality;
- Expert Reports and the Overviews/summaries in the CTD Module 2 should always be generated from an electronic source document;
- if scanning is unavoidable, readability and file size should be balanced; the following is recommended: resolution 300 dpi (photographs up to 600 dpi), avoid greyscale or colour where possible, use only lossless compression techniques;
- the maximum individual acceptable file size is approximately 100 MB. The main consideration is to format in such a way as to ensure clarity, speed of download and ease of review. Further guidance should be sought from the EMEA regarding individual larger files as to their acceptability;
- fonts should be chosen of a type, colour and size such that they allow easy reading of documents on screen (1024 x 768 pixels) or after printing; examples of such font-types are:
  - Times New Roman, 12-point, black;
  - Arial, 10-point, black;
- all fonts used in a document (except Times New Roman, Arial and Courier) should be embedded, including all the characters for the font; in other words, limit the number of fonts used in a document and avoid customised fonts;
- if colours other than black are used, colour reproduction after printing should be tested before submission;
- print area for pages should fit on an A4 sheet of paper; margins should allow binding in multi-ring binders without affecting readability.

Additional details on PDF can be found in the ICH eCTD Specification Document, Appendix 7.
Please also refer to the recent EMEA announcement regarding PDF requirements for product information: http://www.emea.europa.eu/htms/human/qrd/docs/43183607en.pdf and the related documents.

Q5. Does EMEA accept the electronic application form in XML for the Centralised Procedure?

EMEA encourages, but does not currently require, submission of the electronic application form (eAF) in XML format for new applications, variations and renewals. If the eAF is provided, the current specifications published by Notice to Applicants (NTA) should be followed: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm.

It should be noted that, while EMEA can view the XML electronic application form, if provided, via use of the stylesheet, no system is yet in place for automatic processing of the structured data within the form. Such a system is under development.

The application form (new, variation, renewal) is also still accepted in PDF format.

SUBMISSION MEDIA

Q1. Can I submit my eCTD application together with specific hardware to aid the review of the eCTD?

The EMEA will not accept any hardware (laptops, desktops, zip drives, etc.) from applicants in connection with the submission of information in electronic format. The electronic information or eCTD should be directly readable and usable on the EMEA's hardware (e.g. CD/DVD drive) using its own software. It is the policy of EMEA to maintain desktop configurations and IT infrastructure in line with common, office standards.

Q2. Must hard media be used for the submission of eCTD i.e. can secure email (Eudralink) be used?

Hard media (e.g. CD, DVD) must be used for the submission of all eCTDs. Eudralink *can* be used for eCTD in addition to hard media, but *not* as the *sole* medium for submission. It is appreciated that it may be necessary, at certain key milestones in the procedure (e.g. for the provision of the translation documents post-Opinion), to submit an eCTD submission or documents via Eudralink in the first instance in order to ensure that the documents are received in a timely manner by EMEA and work can commence. It is expected, however, that this interim 'working' eCTD or documents will be followed as soon as reasonably possible by an exact copy of the same submission on hard media, (or an eCTD submission if only the documents were submitted previously) and it is this eCTD which will become the formal EMEA record. eCTDs will be appropriately processed within the EURS only once received on hard media.
The EMEA Central Information Group (CIG) strongly advises that eCTD sequences should ONLY be submitted via CD or DVD as far as possible to ensure that only one communication channel is used. Advance submission via Eudralink should only be used in situations where a requirement to submit eCTD on hard media would impact submission deadlines. Please note that this requirement for hard media applies to EMEA as an agency, and may not be reflected in all National Competent Authorities involved in the Centralised Procedure – individual guidance from NCAs should be sought if necessary.

(PIM submissions, on the contrary, need not be included within the eCTD on all occasions, and can be submitted solely by Eudralink).

Q3. How should the hard media containing the eCTD be labelled?

Each CD or DVD submitted with an eCTD should include the following label information, clearly presented and printed on the media:

- The applicant name
- The product (invented) name(s)
- The International Non-proprietary Name (INN) of the product
- The full application number (if known)
- The sequence number(s) of the eCTD submissions contained on the CD/DVD
- The submission date (YYYY-MM)
- Number of media units per full set and an indication of the place of the individual CD/DVD within this set
- The submission type of each eCTD submission(s) contained on the CD/DVD (e.g. Initial Application, Variation Type II), as per the eCTD envelope information
- A description of each submission type of each eCTD submission(s) contained on the CD/DVD (e.g. 'supplementary information following validation')

EMEA also requires that a signed original paper copy of the Cover Letter is included with hard media.

Q4: How should the hard media be packaged?

The submission media should be packed adequately to prevent damage to the media and their content thus ensuring that they arrive in a usable condition. Particularly vulnerable are CD-R jewel cases shipped in envelopes without bubble-type protective material or stiff backing. All the contained media units should be appropriately labelled as described in Q3 above.

Q5. Can DVD be used for submission of eCTDs in the Centralised Procedure?

Yes – DVD-R/DVD-ROM (including dual layer) is accepted. In fact the provision of DVD over multiple CDs is strongly recommended by EMEA. CD-R conforming to ISO 9660 can be accepted; however, if an individual eCTD submission is of such a size as to span several CDs, the provision of DVD is much preferred as this allows the technical validation and loading into the repository of the eCTD directly from the hard media, without the need to first recompile the eCTD submission on a server.

Q6. What specific advice should be followed for large eCTD submissions spanning several CDs?

If an individual eCTD submission is of such a size as to span several CDs, the provision of DVD is much recommended. However, if CD-R must be used, when large applications are submitted it is inevitable that the application will necessarily span multiple CDs. Where possible, individual modules should not be split over multiple CDs (e.g. if possible, Module 1 should be contained on a single CD, Module 2 should go onto the next CD even if this requires CD 1 not to be filled to capacity and so on). If, in the case of larger modules, where a split over multiple CDs is inevitably necessary, subfolders should be distributed in sequence, and these subfolders should not be split between CDs, even if this requires a CD to be sent not full to capacity.

VALIDATION

Q1. How is the applicant advised to handle technical (eCTD specification) and business (content) validation changes in the eCTD?

It is important that there is a clear understanding of the distinction between:
Technical validation (the automated tool validation effected on an eCTD submission by checking the DTD and technical components of the submission) and;
Business validation (validation of the content of the submission, by a number of regulatory affairs/scientific and inspection sector staff members)

Upon receiving the eCTD hard media, EMEA performs technical validation testing of the eCTD. On successful completion of this validation step EMEA begins business (content) regulatory validation procedures as for any type of submission received. Upon successful completion of regulatory validation procedures, the submission is accepted for evaluation. The applicant is asked to submit copies of the eCTD to other regulatory agencies in accordance with the published list: http://www.emea.europa.eu/htms/human/presub/q23-1.htm.

Where there is an error found during *technical* validation, the submission will not be loaded into the review system and a replacement sequence 0000 (or sequence as appropriate) should be requested from the applicant by EMEA.

Following the technical validation of an initial MAA submission, the EMEA CIG will send the technical validation report to the applicant only if there are technical issues with the eCTD reported. Similarly, technical validation reports for subsequent eCTD submissions (e.g. Responses, Variation Applications etc.) will be sent only if there is a technical error identified.

Where there is an issue discovered during *business* validation (i.e. content validation identifies missing sections or administrative errors), an updated (lifecycle) sequence should be requested from the applicant by the EMEA, correcting the errors, with replacement or additional new documents as required. The applicant should not send a replacement of the original sequence.
For example, if missing information is reported in sequence 0000 during business validation, this information should be included in a sequence 0001. The sequence 0001 can also be used to introduce necessary technical changes that may be required as a result of warnings (not errors) reported during technical validation.
If, as a result of validation, information is also requested at a later stage of the procedure (e.g. within 30 days), this should be submitted as a sequence 0002 after the initial validation responses, or could be included with the following eCTD sequence sent at the next specified procedure milestone.

Q2. What happens if I receive differing validation feedback from EMEA and the Rapporteurs?

In the Centralised Procedure, it is EMEA that is responsible for the technical validation of the eCTD on behalf of Rapporteurs and all recipients of the eCTD, and for the content validation before assessment begins. Any issues raised by the Rapporteurs should therefore be addressed in the course of the procedure. If an eCTD is deemed to be technically valid by EMEA, but cannot be loaded into a Rapporteur's eCTD review system (if this differs from that of EMEA), then Rapporteurs and CHMP members should pursue a line of enquiry with their own eCTD review tool vendor to ensure consistent handling of the eCTD. The use of a central repository for the Centralised Procedure in the future will avert such issues, as will the use of EU validation criteria (see Q3) before the Central repository is fully implemented.
If any agency experiences an issue with upload of the eCTD locally following EMEA validation, the applicant will be informed immediately, yet the procedure should continue as the agency in question reviews the documentation in the submission without the use of a review tool.

Q3. How is consistency of interpretation of the eCTD specification assured by eCTD tool vendors? How can I assure that the eCTD will be similarly handled by all review tools in use by Competent Authorities?

Interoperability of eCTD builder and review tools, and differing interpretations of the standard (the eCTD specification) have been an issue from the beginning of implementation of the eCTD and this has been extensively worked upon within the context of the ETICS project in the framework of ICH. http://www.etics.us/.
Under the supervision of the European Telematics Implementation Group for eSubmission (TIGes), a harmonised, unambiguous set of *technical* validation criteria to be applied by *all* tools to *all* eCTDs in *all* European procedures has been developed. These criteria cover general eCTD technical validity requirements, as well as criteria particular to the EU environment and procedures.
These criteria will be implemented in the chosen European Review System (EURS) implemented at EMEA and in use by many NCAs, and should also be implemented in other tools on the market to ensure interoperability.
The EU validation criteria are available at http://esubmission.emea.europa.eu

Furthermore, the validation engine integrated within the chosen EURS used by EMEA is available to applicants free of charge, to allow applicants to check the technical validity of the eCTD and likelihood of successful technical validation by EMEA prior to submission. The validation engine can be obtained by contacting the providers of the EURS (eurs@extedo.com)

REGIONAL REQUIREMENTS

Q1. As the eCTD is an international standard, are there particular areas of divergence in technical eCTD requirements to be aware of between the US and the EU?

The eCTD is indeed an international standard and is also implemented in the US and accepted by the FDA. However, whilst once of the primary objectives of introducing the eCTD is to facilitate the preparation of applications intended for multiple regions, care must be taken over the adaptation of the submission to meet regional requirements, as these can, and do, differ. The FDA has issued specific guidance with regard to the provision of the eCTD: http://www.fda.gov/cder/guidance/7087rev.htm.

Particular areas of divergence between eCTD requirements for the US and the EU include:

- The requirement for the Study Tagging File (STF) in the US, which is not used in the EU (although a submission containing the STF will not be rejected in the EU);
- Information relating to datasets e.g. data definitions, analysis datasets etc., ISS and ISEs (not submitted in the EU)
- The use of SAS transport files for data in the US, which is a format not accepted by EMEA;
- The use of node extensions, which are not accepted in the US but accepted in the EU (it should be noted however that node extensions are handled in differing ways by review tools, and so their use should be limited where possible).
- Module 1 content and DTD

Applicants should pay attention to the particular requirements of each region and ensure that the eCTD submission has been adapted accordingly.

eCTD AND PIM

Q1. Is it mandatory to submit PIM with eCTD?

No, it is not mandatory to submit PIM with eCTD. Please see http://pim.emea.europa.eu for further details. The EMEA is currently in a pilot phase of PIM implementation for the Centralised Procedure where limited PIM submissions are accepted, and PIM submissions will only be accepted following discussion and prior agreement with EMEA.

Q2. If PIM is submitted with an eCTD submission, how should this be done?

Applicants wishing to submit PIM within the eCTD should consult the current version of the PIM Data Exchange Standard (DES) Specification, http://pim.emea.europa.eu/des/docs.html, section 2.2.

It is expected that PIM submissions will be more numerous than eCTD submissions during a typical procedure, since PIM is a two-way exchange mechanism designed to support the management of the product information, the part of the dossier subject to the most change and rapid amendment during any procedure. Therefore, there will be some PIM submissions made without an accompanying eCTD via Eudralink. However, it is expected that, when a major lifecycle eCTD submission is provided as specified in the response to Q1 under 'Submission Milestones' in this document, then the latest PIM submission will be included within the eCTD submission, if applicable, to ensure alignment. (The PIM submission does not *have* to be included within the eCTD submission at such points, however, and can be submitted as a separate PIM submission even if submitted simultaneously with the eCTD, as is detailed in the PIM specification).
It is the intention that the PIM review system will be integrated with the EURS in order to provide a comprehensive review environment for assessors.

eCTD REVIEW TOOLS

Q1. Will EMEA use a dedicated review tool to process and view my eCTD?

An eCTD submission can be viewed without the need for a dedicated review tool; the use of Acrobat and a web browser are sufficient to navigate through the submission using the dynamic table of contents and view the files contained therein. However, without a dedicated review tool, the full potential of the eCTD in terms of lifecycle management cannot be realised, as use of the advanced functionality provided with the eCTD for the purposes of managing the relationship between submissions and files cannot be made.
EMEA has therefore chosen a specialised eCTD review tool to process and view eCTDs submitted via the Centralised Procedure.
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 these views by using the operation attributes of individual files, and other 'meta data' of the submission itself.

EMEA's chosen eCTD review system is EURS is Yours® (EiY) from Extedo. This tool is also sometimes referred to as the chosen 'EURS' or European Review System, since it was selected in December 2006 by a panel of assessors and IT experts from EMEA and NCAs in a European procurement procedure as the preferred and most functionally-rich eCTD review tool available on the market, to be used by EMEA and all NCAs that choose to implement it.
The tool has been installed at EMEA since June 2007, and EiY will also be the tool used with the future central repository, once this is fully implemented (see Q&A on Strategic Aspects of the EMEA eCTD Implementation Policy).

Q2. Will National Competent Authorities also use a review tool or tools to process and assess my eCTD in the Centralised Procedure?

The EMEA has chosen to implement EURS is Yours (EiY), as the European Review System, and provides this tool to all National Competent Authorities (NCAs) that choose to implement it. An EURS (and Central Repository) Implementation Group, representing 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.

To date, more than 20 National Competent Authorities have installed EiY. However, the state of implementation of the tool within the Agencies differs significantly. In some NCAs, the tool is fully implemented, with all assessors using it to access and review submissions. In other NCAs, implementation is limited to a specific group before rollout to the wider Agency. In some NCAs, the EURS is installed as a stand-alone application, and in other Agencies, work is progressing to integrate the tool with bespoke workflow systems and document management systems already implemented.

However, there is no requirement for all NCAs in Europe to use the EiY tool, although it is provided and recommended. Certain NCAs do not use EiY, but have instead different off-the-shelf systems installed for the review and processing of eCTDs, and some NCAs may use bespoke systems. The presentation (cosmetic) of the eCTD will differ slightly with each review tool; however the important aspects of interoperability between different eCTD review systems in use in the EU are adherence to the eCTD specification in the eCTD submissions provided, and common interpretation of the specification in terms of technical validation checks used by the tools (the EU Validation Criteria http://esubmission-draft.emea.europa.eu are crucial here).

Furthermore, it is possible that some assessors in certain NCAs will continue to access eCTD submissions without the aid of a review tool, as the harmonisation efforts continue.

COVER LETTER

Q1. What information pertinent to the eCTD should be provided in the Cover Letter?

EMEA requires that the original signed paper copy of the Cover Letter is included with the hard media. If digital signature that is compliant with the European Electronic Signature Directive (e.g. 'SAFE') is used for the application, then a 'flattened' version of this signature is to be included in the Cover Letter.

At a minimum, the following information should be provided in the Cover Letter:

- The applicant name and address
- The submission date (YYYY-MM-DD)
- The type of submission
- A description of the submission
- The submission sequence number (according to the ICH eCTD Specification Document), i.e. 0000 in the case of a new application.
- The related sequence number (if applicable)
- The product (invented) name(s)
- The ATC code (for initial applications only)
- The name(s) of the active substance(s)
- The full application number (if known)
- Regulatory and technical point of contact for the submission.
- Data security/virus scan information (name and version of virus checker)

However, experience has shown that is can be immensely useful if an annex to the Cover Letter is provided in the form of an eCTD 'Reviewer's Guide' or similar, that may contain the following sections if applicable, in addition to those specified above:

- Particularities relating to presentation and delivery of the eCTD (hard media)
- Information on file sizes by module
- Legacy documents and scanned pages details
- File formats (if any particularities to report)
- File size (if exceeding 100MB restrictions)
- Files referenced at multiple locations within the backbone
- Specifications adhered to
- Documents with relevance to more than one CTD-module
- Hyperlink appearance and strategy
- Bookmarks
- Particularities of module organisation
- Distribution list
- Documents available on request

This additional information is not all required, but may be useful, particularly if there are specificities of the eCTD submission about which the reviewers should be informed.

SECURITY

Q1. How is the security of the eCTD assured?

The following points should be noted in relation to security:

- The physical security of the submission during transportation/transmission is the responsibility of the applicant.
- Once received within the EMEA, security and submission integrity is the sole responsibility of the Agency. The Agency has in place appropriate measures to prevent loss, unauthorised duplication and/or access or theft of regulatory information, whether such information is presented on paper, using electronic media or distributed through the Agency's network.
- Appropriate security measures are in place for offline and transmission downloads.
- The use of, and subsequent validation of, the MD5 checksum allows the recipient of the eCTD to ascertain whether files in the submission have been changed since the checksum was generated.

Q2. Can I password-protect the eCTD submission, or individual files within the eCTD submission?

One-time security settings or password protection of electronic submissions for security purposes is *not* acceptable during transportation/transmission from the applicant to the Agency.
Applicants should also *not* include any file level security settings or password protection for individual files in the eCTD. Applicants should allow printing, annotations to the documents, and selection of text and graphics. Internal security and access control processes in the regulatory authority should maintain the integrity of the submitted files.

Q3. What are the requirements for virus-checking of the eCTD?

The applicant is responsible for checking the submission for viruses and for informing the Agency of the type of software used for this purpose. Checking should be performed with at least one, but preferably more, up-to-date virus-checkers.

After receipt at the Agency, a similar, multiple programme, internal virus check will be performed. A positive check can constitute sufficient grounds for refusal of the eCTD.

Q4. Should the eCTD be encrypted?

Encryption is not considered necessary if the information is sent using a physical media. The applicant should assume all responsibility for the media until it is delivered to the regulatory authority

Q5. How should the MD5 checksum for the eCTD be used?

A checksum (MD5 or other) should be included for each file in the eCTD, allowing the recipient to verify the integrity of physical files in the submission.
An MD5 checksum of the XML eCTD index (index.xml) should also be included. Applicants should name this checksum file index-md5.txt, and include it as a file (with one line of content and with no header line) in the same directory as the XML eCTD instance.
It is not necessary to print the MD5 checksum for inclusion with the hard media submission, although this information can be provided if desired.
An invalid checksum will result in the rejection of an eCTD submission as technically invalid.

PRACTICAL PROCEDURES FOR SUBMITTING

Q1. To whom should the hard media containing the eCTD submission(s) be addressed?

2 copies of the eCTD on DVD/CD should be submitted to the EMEA at the following address:

Central Information Group (CIG)
European Medicines Agency (EMEA)
Loading Dock
Ontario Way
Canary Wharf
UK - London, E14 4HB

ELECTRONIC SIGNATURE

Q1 What is the position of EMEA regarding the use of electronic signatures within the eCTD?

'Advanced electronic signatures' are currently accepted in the EU as being legally equivalent to handwritten signatures (Directive 1999/93/EC3).

An advanced electronic signature is a symbol an individual includes in an electronic document with the intention of identifying himself or herself. An electronic signature is generally defined as any letters, characters, or symbols manifested by electronic or similar means and executed or adopted by a party with an intent to authenticate a writing. Examples include:

- A PIN number or a code that the sender of the message uses to identify him/herself

Digital signatures are a subset of electronic signatures. It is important to differentiate between digital signatures and other forms of electronic signatures as digital signature technology serves a much more specialized market than electronic signatures and poses particular legal issues. Digital signatures will be accepted by EMEA in the context of the Centralised Procedure provided that they are compliant with the European Electronic Signature Directive (e.g.'SAFE'), but the necessary software to 'read' these signatures is not available widely within the Agency, and EMEA does not currently have the necessary software components to validate these digital signatures. 'Flattened' or embedded digital signatures are preferred.

EMEA will also accept, for applicable documents within the eCTD, (covering letters, Application Forms, export reports, certificates etc), a handwritten signature that is scanned or embedded as a graphic file in the electronic (PDF) document.

[3] See http://europa.eu.int/comm/dg15/en/media/sign/index.htm

eCTD ENVELOPE

Q1. How is envelope metadata provided with the eCTD used by EMEA?

The metadata provided by the applicant with the eCTD is extremely important, since it is automatically extracted by the EURS and is used to display and group eCTD submissions, and indicates relationships between individual sequences for effective lifecycle management of the application.
The particular envelope elements used by the review tool for display and management of submissions are <sequence number>, <applicant>, <submission type>, <invented name>, <inn> and very importantly, <submission description>.
It is highly recommended therefore that Applicants ensure absolute consistency in the inclusion and presentation of metadata applicable to a number of submissions (e.g. applicant name, inn), as if matching terms are not used, the review system cannot automatically recognise a relationship between certain submissions/sequences. It is appreciated that there may be legitimate reasons for the meta-data to change over the lifecycle of the product and this is technically supported. However, under normal circumstances, consistency, quality and accuracy should be assured.

For example, as it is an envelope element which is used, (together with the related sequence element if present), to group together submissions relating to a particular regulatory activity (e.g. variation type II procedure), it is also important that the full application number is included in the envelope where possible (e.g. EMEA/H/C/000123/II/27), particularly in a post-authorisation phase where this number is usually known by the applicant.

Also worthy of note is the use of free text for <submission description> – the information provided in this field is of key importance to product team members and assessors in identifying at a glance the precise contents of a particular sequence, since more instructive/substantive information can be provided for this element above and beyond the <submission type> element, where the selection of values is more limited. Using the <submission description> element, submissions relating to multiple parallel variation procedures can be easily identified and grouped together. The contents of the <submission description> element should therefore be concise but clearly indicative of the substance of the submission in question.

The <submission description> can also serve to determine the differences between sequences where the same value for <submission type> must be used for multiple submissions (e.g. 'supplemental information') due to the fact that an completely exhaustive set of values for <submission type> is not implemented in the eCTD EU M1 specification.

Q2. How should the application number be included in the eCTD envelope?

The application number for a new application via the Centralised Procedure is not generated until such time as the initial submission is received by EMEA, and key information from this initial submission is loaded into the EMEA tracking database.
The application number for new applications can therefore normally not be provided to applicants prior to submission.
Applicants should therefore provide the following envelope element value (or similar) for <application number>:
'To be advised'.

Similarly, as the application number is not known at the time of initial submission for a new application, the INN, common name or invented name should be used for the root folder name of the submission.

The EMEA will give an official number to all procedures. If this is known (e.g., FUMs already agreed, SO, etc), the applicant is encouraged to use this full reference, including the procedure application number (e.g. II/27) in the eCTD envelope.
Applicants should refrain from numbering initial variation application submissions, or any procedures for which the exact application/procedure number is not known. For variations, it is appropriate at least to

indicate the type of procedure, e.g. type IA, IB, II… but the procedure application number will only be given upon receipt of a hard copy by the Agency and this number will be assigned to the eCTD submission as a reference by EMEA, within the Agency's review system.

TEST SUBMISSIONS

Q1. Does EMEA accept test eCTD submissions for the Centralised Procedure? What is the procedure for submitting a test eCTD?

EMEA encourages the submission of test eCTDs, particularly if the applicant has limited experience of producing eCTDs and would like to investigate particular areas of technical concern to ensure technical validity at the time of formal submission. The test submission process at EMEA for the Centralised procedure is an informal process, intended to accord pragmatic assistance for the applicant.

- A test eCTD can be provided on CD or DVD (DVD is preferred) at any point up to 2 weeks prior to the filing date. EMEA cannot guarantee that any test submission provided within 2 weeks of the filing date will be processed in sufficient time as to allow the resolution of reported technical issues.
- The test eCTD should be as representative as possible of the final eCTD submission, particularly in terms of structure, envelope and metadata used. The individual files contained within the submission however will not be reviewed, so 'dummy' files can be submitted.
- The test submission should be appropriately packaged so as to ensure damage to the hard media is not sustained in transit, and the CDs/DVDs should be appropriately labelled as to ensure easy identification of the test submission and its purpose (here applicant name, invented name if known, INN and type of application and 'TEST eCTD' should suffice, as well as any information relating to the number of media units and submissions contained therein for organisation if appropriate).
- The root folder name of the test eCTD should include the word 'Test'.
- The eCTD should be further accompanied by a brief paper cover letter explaining the purpose of the test submission, and indicating applicant contact details for feedback on the eCTD.
- 2 copies of the test eCTD should be provided on 2 sets of CDs/DVDs, in order to eliminate hard media corruptions if the eCTD cannot be accessed from a particular disk provided. The second copy can also be used to test CD/DVD writer/publishing compatibility with EMEA CD/DVD reader hardware if different versions are under consideration by the applicant.
- The test eCTD will be validated by a technical sector of EMEA with eCTD expertise and business knowledge. Information will not be passed on to the Product Team Leader (PTL) or business team for the product unless there are specific questions arising that relate to business requirements or business issues with the eCTD. The test eCTD is therefore not subject in any way at this stage to a business 'pre-validation'. The tests are strictly technical. There is no content review of the submission.
- The test eCTD will be validated using the EMEA's eCTD review system, 'EURS is Yours' (EiY), and the submission will be viewed within the review tool in order to ascertain that the presentation of the dossier is as expected, that documents can be accessed, and that correct use of structure and metadata has been made. Hyperlinks, if provided in documents, may be tested if functioning. Particular aspects of the eCTD, if highlighted by the applicant, will also be checked.
- Feedback is usually provided by EMEA within 1 week of receipt of the test eCTD. The applicant will be provided with a copy of the technical validation report generated by EiY, and any particular issues will be highlighted along with a recommendation for resolution. The applicant will be advised if further liaison with the PTL or product team is recommended with regard to possible business issues.
- The process of submission of test eCTDs can be an iterative one, if considered necessary to ensure adequate resolution of any issues reported.

SUBMISSION MILESTONES

Q1. When, in a procedure, at a minimum, does EMEA expect an eCTD submission to be provided?

The provision of information by the applicant during a procedure depends of course on the nature of the procedure and the specificities of the application and the assessment. All information, whether it be required deliverables/responses or supplemental information, should be provided in eCTD format and documents located as appropriate within the eCTD structure.

There are, however, in any typical procedure, key milestones when an eCTD submission with relevant updated files/information is expected in order to maintain a meaningful lifecycle for the application and reflect the procedure. The number of additional individual eCTD submissions provided within these milestones depends on the factors mentioned above.
The key milestones for e.g., an initial marketing authorisation procedure when the submission of an eCTD is expected are as follows:

1. Initial submission (Day 0 of procedure)
2. Response to business validation issues (if required)
3. Response to List of Questions (i.e. Day 121 for a new application)
4. Response to List of Outstanding Issues (i.e. Day 181, if required)
5. Application as agreed at Opinion (inc. agreed EN product information if changed at CHMP)
6. Provision of translations (i.e. Day 215 for a new application)*
7. Provision of final agreed translations following linguistic review (*it is not also required to send interim working versions of the product information before this point as eCTD*) **
8. Decision (i.e. final amended documentation if any changes occur during the Standing Committee phase)

By analogy, the same principle applies for all post-authorisation procedures, i.e., an eCTD submission is expected at day 0 of the application procedure, and subsequent sequences should then be provided in accordance with the corresponding milestones for that procedure, through to approval.

With these submissions provided for each application at a minimum, the 'current' lifecycle view of all of the information comprising the approved application can be compiled using eCTD review tools.

* Note that, in accordance with the information given under the section 'Submission Media', Q2, It is appreciated that it may be necessary, at certain key milestones in the procedure (e.g. for the provision of the translation documents post-Opinion), to submit an eCTD submission or documents via Eudralink in the first instance in order to ensure that the submission is received in a timely manner by EMEA and so that work on the documents can commence. It is expected, however, that this interim 'working' eCTD or documents will be followed as soon as reasonably possible by an exact copy of the same submission on hard media, and it is this eCTD which will become the formal EMEA record of the documentation applicable at a certain point in the procedure.

** Note also that it is not required that interim working versions of the product information documents exchanged during the linguistic review phase are followed up by an eCTD containing PDFs, or on hard media – only the original and final agreed translations should be submitted in this manner.

FILE NAMING

Q1. What file naming conventions should I use in the eCTD submission?

To function properly, the eCTD backbone files must have specific names (e.g.index.xml, eu-regional.xml).
Other file names (all modules) have fixed and variable components, and should be indicative of contents. Components are separated by a hyphen. No hyphens or spaces should be used within each component.
The file name should allow the reviewer to infer some concept of the file's content relative to other files, and differentiation should be provided between file names to enable unambiguous concurrent review of files.
The file and path name together should be less than or equal to a maximum of 230 characters including the appropriate file extension. Only letters (lower case), numbers, or hyphens should be used in the name. Refer to the current EU M1 specification v1.3 for further information on file naming: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm

Whilst the leaf title, rather than the file name, is generally used by EMEA to identify and work with files in the eCTD, there are specific requirements for some product information documents that facilitate internal handling. Product information files submitted to EMEA in Word format outside the eCTD backbone as 'working' documents should be named according to the following convention:

- Word files (submitted in a separate folder and not included in the eCTD XML backbone):
  - ProductName-H-ProductNumber-ProcedureType-ProcedureNumber-PI-language code
  - Example: **WonderPil-H-640-S-15-PI-en**

Furthermore, EMEA is aware that a discrepancy currently exists between the eCTD file naming convention, and the PDF file naming requirements for EPAR documents (http://www.emea.europa.eu/htms/human/qrd/docs/43183607en.pdf). The eCTD file naming convention dictates that a country code, document type and variable part that should be applied to each file name (cc-spcdoc-var.ext) , whereas the EMEA requirements dictate that the EMEA product number and language code should be applied to each PDF document to be used for the EPAR (**H-**[EMEA product number]-**PI-**[2 letter language code]).
Until such time as the requirements are aligned, the eCTD file-naming convention should be applied to all product information documents included in the eCTD, but at the time of finalisation of the dossier and publication of the EPAR, a separate set of copies of the PDF documents, named according to the EMEA requirements, should be submitted in a zip file to EMEA outside the eCTD. This is a temporary solution resulting from differing processes for review and publication of the documents, and will be resolved in 2009.

Q2. What is the importance of eCTD leaf titles as opposed to file names?

The importance of leaf titles[4] as opposed to file names must be emphasised as eCTD-only and the use of review tools for accessing and working with the eCTD are promoted for the Centralised Procedure.
File names are not generally highlighted to assessors working with the eCTD submission using a review tool (these are only seen if navigation through the eCTD via the folders is employed) – instead, it is the eCTD leaf titles that are displayed by the tool in the tree view and used to identify the files.
Whereas file names are used by systems, eCTD metadata (attributes and leaf titles) are used by assessors for navigating through the eCTD submission using a review tool. There are no leaf title naming conventions as such; however, leaf titles should therefore be concise and indicative of file content. Is it

[4] The eCTD content is made up of multiple files. The eCTD contains a "<leaf>" element for each of these files. Each <leaf> element has associated attributes that provide important information on the file to which the element relates, including the location of the file in the folder structure, its unique ID, version number, MD-5 checksum (a way of ensuring that the file hasn't been changed since its creation) and a special attribute called the "operation" attribute that facilitates version control.

acceptable to use internal codes in parenthesis at the end of leaf title names; however internal codes should not be used as the sole identification of a file via the leaf title.

Q3. How are eCTD folder and file names used by EMEA?

Although it is considered that the leaf titles and attributes are of more importance in the eCTD, the file names and folder names used in the eCTD can be viewed in an 'attributes pane' for all sections and document using the EMEA's eCTD review tool. They are not used as the primary means of identifying sections and files in the tree structure however; the leaf titles are used for this purpose as mentioned in Q2 above. It must be mentioned that EMEA is *not* using systems or processes that involve parsing the file names to identify different components of the submission, nor is EMEA using the folder names in the directory path.

STRUCTURE OF THE eCTD DOSSIER

Q1. Where should the justifications for missing documents be located in the eCTD?

For new applications, detailed statements justifying absence of data or specific CTD sections should be provided in the relevant Quality overall summary and/or non-clinical/clinical overviews. Note that placeholder documents highlighting 'no relevant content' should not be placed in the eCTD structure, as these would create a document lifecycle for non-existent documents and unnecessary complication and maintenance of the eCTD.

Q2. How is the metadata provided with the eCTD dossier used by EMEA and NCAs?

The leaf attribute metadata provided by the applicant is considered important to EMEA and NCAs, since this information is displayed by review tools and is used for identifying documents and sections, and becomes particularly important in managing the lifecycle of the submission.
For example, the ICH eCTD Specification, v3.2 describes 6 eCTD Heading Element Attributes for use in the eCTD to structure the eCTD content. Five of these attributes are in Module 3:

- Substance
- Drug Product/Drug Substance Manufacturer
- Product Name
- Dosage Form
- Excipient

These attributes correspond to elements in the eCTD that may be repeated, and are used to define specifically what each repeated section covers.
For example, in an eCTD covering two active ingredient manufacturing sites, the directory structure for the eCTD may be broken into two paths which will contain documents for the different sites, and the XML will be similarly structured (see p6-11 of the ICH eCTD Specification, v3.2).
The extent to which a single eCTD can cover multiple substances, manufacturers, products and excipients, and the use of these attributes to describe what is being covered is largely left up to the applicant. Whilst this has the advantage of making the specification versatile and adaptable to a wide range of applications, it also means that eCTD can be structured in a number of different ways. These potential variations in structure and scope can affect the presentation of the dossier using eCTD review tools that 'read' the XML, and affect eCTD repositories that are used to store the eCTD files and directory structure.
In addition, the way an eCTD is structured will affect how the lifecycle of the eCTD can be managed over time, and therefore, the structure of the first eCTD for a product or product range needs careful consideration. For example, if an eCTD is built to cover 100mg and 200mg tablets, and common documents are submitted for both strengths, if a line extension is introduced to add a 150mg tablet, then the applicant needs to decide whether to replace 100/200mg documents with a 100/150/200mg document, or to create a new standalone 150mg document and introduce another 32p and 23p section to the existing eCTD. Another option would be to build an entirely different and new eCTD for the 150mg tablets.

Guidance is currently being developed on specific use of attributes and structure of the eCTD, particularly in M3, and whilst this guidance is under development, EMEA should be contacted in relation to specific queries and advice.

Q3. Does EMEA have any general guidance regarding how hyperlinks should be used within the eCTD?

In general, hypertext links are encouraged within the eCTD to facilitate swift navigation around the dossier, but should not be overused. The eCTD should be structured and links provided in such a way as to ensure that the reviewer is constantly aware of the overall structure and narrative flow of the dossier. For example, Module 3 is highly structured and defined to a relatively low level of granularity in the specification. Therefore, only minimal use of hyperlinks should be necessary.
For example, when the same citation appears on a page more than once, it is recommended that a link only to the first instance of the citation per page is provided.

The greater the number of hyperlinks contained in an eCTD dossier, the longer it takes to technically validate the submission, and the greater the likelihood of non-functioning hyperlinks. The use of 'obvious' and therefore redundant external links is discouraged with a view to future lifecycle management. Note that assessors are familiar with the structure of the eCTD and can therefore also navigate using the ToC created for a submission or assembled during the current and cumulative view on an eCTD.

However, if hyperlinks are only to be included where considered necessary and considered to add real value, it is important that the way in which the eCTD titles (i.e. the backbone entries visible as the eCTD "TOC") are used is consistent with how the documents themselves are referred to within other documents, for example summary documents. If the title presented by the review tool in the eCTD TOC and the reference in a summary document do not match, then this negates the use of the backbone and a hyperlink is needed.

For Non-clinical/Clinical, there is a less defined structure within Modules 4 and 5 and the placement of studies and their names may vary across submissions, meaning that a larger amount of linking from summaries is of benefit. Furthermore, changes will occur less frequently to already-submitted content in Modules 4 and 5 vs Modules 3 and the issue of broken links over the application lifecycle is therefore less critical.

Q4. How should the Day 121 Response to Questions be formatted using the eCTD Structure?

The eCTD structure can be used to accommodate the responses to the List of Questions in the following way (as per the Notice to Applicants guidance:
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/ctd_06-2006.pdf page 36) :

- A document which lists all the questions with the corresponding narrative text response for each question should be placed in the 'Responses to Questions' section of M1.
- Where responses also contain new or updated data/documents relating to Modules 3, 4 and/or 5, such data/documents should be placed in the relevant sections of those Modules. This may also apply to Module 1 (e.g. revised product information), as well as to Module 2 in cases where extensive data/documents would require inclusion of the relevant summaries and/or overview sections.
- Where new or updated documents are required, hyperlink(s) from an appropriate location(s) in the consolidated Q&A document to the new or updated document(s) elsewhere in the eCTD dossier should be included.

Q5. What happens if the EMEA receives an STF file? Is it a requirement for study reports to be organized using node extensions for the EU?

Whilst the Study Tagging File (STF is a requirement in the US, it is NOT a requirement, nor is it encouraged, in the EU). EMEA will accept the STF file if included in an eCTD dossier (i.e. the submission would not be rejected), but we would *highly recommend* that node extensions are used instead for EU to organise the study reports.

CONVERSION OF EXISTING APPLICATIONS TO eCTD

Q1. After 1st July 2009 when a MAH will be encouraged to start using the eCTD format for post-authorisation submissions, is it necessary to submit a full, reformatted eCTD for already authorised products?

No, there is no obligation to submit a full, reformatted eCTD for already authorised products.

However, if Marketing Authorisation Holders wish, they may provide the EMEA with information reformatted as eCTD for their already authorised products. In this case the same principles as when changing from the 'old' EU-format (NTA, Volume 2B, 1998) into the new EU-CTD-format (NTA, Volume 2B, 2001) will apply. Reference is made to the "Questions and Answers on the Presentation and Content of the Common Technical Document (CTD)", published on the European Commission website (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2b).

In particular, EMEA would encourage the submission of reformatted quality information in eCTD, in order to facilitate the handling of variations and line extensions. The eCTD submission should include the complete Quality part, including any ASMFs (if applicable). A signed declaration from the MAH must also be submitted as an annex to the Cover Letter stating that the content/data of the submitted Quality Module in eCTD format is identical to the currently approved Quality part and that there have been no changes to the dossier content as a result of the provision of an eCTD submission.

The submission of reformatted documentation (commonly referred to as a *'baseline'* submission, although the corresponding eCTD DTD submission type value for such a submission with re-formatted information is '*reformat*') should preferably occur simultaneously (but separately) with the submission of a variation, line-extension or renewal. A clear distinction between the reformatted (unchanged) information and the documentation supporting the simultaneously submitted variation / line extension or renewal should be made. Further details are provided in the response to Q2 below.

Although it is expected that, in the majority of cases, an eCTD 'baseline' submission will be provided as a sequence 0000 for a product where there has been no previous eCTD submission for a product with an ongoing lifecycle, EMEA would also exceptionally accept a 'mid-lifecycle baseline' if appropriate (e.g. if an applicant has already started to use eCTD mid-lifecycle for a product without first submitting a 'baseline', but would at a later stage like to provide a full module 3 baseline).

Q2. How should reformatted information in eCTD format be submitted to EMEA, if the MAH chooses to provide this information along with a post-authorisation application?

The submission of reformatted documentation (*baseline*) should preferably occur simultaneously (but separately) with the submission of a variation, line-extension or renewal. A clear distinction between the reformatted (unchanged) information and the documentation supporting the simultaneously submitted variation / line extension or renewal should be made.

The MAH should provide a 'baseline' sequence 0000 with the reformatted approved information. The Cover Letter should clearly indicate that the submission does not form part of an application procedure as such and is not for review, but is merely provided as an eCTD 'baseline' and an aid to lifecycle management. The envelope element 'submission type' chosen for this reformatted submission should be '**reformat**' (available in current EU M1 v1.3), and the envelope element 'application number' should contain the application number of the initial MAA. The 'submission description' envelope element should be used to clearly indicate the baseline nature of the submission.

The variation, line extension or renewal application information should be sent as an eCTD sequence 0001, with envelope metadata appropriate to the type of submission, and all new or updated files required for the submission.

For a 'mid lifecycle baseline' submission (see Q1 above) the appropriate sequence number should be used in accordance with the ongoing lifecycle.

Q3. Can an MAH change to the eCTD format in the middle of an initial application procedure?

Yes, although this is not generally encouraged – applicants are advised to start an application in eCTD format rather than switch formats mid-procedure.
If a switch is made mid procedure, a clock stop period should be used for the conversion and the main principles detailed in Q1 and Q2 above apply.

If your questions are not adequately addressed by this document, please forward your query or comment to **eCTD@emea.europa.eu.**

Document Revision History:

Version	Date	Details
0.1	November 2007	Intial Draft
0.2	January 2008	Comments from EMEA Business Team
0.3	June 2008	Comments after public consultation
0.4	July 2008	Further minor amendments following EFPIA comments on v0.3
0.5	December 2008	Further minor amendments following EMEA internal review, and increased experience with eCTD.