Electronic Submission and the MRP/DCP: How to Compile a Dossier That Will be Accepted at the European Agencies

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vorgelegt von
Dr. Ludger Benning
aus Soest (West.)

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Erster Referent: Dr. Peter Bachmann (Betreuer)

Zweiter Referent: Dr. Christa Wirthumer-Hoche

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General Information

The results of this thesis are based on the legal framework of the 2004 review of the pharmaceutical legislation in the EU, i.e. Directive 2004/27/EC amending Directive 2001/83/EC [1] and Regulation (EC) 726/2004 [2] replacing Regulation (EC) 2309/93; in the following called the new pharmaceutical legislation or 2004 review.

List of Abbreviations

AFSSPS	Agence francaise de securite sanitaire des produits de sante (NCA France)
AR	Assessment Report
CTD	Common Technical Document
CBER	Center for Biologics Evaluation and Research (FDA)
CDER	Center for Biologics Evaluation and Research (FDA)
CMD(h)	Co-ordination Group for the Mutual Recognition and Decentralised Procedures – human
CHMP	Committee for Medicinal Products for Human Use
CMS	Concerned Member States
CP	Centralised Procedure
DMA	Danish Medicines Agency (NCA Denmark)
DGMP	Directorate-General for Medicinal Products (NCA Belgium)
DCP	Decentralised Procedure
DTD	Document Type Definition
eAF	electronic Application Form
eCTD	electronic Common Technical Document
EMEA	European Medicines Agency
ESTRI	Electronic Standards for the Transfer of Regulatory Information
ETICS	eCTD Tool Interoperability and Compliance Study
EU	European Union
FDA	Food and Drug Administration (NCA USA)
ICH	International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISE	Integrated Summary of Efficacy
ISO	International Organisation for Standardisation
ISS	Integrated Summary of Safety
MAA	Marketing Authorisation Application
MEB	Medicines Evaluation Board (NCA Netherlands)
MHRA	Medicines and Healthcare products Regulatory Agency (NCA UK)
MPA	Medical Product Agency (NCA Sweden)
MRP	Mutual Recognition Procedure
NCA	National Competent Authority
NoMA	Norwegian Medicines Ageny (NCA Norway)
NDA	New Drug Application

NEES	Non eCTD Electronic Submission
PIM	Product Information Management
RMS	Reference Member State
RPS	Regulated Product Submission
SmPC	Summary of Products Characteristics
SPL	Structured Product Labelling
STF	Study Tagging File
XML	Extensible Markup Language

Summary

In keeping with efforts to rationalise and harmonise the regulations of medicinal products the ICH has developed standardised specifications for the Common Technical Document (CTD) and its electronic version the eCTD. The eCTD standard describes a message format and protocol for transferring submission documents and processing instructions to an agency system. The eCTD standard provides a mechanism to record all interaction between industry and agencies in a way that highlights changes between multiple submissions. This lifecycle view of the submission is achieved through the use of the so called XML format. The XML format describes each document in the submission. Additionally, it provides instructions to the receiving system allowing the management of data, which describe the submission. Based on the XML format additional specifications have been developed by various regions for content within the eCTD standard. Often these replace unstructured document files (e.g. –pdf, -doc, -rtf) with highly structured XML documents exemplified by the FDA's Study Tagging File or Europe`s electronic Application Form as well as labelling initiatives such as the FDA's Structured Product Labelling and EMEA's Product Information Management. This trend can be seen as the continuous extension of the eCTD standard making the submitted information more granular and more manageable by automated systems. This generally improves the quality and efficiency of the regulatory review process.

The eCTD standard is now in Step 5 of the ICH process – implementation by the national competent authorities. The Member States are progressing with implementation of the eCTD standard at quite different rates. Therefore, eCTD readiness and experience to date varies dramatically from country to country within the EU. Only a minority of European national competent authorities already accept or plan to accept electronic-only submission of marketing authorisation applications by the end of 2008. In contrast, the majority of the national competent authorities still require paper based dossiers due to national archival law or due to the fact that the necessary electronic work flows are not in place. As per November 2007, 23 Member States still need to implement legally binding requirements completely covering electronic-only submission of marketing authorisation applications of all types - initial, variation and renewal, so that no additional paper copies are needed.

Nevertheless, more and more Member States are moving towards the eCTD standard. Full adoption of the eCTD standard is targeted by the end of year 2009. Unfortunately, some national competent authorities have followed an aggressive e-submission/eCTD implementation schedule and have already succeeded in having legislation changed to permit electronic-only submissions. However, these are not necessarily eCTDs. Currently, electronic submission based on the eCTD standards represents only a minor fraction of all electronic submissions within the EU. As a detour to the eCTD standard, national competent authorities such as MHRA (UK) and DGMP (Belgium) have implemented various national requirements representing no standard, but in fact individual procedures and acceptance criteria resulting from their bespoke e-submission process-

ing system that accepts a variety of electronic submission types. Therefore, submitting and managing an eCTD - especially in support of marketing authorisation applications following the MRP or DCP – might be a regulatory minefield. To successfully navigate these waters applicants need to know what the eCTD standard is capable of providing, how sequences should be related, how much hypertext linking is desirable, and when to replace, delete, append and submit new files. In this connection it should be noted that harmonised best practice guidance on how to do eCTDs for MRP/DCP submissions is currently under development.

Due to the flexibility of the EU Module 1 specification all administrative and prescribing information that is common to all Member States can be submitted to all Concerned Member States and the Reference Member State within one sequence. Also all country specific information of Module 1 including “additional data” can be incorporated in one single sequence for all Member States. On the other hand, the current version of the eCTD standard is not able to provide:

- Communication from applicant to the NCA and vice versa,
- Implementation of country specific information in Module 2-5,
- Reuse of different parts of documentation across sequences in consideration of lifecycle meta data.

The solution for these shortcomings of the eCTD standard might be the new standard for electronic submission called Regulated Product Submission. The Regulated Product Submission standard is the American answer to European eCTD. It has been initiated by Health Level Seven – a standard organisation similar to the International Organisation for Standardisation. The Regulated Product Submission standard creates a regulated product submission message based on XML including meta data, which is general enough to handle all regulated products and which contains enough information to allow regulators to support structured review. It is intended that the Regulated Product Submission standard will be used worldwide for regulated products, including but not limited to foods, medical devices, human and veterinary medicinal products. The Regulated Product Submission standard allows for document lifecycle, reuse of documents across applications, product/submission management, submission lifecycle, computer aided review, visibility into product/submission, and regional/product differences. Therefore, the Regulated Product Submission standard might overcome the difficulties especially in support of marketing authorisation applications following the MRP or DCP in Europe based on the current eCTD standard.

All in all, electronic submission standards in the pharmaceutical industry have made significant progress in the last few years, with both industry and regulatory bodies acknowledging the benefits. It can only be anticipated that these standards will continue to evolve and new standards will be proposed. Nevertheless, any standard should be designed with one ultimate goal – providing safe and effective healthcare to patients.

1. Introduction

Since 1990, the International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has been working to create a standardised framework for drug registrations. The aim of this standardised framework is to harmonise, as far possible, the structure and content of the technical information submitted in support of marketing authorisations. The ICH has been driven by representatives of three regions Japan, the EU, and the US –and several other countries working as observers. In November 2000 the ICH Steering Committee ratified guidelines developed by the ICH M4 working group describing the Common Technical Document (CTD) for the registration of pharmaceuticals for human use. This meant the CTD as paper version has achieved Step 4 status, signifying that consensus has been reached by the ICH member parties and that each party commits to incorporate the ICH guidelines into each region's own regulatory framework. Completion of this final step is known as Step 5. In the case of the US the FDA has formally adopted the ICH guidelines as FDA guidance. In Europe, Volume 2B of Notice of Applicants was revised in July 2001 to accommodate the CTD within the European legislative system. As of July 2003 it became mandatory for applicants to submit dossiers in the EU and Japan using the new CTD paper format. It is also the recommended paper format in the US.

Beginning in the mid 1980s and progressing to the mid 1990s, there were a number of regional efforts to create an e-submission/e-review standard including e.g. CANDA[1] (USA), DAMOS[2] (Germany), SEDAMM[3] (France), and eNDA[4] (US). More recently, as a result of the harmonised structure and content of the CTD paper format within the ICH regions, momentum has been building on the electronic submission front. The ICH M2 ESTRI (Electronic Standards for the Transfer of Regulatory Information) working group developed the electronic message exchange standard for CTD called electronic Common Technical Document (eCTD). The eCTD is the electronic version of the paper-based CTD. The eCTD specification lists the criteria to consider an electronic submission as technically acceptable. Furthermore, the eCTD standard describes the means to create and transport an electronic submission that meets the definitions of the CTD – its focus is to provide the ability to transfer the CTD from industry to a regulatory authority. At the same time the eCTD takes into consideration the need to help throughout the lifecycle of an electronic submission or dossier. The eCTD standard based on the initial specification version 3.0 reached Step 4 in October 2002, and is now being implemented regionally, taking it to Step 5.

For the first time in 22 years of standards development, there is one standard for submission content and one standard for the electronic submission of that content for all of Europe, Japan, US and Canada. Nevertheless, there were significant misinterpreta-

[1] Computer Assisted New Drug Application
[2] Drug Application Methodology with Optical Storage
[3] Soumission Electronique des Dossiers d'Autorisation de Mise sur le Marché
[4] Electronic New Drug Application

tions of the eCTD specification by tool developers and pharmaceutical companies. Therefore the M2 ESTRI working group has taken two significant steps to address this issue:

1. The list of 23 criteria for a technically sound eCTD known as Q&A #36 was published in May 2005 on the ICH / ESTRI web site.
2. In November 2005, the M2 group formed a sub-group, which then undertook an extensive project to test eCTD tool interoperability and compliance. This project is known as the eCTD Tool Interoperability and Compliance Study (ETICS).

As per February 2007 the FDA received 7000 eCTD sequences almost representing 600 applications (CBER and CDER) [3]. The FDA will withdraw the eNDA standard at the end of 2007 [4]. Therefore, the only options for the submission of a New Drug Application (NDA) will be the eCTD standard or paper based on the CTD standard. Elimination of the paper submission option requires a legislative change, which is to date not implemented, but the submission based on the eCTD standard is strongly preferred. Japan is currently accepting paper CTD submissions and has its own unique requirements for a cumulative XML backbone. Very few eCTD submissions have been provided to the Japanese authority to date. At the EMEA 99 % of all new submissions are based on an electronic format plus one paper version. But the electronic format is not necessarily based on the eCTD standard. As per January 2007 the EMEA received 280 eCTD sequences within the framework of the Centralized Procedure (CP) representing 60 applications. While very few eCTDs have been rejected due to technical compliance issues, non-critical issues have been reported with 95% of first submissions received [5]. The EMEA is still developing its eCTD validation policy. It is intended that a new validation and review system will be operational in year 2007. Although a paper version of the dossier is still required and the submission of a dossier based on the eCTD standard is only an option, there is a very strong preference for an eCTD [6]. So the EMEA accepts an eCTD with accompanying paper for Module 1 and Module 2. Acceptance of submissions based on the eCTD standard was originally scheduled for February 2008 [7]. Currently, the EMEA plans to issue a statement of intent that from July 2008 it will be possible to submit electronic-only without paper [18]. Electronic-only submission will be a requirement from January 2009. Furthermore electronic submission based on eCTD standard will be a requirement for the CP from July 2009 [23]. In contrast to the EMEA the European agencies are currently in the process of determining their technical strategy that will enable them to accept eCTD. But mandatory paper versions based on the CTD standard are still expected to be provided until the individual authorities have revised their legal requirements removing the paper version as the dossier of record. The current target time period for accepting only eCTD submissions is the end of year 2009 in Europe.

This thesis is to present the current implementation status at the different national competent authorities in the European Union (EU) in relation to their ability to process

electronic dossiers. Furthermore, this thesis will focus on issues of the compilation of electronic dossiers based on the eCTD standard in support of the Mutual Recognition Procedure (MRP) and Decentralized Procedure (DCP). Conclusions and recommendations addressing applicants in general intending to submit electronic dossiers should be developed. A short introduction into the basics of electronic submission will assist the reader in fully comprehending some of the terminology used in this thesis.

2. Legal Framework of National Procedures (EU)

Within the legal framework of the 2004 review of the pharmaceutical legislation in the EU two national marketing authorization procedures are described: the MRP and the DCP. A marketing authorization granted in accordance with the mutual recognition or decentralised procedure will have harmonised content of Summary of Products Characteristics (SmPC), package leaflet (PL) and labelling. As some national requirements for the outer packaging still remain, a “Blue Box” already known from the CP was implemented. The process for the harmonisation of the SmPC is formalised and the arbitration decision making process is simplified and accelerated along the lines described for the CP. A co-ordination group Mutual Recognition and Decentralised Procedures - human (CMD(h)) was established, and a legal framework was implemented describing the duties and responsibilities of this co-ordination group. Applicants can withdraw applications submitted via the DCP or MRP from one or more Member States at any point in time during the procedure. However, a withdrawal of the application in the disagreeing Member States during the period of assessment phase II in the DCP, or at any time during the period of the European Mutual Recognition phase of the MRP will not prevent the points of disagreement, if based on a potential serious risk to public health, from being referred to the CMD(h).

2.1 Scope of Mutual Recognition Procedure

The 2004 review of the pharmaceutical legislation stipulates that a national marketing authorisation should be recognised via the MRP if a national marketing authorisation was already granted by a Member State’s competent authority (Art. 28, Sec. 2 of Directive 2001/83/EC as amended). If this requirement is fulfilled and the marketing authorisation holder intends to market the medicinal product in more than one Member State, the marketing authorisation holder requests the Reference Member State (RMS) to prepare an assessment report (AR) on the medicinal product or, if necessary, to update any existing assessment report. The assessment report together with the approved SmPC, labelling and PL will then be sent to the Concerned Member States (CMSs) and to the applicant.

Under this procedure an existing marketing authorisation is extended to other Member States thanks to the system of mutual recognition. The aim of this procedure is the mutual recognition of national approvals. This procedure is valid for all other medicinal

products not listed in the Annex and for those medicinal products described in Art. 3 Sec. 2 of Regulation (EC) 726/2004. The Mutual Recognition Procedure starts on a national level, but the approval process will be extended on a European Level represented by all CMSs involved. Any appeal will be automatically referred to the CMD(h) or the Committee for Medicinal Products for Human Use (CMHP) located at the EMEA. Decisions by the EMEA as appeal authority have binding character. The following flowchart gives a rough overview on the whole Mutual Recognition Procedure especially in terms of timing. For more details, please refer to the corresponding guidelines.

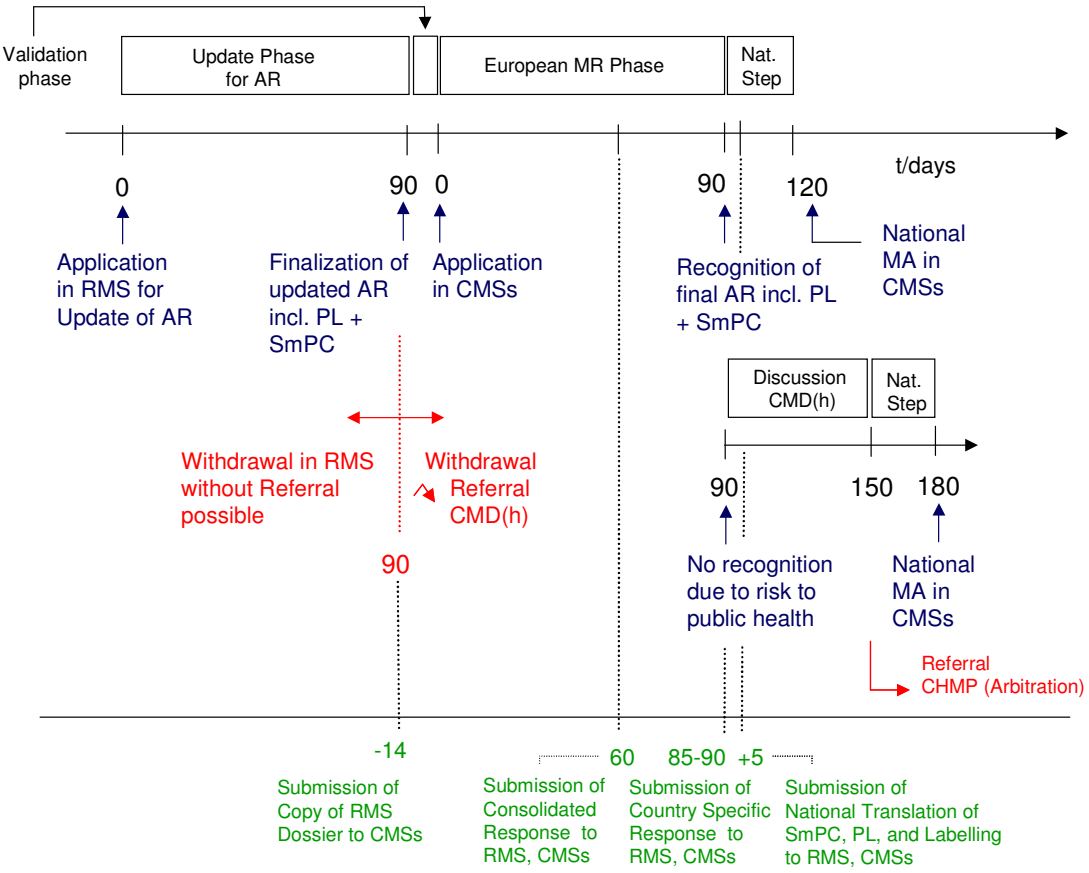


Figure 1: Flow-Chart of the Mutual Recognition Procedure.
Based on “Best Practice Guide for the Decentralised and Mutual Recognition Procedure” [8],”NtA Volume 2A Procedures for marketing authorisation Chapter 2 Mutual Recognition” [20], Art. 28, Sec. 1-2, 4-5, and Art. 29, Sec. 1-6 of Directive 2001/83/EC as amended.

The primary objective of the MRP is to avoid unnecessary duplicate efforts during assessment of a marketing authorisation. In accordance with Art. 17, Sec. 2 of Directive 2001/83/EC as amended Member States are obliged to decline the assessment of a

national application, if the application is already under review of another Member State and must advise the applicant that the MRP has to be applied.

2.2 Scope of Decentralised Procedure

The flow chart within figure 2 gives a rough overview about the whole Decentralised Procedure especially in terms of timing. For more details, please refer to the corresponding guidelines.

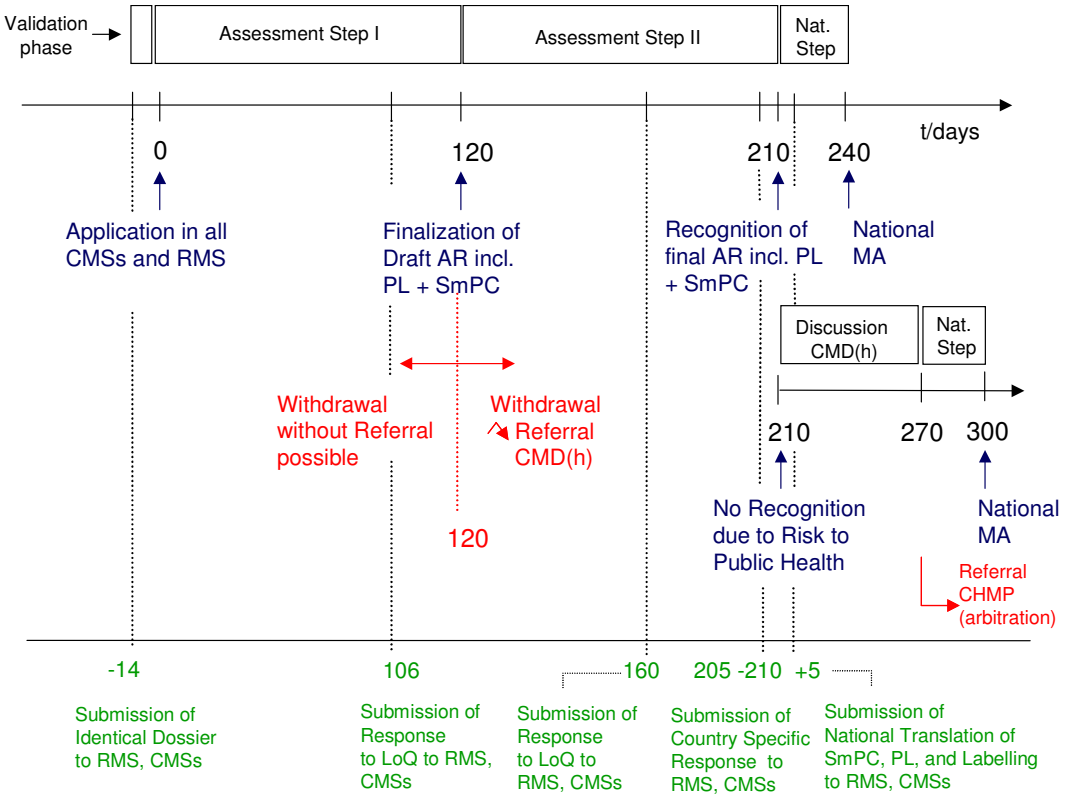


Figure 2: Flow-Chart of the Decentralised Procedure.
Based on “Best Practise Guide for the Decentralised and Mutual Recognition Procedure” [8], “NtA Volume 2A Procedures for marketing authorisation Chapter 2 Mutual Recognition” [20], Art. 28 Sec. 1, 3-5, and Art. 29 Sec. 1-6 of Directive 2001/83/EC as amended.

In contrast to the MRP the DCP applies to medicinal products which were not previously authorised in any Member State (Art. 28 Sec.3 of Directive 2001/83/EC as amended). Furthermore, if the applicant intends to market the medicinal products in more than one Member State in which the medicinal product has not received a marketing authorisation at the time of application, the new pharmaceutical legislative stipulates that the applicant shall simultaneously submit an identical dossier to the RMS and

the CMSs. The RMS is then requested to prepare a draft of the assessment report, SmPC, PL, and labelling after receipt of a valid application.

Under this procedure the marketing authorisation is obtained from each Member State. The aim is a concertation procedure between different Member States before the first marketing authorisation is granted. The Decentralised Procedure is also valid for all other medicinal products not listed in the Annex and for those medicinal products described in Art.3 Sec.2 of Regulation (EC) 726/2004. But, in contrast to the Mutual Recognition Procedure this procedure is only applicable when no marketing authorisation is granted in the EU. Furthermore, Member States have to reject an application for the DCP if a marketing authorisation of a medicinal product already exists in another Member State. The applicant will be forced to submit a new application for the MRP (Art.18 of Directive 2001/83/EC as amended). Similarly to the Mutual Recognition Procedure any appeal will be automatically referred on an European level organised either by the CMD(h) or the CMHP. But the EMEA only has the function of an appeal authority within the Decentralised Procedure.

3. Basics of Electronic Submission

The eCTD specification describes a message format and protocol for transferring submission documents and processing instructions to an agency system. The eCTD standard provides a mechanism to record all interaction between industry and agencies in a way that highlights changes between multiple submissions. This lifecycle view of the submission is achieved through the use of the so called XML format. The XML format describes each document in the submission. Additionally, it provides instructions to the receiving system allowing the management of data, which describe the submission. These data are known as meta data, and examples at the submission level include information about kind of submission, the receiving agency, and the submitting applicants. Examples of meta data at the document level include version information, language, descriptive information such as document names and timestamps. Overall, XML's ability to separate content from structure is the key to its versatility and growing popularity. Its uses are many, allowing users to reformat and restyle for different media, identify components, interchange data, reuse parts, and maintain and output multiple versions of the same document.

As a consequence, additional specifications have been developed by various regions based on the XML format for content within the eCTD standard. Often these replace unstructured document files (e.g. –pdf, -doc, -rtf) with highly structured XML documents exemplified by the FDA's Study Tagging File (STF) or Europe`s electronic Application Form (eAF) as well as labelling initiatives such as the FDA's Structured Product Labelling (SPL) and EMEA's Product Information Management (PIM). This trend can be seen as the continuous extension of the eCTD standard making the submitted informa-

tion more granular and more manageable by automated systems. This generally improves the quality and efficiency of the regulatory review process.

3.1 NEES versus eCTD

In the past, applicants had three choices when submitting a marketing application electronically to a competent authority such as the FDA:

1. Use the eNDA/eANDA format,
2. use what is called a ‘‘hybrid’’ submission[5], or
3. use the eCTD format.

The first and second one are known as non-eCTD Electronic Submissions (NEESs) representing rather a national requirement than an internationally accepted standard. The different national NEES requirements are not normally based on the XML format. They use granular pdf files, CTD folder structure as well as naming conventions, and electronic navigation by means of hyperlinks or bookmarks defined by country specific guidelines.

The eCTD standard sets itself apart technically from the different national NEES requirements in that the submission’s table of contents is no longer submitted as a pdf-file. Based on the eCTD standard, reviewers and submitters are able to easily browse submissions using a common web browser. Dossiers can be viewed comprehensively with each amendment layered against the original submission rendering the lifecycle and documentation of a product as it changes over time in an easily viewable and understandable format. Specifically, using the XML format allows an applicant to update the application’s table of contents automatically as new amendments are filed so that sponsors and reviewers can have access to a real-time, up-to-date, cumulative table of contents. This provides easy and immediate access to all files included in an application, regardless of when they were included or in what submission they are located. This type of flexibility and efficiency has never previously been possible at either the applicant or reviewer levels.

Applying the eCTD standard to the XML format also provides reusability of the applicant’s submission documents for different regional markets. Five core modules make up the submission, with the first module containing all of the region-specific documentation. Interchanging this first module with another agency’s module allows for efficient re-submission within different markets without having to change the documentation or meta data within the other four modules. Another advantage is that through the creative use of the XML meta data, the table of contents can be displayed in various ways, allowing for discipline-specific views of an application (e.g., Chemistry vs. Clinical), cumulative lifecycle views showing all documents and their current state, submission-

[5] Hybrids are based on the older eNDA format with the table of contents organized using the newer CTD headings.

specific views displaying only the delta between submissions, module-specific views, etc., all further particulars promoting review and assembly efficiency.

3.2 XML Essentials

The eCTD standard is based on the XML (Extensible Markup Language) – an enabling technology and a thriving open standard of the World Wide Web Consortium (W3C). In some ways it is incredibly simple and straightforward – yet at the same time it is very powerful. In its simplest form, it encapsulates and organizes readable text based information using tags. Such a tagged text file is considered “well-formed” if the tags follow the rules of XML. The following well-formed XML fragment demonstrates the submission of chapter 3.2 of the thesis as a single pdf document.

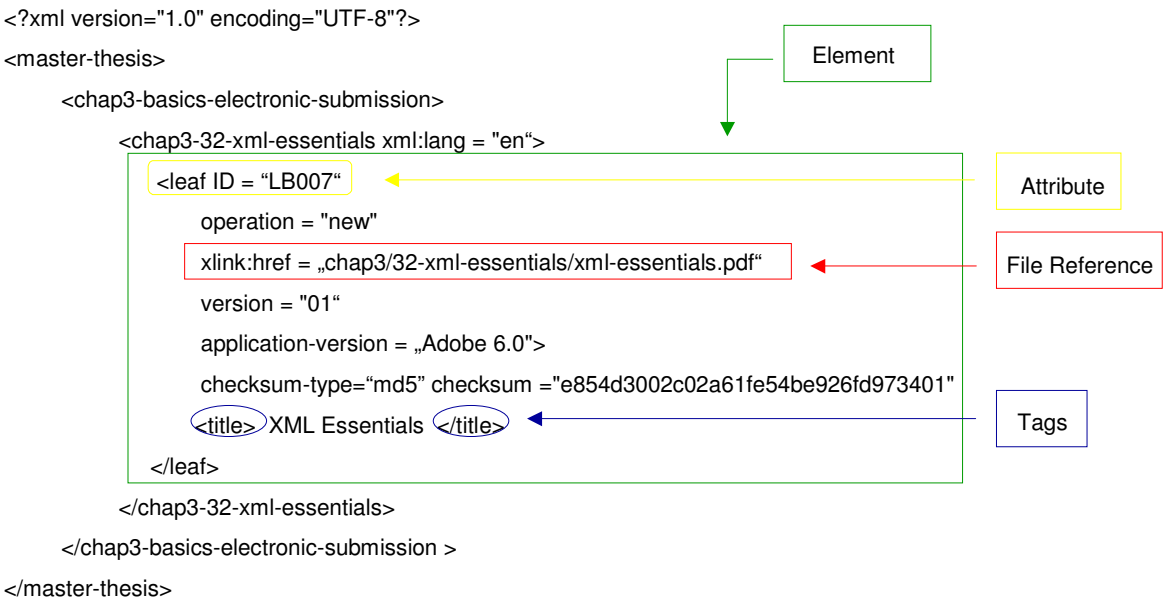


Figure 3: Example of a well-formed XML fragment.
Based on ICH eCTD Specification Version 3.2, February 2004 [9].

In the example above, a <leaf> element underneath the <chap3-32-xml-essentials > tag was created. Each element must have a beginning and ending tag (e.g. <title> and </title>) to be considered well formed. The relative location and file name of the pdf file containing the content of chapter 3.2 was provided in the “xlink:href” attribute of the <leaf> element. Additional information based on appropriate attributes of the <leaf> element such as the “ID”, “operation”, “version”, “application version”, “checksum-type”, and “checksum “ was also included. Finally, a descriptive title “XML Essentials” of chapter 3.2 in the <title> sub element of the <leaf> element was provided. According to

a separate file organization table which covers files that constitute the backbone itself plus necessary additional files to make the submission complete, readable and processable, the numbering and title of the tag <chap3-basics-electronic-submission>and the numbering and title of the tag <chap3-32-xml-essentials > is clearly defined. Based on this given information the following can be concluded from this XML fragment:

- This submission includes the file “xml-essentials.pdf” in the relative directory “chap3/32-xml-essentials”.
- The file representing version “01” is new and can be clearly identified by its ID “LB007”.
- Any modification of the pdf file during review or submission can be identified by the value of MD5 checksum “e854d3002c02a61fe54be926fd973401”.
- The primary language used by the file in this entire section of the submission is “English”.
- The version of the software application that was used to create this file was “Adobe 6.0”.
- The numbering and title of this section is “3.2 XML Essentials”

It should be noted that this XML example does not necessarily contain all of the elements and attributes that should be used when preparing an eCTD submission. In addition to these simple formatting rules, Document Type Definition files (DTD) can be used to describe much more rigorous rules and complex structures. An XML file, which is created in accordance with a DTD, is known as an XML instance.

The Module 2 - 5 architecture can be found in figure 4 comprising a directory structure and a XML instance with leaves. The ICH eCTD specification describing Module 2 – 5 includes a DTD file. This eCTD DTD defines an XML instance named “index.xml”, known in ICH terms as the backbone[6] of the eCTD that is located in the sequence folder. The EU Module 1 architecture is similar to that of Modules 2 to 5, comprising also a directory structure within a subfolder of Module 1 and an additional backbone with leaves. This regional backbone must be a valid XML file according to the EU regional DTD. The regional backbone represented by the eu-regional.xml file contains meta data for the leaves, including pointers to the files in the directory structure. In addition, the EU regional DTD defines meta data at the submission level in the form of an envelope. Therefore, the root element of the regional backbone contains two elements: “eu-envelope” and “m1-eu”. The EU leaf element is identical to the leaf element described in the ICH eCTD DTD. Based on this regional backbone, region-specific information that is common to all submissions in the different Member States can be submitted to a regulatory authority. However, at the same time the EU Module 1 specification allows for country specific information to be included in Module 1, if required. Country specific information could relate to the details of the business process applied

[6] Common name given to XML instance that describes files and meta data in one eCTD submission.

(e.g. specifying the number and names of those parts for which a paper copy is still requested) and local preferences for file formats or documents (“Additional Data”).

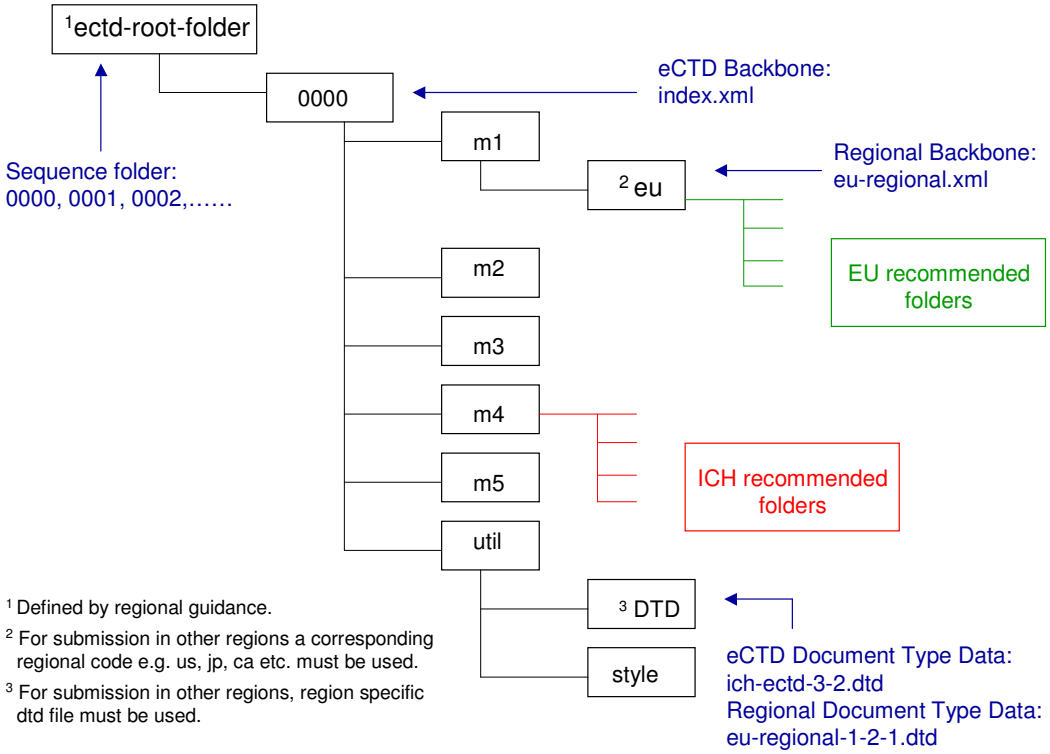


Figure 4: eCTD architecture Module 1-5.
Based on ICH eCTD Specification Version 3.2, February 2004 [9] and EU Module 1 Specification Version 1.2.1, October 2006 [10].

As a result each eCTD submission is comprised of the ICH backbone and the regional backbone as well as related content files located in the corresponding subfolders of Module 1 - 5. Most of these content files are requested as files in pdf format. Backbones and content files are submitted to the competent authority as a submission sequence. The sequence is a 4 digit number with leading zeros, beginning at “0000”. The original submission and subsequent amendments and variations should use the same ectd-root-folder name. Submissions will be differentiated by subfolders named according to the sequence number (“0000”, “0001”, “0002”…etc.) of the submission in that region. XML style sheets[7] can be used to render the XML content to various views, to permit viewing in a web browser. The eCTD specification includes a style sheet provided by the ICH M2 to permit simple viewing of a single eCTD sequence using a web browser.

[7] W3C specification related to the XML specification

XML files may be either well formed or valid. An important step before submission of an eCTD sequence is validation of XML content against the relevant DTD. The overall eCTD is described by the XML backbone in compliance with the ICH eCTD version 3.2 DTD. In the US, EU and Canada, Module1 is based on an XML backbone specified by regional DTDs. An XML instance may be checked for compliance using a "validating parser". Several eCTD tool vendors provide validating parsers embedded in their software applications. Most XML editors include validating parsers. However, validating the XML backbone of the eCTD using a parser, which does not validate the entire eCTD for compliance with specifications and regional requirements, is not sufficient. In a worst case it actually only "scratches the surface". In addition, not all parsers produce identical results.

3.3 Attribute "Operation"

The operation attribute is a key to managing each individual file[8] in a submission. The applicant uses the operation attribute to tell the regulatory authority how the applicant intends the files in the submission to be used. The operation attribute describes the relation between files in subsequent submissions during the lifecycle of a medicinal product. In the very first submission all the files will be "new". In the second, third, and subsequent submissions, all the newly submitted files can have different operation attributes due to having or not having a relation with previously submitted files. Possible values of the attribute operation are "new", "append", "replace" or "delete". Figure 5 describes the effect of the values "new", "delete" and "append" of the attribute "operation".

Within figure 5 the file (leaf) document drug-product-name.pdf was first submitted under node m3.2.p.1 in sequence 0000. It was then determined that it should have been submitted under node m2.3.p. It was sent again in sequence 0001 as a "new" document and a "delete" instruction was issued for the leaf under m3.2.p.1. In sequence 0002 the operation "append" is used. The file (leaf) introduction II.pdf is appended to the file (leaf) introduction I.pdf that was submitted in sequence 0000. The file (leaf) introduction II.pdf is actually "new" in sequence 0002 but it is to be considered by the reviewer together with introduction I.pdf (it is related) and therefore the "append" operation is used. This creates a parent/child pair of documents. The current view or net view shows only the documents/leafs to be considered for review. Documents/leaves, which have been "replaced", or "deleted" are not visible. A "replace" operation is equivalent to a "delete" and a "new" operation meaning that a new document is submitted and is intended to replace a previously submitted document underneath the same node.

One can imagine that after a series of such operations complex scenarios can occur and the view of the submission presented to the reviewer may not always be clear. For example, the current eCTD standard does not contain guidance on the intended status

[8] In this discussion, the terms "file" and "document" are used interchangeably. It must be remembered that a leaf references a file and a single file may have more than one leaf reference it.

of the child leaf if the parent leaf is subsequently “deleted” or “replaced” nor have agencies issued such guidance.

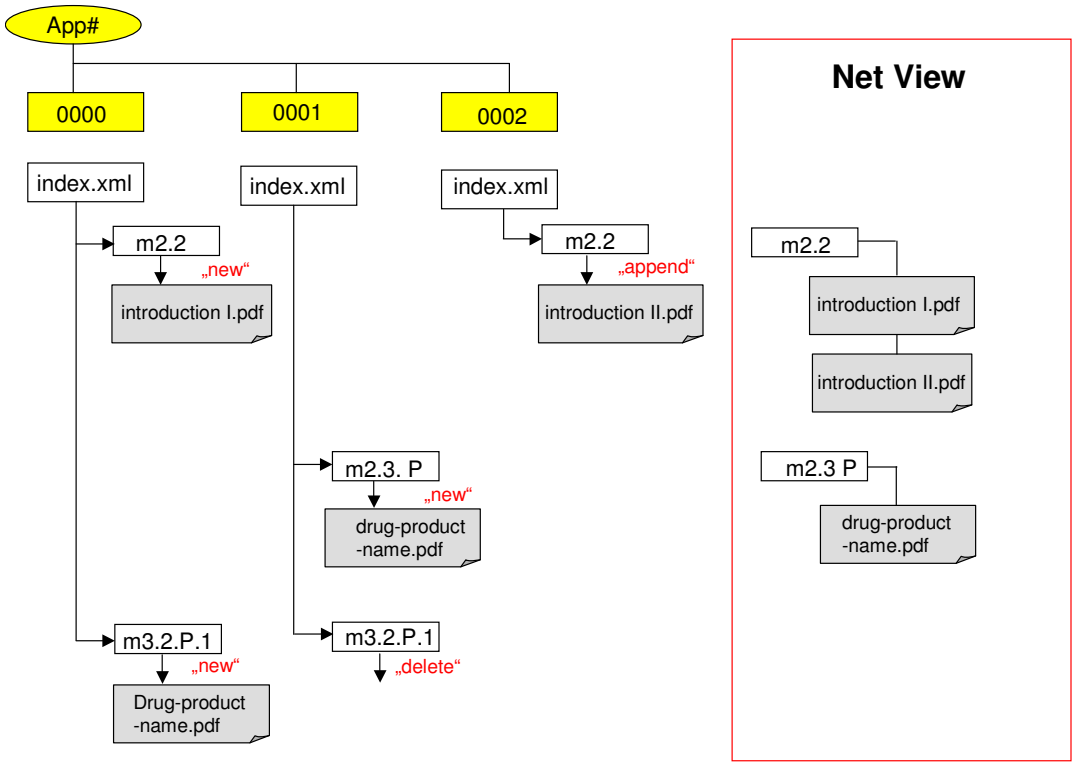


Figure 5: Meaning of the attribute values “new”, “delete” and “append”. Based on ICH eCTD Specification Version 3.2, February 2004 [9].

Currently, the FDA follows the explicit lifecycle model meaning that the delete operation on the parent leaf leaves the child leaf as a standalone file. If the submitter intended the child leaf to be deleted also, an explicit delete operation on the child leaf would be required. In contrast to the FDA the Canadian competent authority (Health Canada) follows the implicit lifecycle model. Therefore, the delete operation on the parent also removes the child leaf from the current view. The deletion of the child leaf is presumed to be implicit in the delete parent operation. Numerous other complex scenarios are possible and the outcomes at different agencies are different. But it should be noted that the EMEA has determined that it will follow the explicit lifecycle model and is currently reviewing this issue as part of the implementation of a new review tool. Health Canada is also reviewing this issue and believes that the explicit lifecycle model should be followed in the future.

4. eCTD Readiness at the National Competent Authorities

The eCTD readiness and experience to date varies dramatically from country to country within the EU. Complicating matters in the EU is the fact that there are 27 member states with a total of 31 National Competent Authorities (NCAs). In some cases, there are interim requirements in place, which follow the CTD table of contents but do not implement the XML backbone. In spite of this unharmonized situation among the European NCAs most marketing authorisation application (MAA) submissions (more than 90%) in Europe follow the national procedure and are submitted to a single NCA in the end [11]. Of these NCAs, several have followed an aggressive e-submission/eCTD implementation schedule and some have already succeeded in having legislation changed to permit “electronic-only” submissions. However, these are not necessarily eCTDs. In fact, electronic submission based on the eCTD standards represents only a minor fraction of all electronic submissions within the EU. The current situation on the electronic submission front can be found in figure 6.

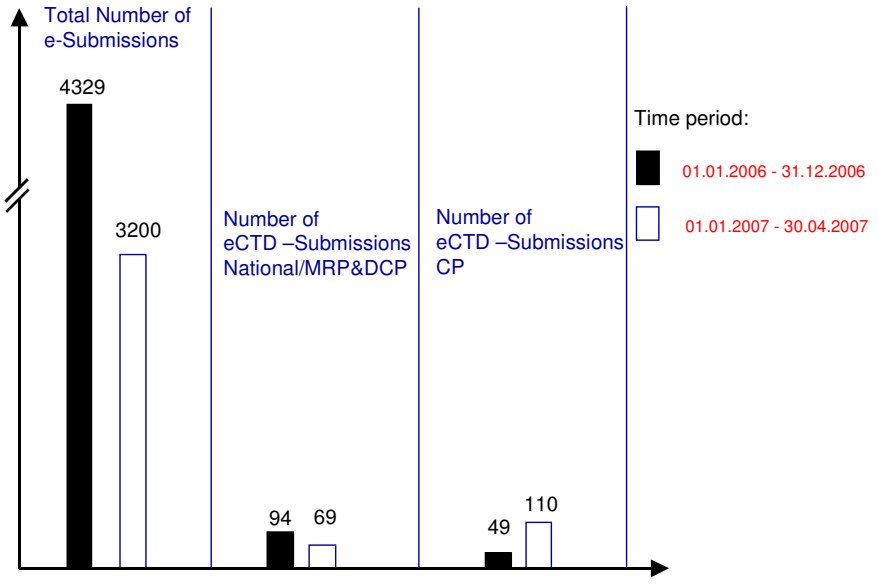


Figure 6: Survey of electronic submissions in the EU.
Number of submissions includes new applications and following submissions (variations, renewals, etc.) [13]

4.1 Comparison of Implementation Status

At the Reykiavik meeting in February 2005 the Heads of Medicines Agencies (HMA) adopted the end of 2009 as a target date for ICH`s eCTD implementation [12]. This means that by the end of 2009 all members of the European Regulatory Network will

be required to have the infrastructure and the processes in place to handle electronic submission of MAAs based on the eCTD standard without paper. Full adoption of eCTD is defined as follows:

- No requirement for any accompanying paper submission or paper archive copies,
- valid for all European procedures (CP, MRP/DCP, national procedures), and
- valid for all types of submissions (MAAs and renewals, Type IA/IB and Type II variations, responses, commitments)

However, full adoption does not imply that the electronic submission of a new dossier will be mandatory by the end of 2009 for all NCAs.

In the following paragraph the situation regarding the implementation status is described for all Member States. The evaluation of the implementation status is primarily based on all information which is currently available via the corresponding websites of all NCAs. Additionally, some of the following points were highlighted by representatives of the NCAs in various public meetings: For more details refer also to the corresponding electronic submission guidelines in the annex, if they are available.

Portugal:

- Since February 2005 the NCA Infarmed requests electronic-only submission of all national MAAs for new products. Several formats are accepted.

UK:

- Since August, 2005 the NCA Medicines and Healthcare products Regulatory agency (MHRA) accepts electronic submission of MAAs of all types - initial, variation and renewal, no additional paper copies are required.
- MHRA accepts both eCTDs and NEESs. In order to facilitate Industry's transition to eCTD, from March 2007 the MHRA accepts electronic submissions that are compliant with the eCTD folder structure and file naming conventions but which do not have the accompanying XML backbone.
- MHRA intends to make eCTD submission a national mandatory requirement. Targets for the eCTD compliance of all initial submissions (and subsequent changes) for new active substances by April 2008 and for all new applications by January 2009 have been set.
- Paper-only applications will not be accepted by the MHRA after December 2007 [14].

Belgium:

- Since October 2005 the NCA Directorate-General for Medicinal Products (DGMP) accepts electronic submission of all MAAs.

- Since January 2007 the eCTD standard (**full eCTD**) is the recommended format for new MAA`s. But other formats are also accepted:
    1. **Partial eCTD**: CTD structured dossier with an XML based application form. This is a hybrid format including CTD structured dossier, eAF, eCTD file naming, but no XML backbone.
    2. **Minimal eCTD** applicable only to renewals: This represents a NEES format including CTD structured dossier, eCTD file naming, eAF in word or pdf format, but no XML backbone.
- DGMP intends to mandate the eCTD standard for all submissions including MAAs and following submissions such as variations and renewals etc. in the future.

Netherlands:

- The NCA Medicines Evaluation Board (MEB) stated in March 2006 that paper copies are no longer a requirement.
- The MEB has a strong preference for the submission of electronic regulatory information for all types of submission ranging from new MAAs to PSURS, drug master files and variations. The following formats and timelines are describe in the current guideline dated March 2006:
    1. Full eCTD format based on a combination of CTD and XML/pdf.
    2. NEES format representing a combination of CTD and pdf. Navigation through such an electronic submission is based on electronic tables of content, bookmarks and hypertext links. This format will be accepted until January 2008. This period might be prolonged based on the status of electronic submissions at that time
    3. eMAA representing a combination of the old NtA format and pdf. Navigation is based on the same principle as described in point 2. This format will be accepted until January 2008.
- In July 2007 the MEB stated that from 01.01.2008 any information for a new application or for a change to an existing application made to the MEB is to be submitted by electronic means in the form required by the MEB. No reference is made in the regulation to a period of transition. As matters stand, the date mentioned for the mandatory submission of electronic files in ICH eCTD format, namely 01.01.2008, will be allowed to lapse. Other types of electronic forms of submission will also be accepted. In the near future the MEB will announce the specifications that will apply to them [19].

Norway:

- It is the intention of the Norwegian Medicines Agency (NoMA) to go fully electronic by the beginning of 2008.
- If possible, the NoMA is interested in receiving MAA's in eCTD format.
- Currently there is no guidance in place regarding submission of regulatory information.

Germany:

- Electronic submission of dossiers has been possible since 1999 based on different formats (DAMOS;eCTD, NEES) [23].
- The electronic submission by email of product information SmPC, PL (Module 1.3.1) and Quality Overall Summary, Non-Clinical and Clinical Overview (Module 2.3, 2.4, 2.5) is mandatory as defined in specific ordinance [15].
- Since April 2007 variations in national procedures as well as for the MRP and DCP can be submitted electronically using online forms at the online portal PharmNet.Bund. Upload of variation applications based on XML-format via the online portal is also possible (restricted size).
- The NCAs Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) und Paul-Ehrlich Institut (PEI) requires all applications submitted in paper format at least partly.
- Currently there is no guidance in place regarding electronic submission of regulatory information.

Sweden:

- Currently, the NCA MPA requires all applications submitted in paper format.
- The Swedish government has decided that all public authorities should be able to handle electronic originals by 2010. MPA intends to reach the goal by 2008.
- MPA strongly recommend eCTD format, but will most probably also accept a "standardised" format of NEES as electronic original by 2008, as a step towards full eCTD [16].
- Currently there is no guidance in place regarding electronic submission of regulatory information.

Denmark:

- In addition to the paper version of the dossier, the NCA Danish Medicines Agency (DMA) has a strong wish to receive the entire application in an electronic format.

- eCTD is the preferred format for applications for human medicinal products, however, other formats will also be accepted since 2006.
- The product information must still be submitted in Word format.
- Currently there is no guidance in place regarding electronic submission of regulatory information.

Ireland:

- Launch of Regulatory Information Online Project (RIO). First phase of operations started on 30.03.2007.
- Submission of online applications for Type IA, IB, and Type II variations should be made possible.
- The system provides:
    1. Online forms, documentation upload facilities
    2. Online tracking services for all applications submitted.
- Currently there is no guidance in place regarding electronic submission of regulatory information.

Austria:

- The NCA Österreichische Agentur für Gesundheit und Ernährungssicherheit (AGES) announced in 2003 that they will accept eCTDs if the application form, table of contents, and labelling are still in paper and a full paper copy can be delivered within 3 days.
- Currently, all electronic submissions will be handled within a document management system [13]:
    1. eCTDs are technically validated.
    2. NEESs are only stored electronically.
- Currently there is no guidance in place regarding electronic submission of regulatory information.

France:

- The NCA Agence francaise de securite sanitaire des produits de sante (Afssaps) has been willing to accept NEESs within a limit since 2007. Electronic Dossier folder structure must follow the CTD standard.
- Afssaps is willing to accompany industry in the transition process from paper to the electronic format.
- In the future the Afssaps might strongly discourage paper submissions [17].

- Currently there is no guidance in place regarding electronic submission of regulatory information.

For countries such as Bulgaria, Romania, Estonia, Cyprus, Greece, Spain, Italy, Czech Republic, Slovak Republic, Finland, Hungary, Iceland, Liechtenstein, Lithuania, Luxembourg, Latvia, Malta, Poland, and Slovenia there is no information with regard to the eCTD standard, nor are requirements in relation to NEES available. Additionally, there is no guidance in place regarding electronic submission of regulatory information. The outcome of this analysis is summarized in figure 7.

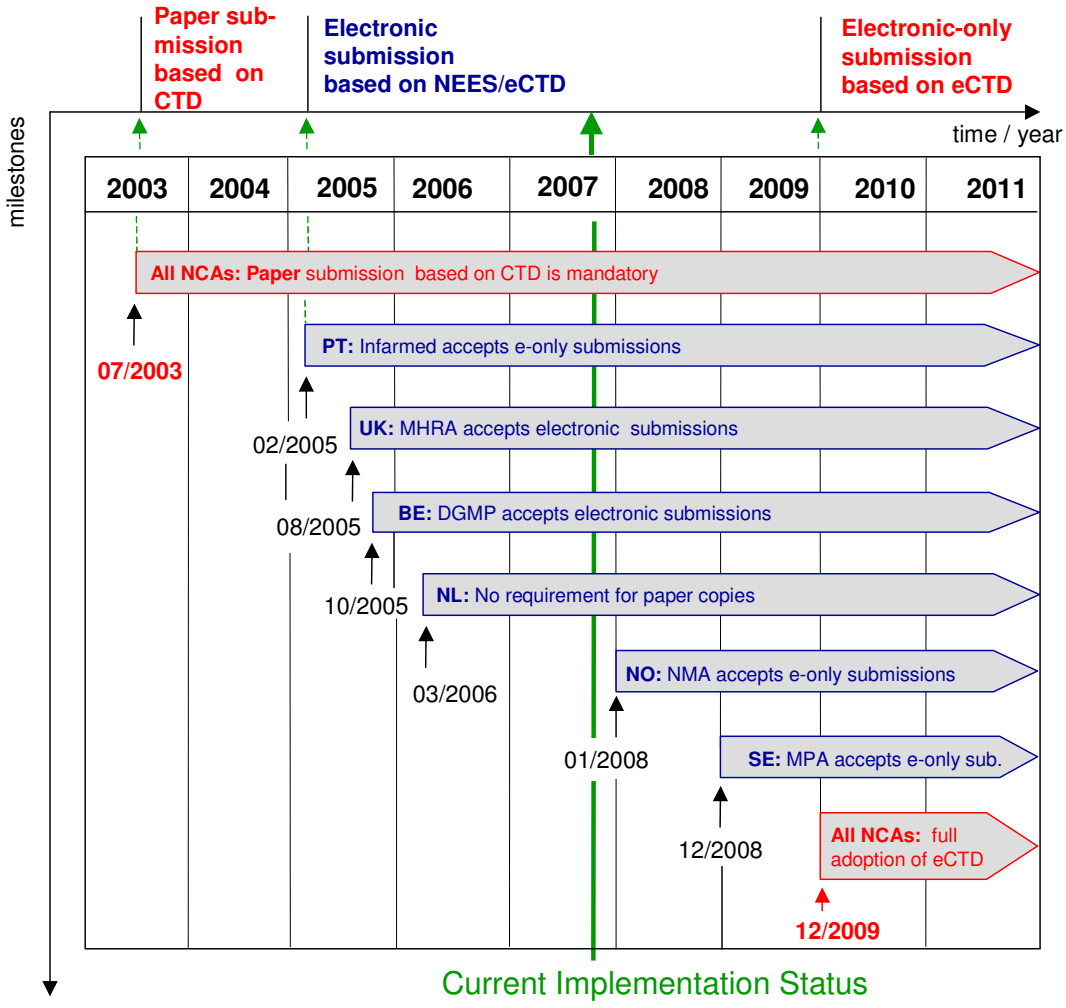


Figure 7: Survey of eCTD/NEES readiness of NCAs in the EU.
Electronic-only submission (e-only) means submission based on eCTD standard and/or based on NEES requirements, i.e. without paper.

This analysis indicates that the implementation status at the different NCA within the EU is not harmonized. Only a minority of European NCAs already accepts or plans to accept electronic-only submission of MAAs by the end of 2008. In contrast, the majority of the NCAs still require paper based dossiers due to national archival law or due to the fact that there are not the necessary electronic work flows in place at the corresponding NCAs. In conclusion, as per November 2007, 23 countries still need to implement legally binding requirements completely covering electronic-only submission of MAAs of all types - initial, variation and renewal, so that no additional paper copies are needed. Furthermore, due to the fact that electronic submission can be realised based on eCTD standard or as a step towards full eCTD based on NEES requirements, the situation on the e-submission front is not at all inhomogeneous within the EU. The latter is a painful situation, especially for those applicants intending to market their medicinal products in more than one Member States, but who are not able or willing to use the CP.

4.2 Comparison of Acceptance Criteria

At the end of the eCTD compilation process an additional step of validation is necessary. Meaning that applicants need to evaluate the structure and content of their eCTD submissions to be checked against the ICH and regional specifications before the dossier can be submitted to the NCAs. However, it may be more important to ensure that the electronic application based on eCTD standard or NEES requirements meets the needs of the NCA regulations and can be archived, processed, and reviewed within specified time frames. Actual experience with eCTD submissions shows that the initial response to an eCTD submission will often be a list of problems with little information provided regarding the impact of these problems, background for the requirement, and next steps. Applicants are often left with many questions after receiving such a deficiency report. Deficiencies listed are sometimes trivial and/or based on misconceptions. For example, as recently as February 2007, the FDA was reporting “non-standard style sheets” as a problem. However the eCTD specification clearly states that applicant-provided style sheets may be included. In addition, the eCTD review tool utilized by the FDA ignores any style sheets, and therefore an applicant-provided style sheet would have no impact.

In the following validation issues of different NCAs such as the MHRA, DGMP, and MEB representing so-called early adopters of the eCTD standard are highlighted. But initially, common validating issues raised by the EMEA as leading competent authority in the EU with regard to the implementation of the eCTD standard will be summarized. It should be noted that a detailed comparison of validation issues of all regions is beyond the scope and purpose of this paper. However, in keeping with the explorative nature of this master thesis, an insight into the topic of validation in relation to some NCAs will be provided. For more details, the corresponding guidelines should be consulted. In the annex, comparison charts of permitted file formats and of regional differences will be provided.

EU - EMEA

In a presentation at the DIA Annual Conference, Philadelphia, PA, June, 2006, Claire Edwards of the EMEA highlighted the following validation issues [5]:

1. File/Folder naming
    - File/Path lengths frequently exceed 230 characters, and also contain invalid characters, which creates an issue at validation.
    - The root folder of the submission should always be the EMEA procedure number in upper cases followed by the subfolder e.g. EMEA-H-0000202/0000. If the submission number is not know, the root folder be named with INN and invented name, as described in the EU M1 specification.
2. Regional Differences
    - The majority of issues encountered come from applications first filed in the US and then in the EU. An eCTD first filed in the US must be adapted to EU requirements, meaning that aspects relating to the specific US regional guidance should be re-considered for the EU. The following should not be included: STF, SPL, SAS transport files (cannot be viewed in the EU).
3. Lifecycle-Management (Attributes)
    - Some confusion over the use of operators, in particular “append” and its impact on the application’s lifecycle:
        1. Co-dependent relationship with leaf 1 file?
        2. Parent/Child hierarchy?
        3. No relationship with leaf 1?
    - Each leaf with operation="replace" should have a "modified-file" with reference to the previous backbone and leaf ID.
    - Cover Letter should always be “New”.
    - Cannot replace a node more than once – if a leaf is replaced by 3 new files, only one “replace” operator can be used - other operators must be “new”.
4. Util folders
    - The EU Module 1 util folder is an additional folder to hold utility files used in EU Region only. This is currently only used for submissions including a PIM format for the labelling information or an electronic Application Form in an XML format. If PIM or eAF is not submitted, then there should be only one util folder at root level that contains all utility files, (eu-regional dtd etc. also included).

5. Additional documents
    - All files should be referenced in the XML backbone.
6. MD5 Checksum
    - Invalid checksum is the most common issue. No eu-egional-md5.txt is required, since this is redundant with the checksum provided in index.xml associated with each leaf including eu.regional.xml.
7. File Format
    - Do not include any file security settings or password protection for individual files specified in the eCTD.
    - Files should allow printing, changes to the documents, selecting text and graphics, and adding or changing notes and form fields.
    - ICH/EU M1 specification should be observed with regard to accepted file formats.

After summarizing validation issues raised by the EMEA, a rough overview of validation issues raised by NCAs such as MHRA, DGMP, and MEB will be presented below based on information extracted from the corresponding country specific guidelines listed in the annex or adapted from current presentations by NCAs.

UK - MHRA

In his presentation at the 9th DGRA Annual Congress, Bonn, June 2007 David Wheeler of the MHRA highlighted the following validation issues [14]:

1. eCTD Submission
    - MA application form MHRA Portal must be completed via Web Services.
    - Module 1 according to EU 1.1 specification (update to 1.2.1 pending) and M2 to M5 according to ICH eCTD 3.2 specification.
    - SmPC as separate Word file using MHRA template.
    - Product life cycle management.
    - Interoperability of eCTDs from different tools.
2. NEES Requirements
    - Single pdf file for M1, M2, etc, requires additional work to split
    - File names - must be preceded by CTD section number. Failure to label the files correctly may lead to the submission being rejected.

3. Web Services Validation Process
    - MA number validation
    - Companies and contacts
    - Substances (actives, excipients)
    - MedDRA terms (indications, contraindications, side effects)
    - Other EDQM reference data (pharmaceutical form, route of administration, packaging materials)

Belgium - DGMP

The following highlights have been extracted from “eSubmission Guidelines New Ways of working at DGMP Version 2.5.1 Aug 2006”:

- Precise file / folder naming and structure are critical.
- Please do not forget to print the cover letter and put it in the envelope when mailing the CD/DVD.
- Do not password protect your files! Or communicate how to get this password clearly to the NCA.
- Hyperlinks must be relative.
- Do not send parts of dossiers by email and parts on CD/DVD.
- Application form - Never submit a scanned document, the option text select should always be available if submitting a pdf file (the DGMP prefers MS Word document if possible).
- Empty folders to be deleted.

Netherlands - MEB

The following points were highlighted by the MEB in various public meetings:

- eCTDs may be invalid due to lack of navigation.
- eTOC, bookmark, hyperlinks.
- Signed cover letter and application form should be submitted both electronically and in paper form.
- Until 01.01.2008 MEB will accept switches from pdf-only to eCTD during the life cycle of the product.
- Word or RTF documents accepted but must be accompanied by PDF rendition.
- Module 2 (pdfs) must always be generated from an electronic source document (not scanned).

This overview about validations issues indicates that the MHRA in the UK, the DGMP in Belgium, and the MEB in the Netherlands have bespoke e-submission processing systems that accept a variety of e-submission types. However, to compensate for the lack of an XML backbone when accepting NEESs, all of these agencies have put into place some complex requirements for file and folder naming and file preparation. The MHRA, for example, requires pdf files of scanned documents to be prepared with OCR text embedded and for the pdf file names to be prefixed with the CTD section number. These are unique requirements and are contrary to the spirit of electronic submission harmonization. Additionally, it should be noted that some of these requirements might change in the course of time. An example is the requirement by the MHRA in relation to the naming of files. As pointed out by David Wheeler at the 9th DGRA Annual Congress, Bonn, June 2007 eCTD file names will be accepted in the future [14]. Another example is the requested so-called cover page by the MEB. In July 2007 the MEB stated that the use of the cover page over the past two months has shown that it has little added value and has actually caused additional problems for the applicants [19]. The MEB has therefore decided, as of now, that it will no longer request a cover page and that applicants are no longer required to send it in.

This analysis also indicates that some NCA have applied certain unique submission content requirements and/or technical requirements, especially in case of NEESs, contributing to the complexity of maintaining compliance. If serious defects are found the application might be deferred to the applicant. The latter can be lead to a serious delay in the review process. As a consequence the time-to-market of the corresponding medicinal product will be prolonged. This is even more important for marketing authorization applications following the MRP or DCP if the applicant intends to market the medicinal products in more than one Member State with different submission requirements.

5. eCTD and MRP/DCP (Practical Constraints)

The eCTD standard has advantages, which can be summarized as follows: For pharmaceutical companies it facilitates changing and reuse of documents, following the changes throughout the lifecycle, creating links to other documents. But eCTD is not only an “electronic CTD”, because it covers the content, meta data, and structure of the application within the XML backbone, spans the full product lifecycle, and always provides the current information in context, without having cross-reference and duplicate information manually, it is more definitive - no file can be modified without any control, it stores the version numbers of the documents.

On the other hand the eCTD standard has an impact on current regulatory practise, especially within multi-national marketing applications based on the MRP or DCP. Therefore, in the following section, the impact of the eCTD standard is determined con-

sidering issues such as “Dossier Compilation”, “Submission Management”, and “Life-cycle Management”. This analysis will be conducted using the following case scenario:

- Medicinal product with the trade name “Prontofer” comprising three different pharmaceutical forms such as oral solution, oral drops, solution, and film-coated tablets.
- All pharmaceutical forms have one strength only
- It is intended by the applicant to receive a marketing authorization from 10 Member States for all pharmaceutical forms following either the MRP or the DCP.
- A second wave covering four additional Member States is also planned.

5.1 Dossier Compilation

The compilation of a dossier based on the eCTD standard needs to include considerations of document granularity, templates, shell documents and country differences in filings. Furthermore, the eCTD file needs to be “reviewer friendly” by use of bookmarks, hyperlinking and tables of contents in individual documents. Additionally, within a MRP or DCP country specific documentation of Module 1 must be provided to the NCAs.

The ICH CTD specifies that Module 1 should contain region specific administrative and prescribing product information. The following items listed in the Notice to Applicants should be included for an initial submission:

- a cover letter,
- a comprehensive table of contents,
- an application form,
- product information documents,
- information on the experts,
- specific requirements for different types of applications (if required),
- an environmental risk assessment (if required),
- information relating to orphan market exclusivity (if required),
- information relating to pharmacovigilance,
- information relating to clinical trials (if required).

In addition, other items such as answers to regulatory questions, rationale for variations and renewal documentation, and additional data can also be included in Module 1. Originally, Module 1 was left to each region to develop, but in contrast to the CTD standard the eCTD standard also accommodates the Module 1 of each region. That means all documents of Module 1, also including country specific additional data, must be provided to the NCAs electronically in accordance with the eCTD standard.

As shown in figure 8 the initial documentation will be provided to all NCAs as a single submission within the eCTD sequence 0000 using the same information for Module 4 and 5 since it is common for all pharmaceutical forms. Due to the fact that the active product ingredient is the same for all pharmaceutical forms, the information of Module 2 and 3 in relation to the active substance can also be used for all products. Even the documentation of Module 2 and 3 that is different for all products regarding the information of the finished product, can be reproduced in the initial sequence. Due to the flexibility of the EU Module 1 specification all administrative and prescribing information that is common to all Member States can be submitted to all CMSs and the RMS within one sequence. Also all country specific information of Module 1 including “additional data” can be incorporated in one single sequence for all Member States.

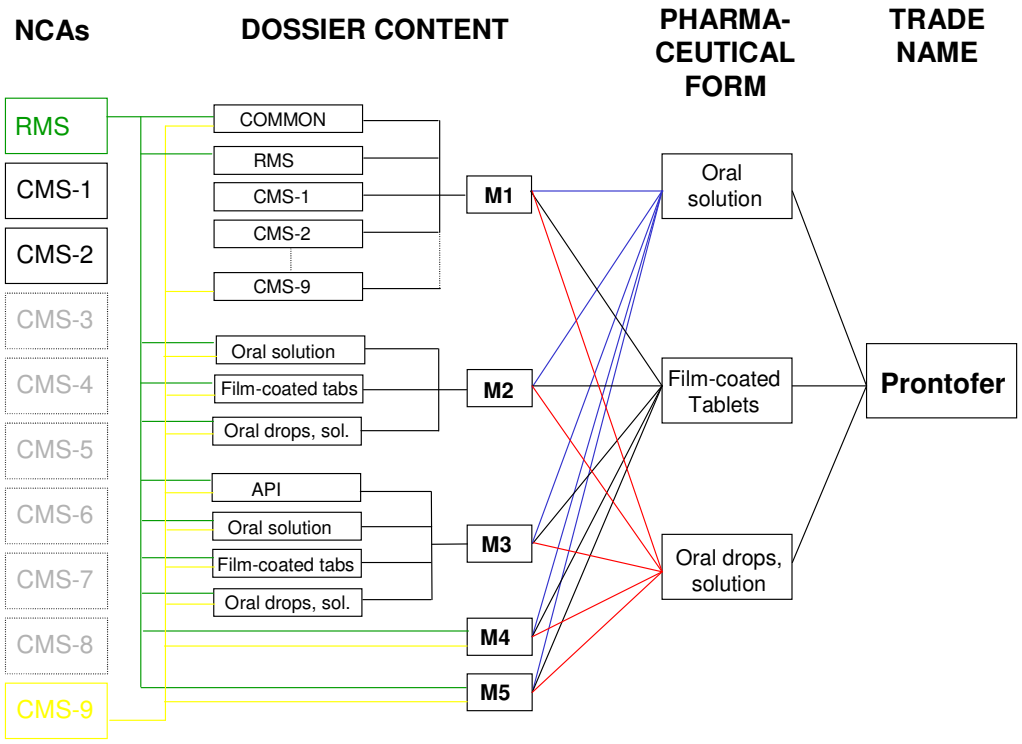


Figure 8: Dossier content of a multi-national MAA following the MRP or DCP.

But, in contrast to Module 1 country specific information of any other Module such as different manufacturers of the finished product in different countries in Module 3 cannot be reproduced within one single sequence, since the ICH specification of Module 2-5 does not allow for country specific information to be included. The latter can only be circumvented by creating country specific sequences for each Member State or groups of Member States having the same manufacturers of the finished products. This finding

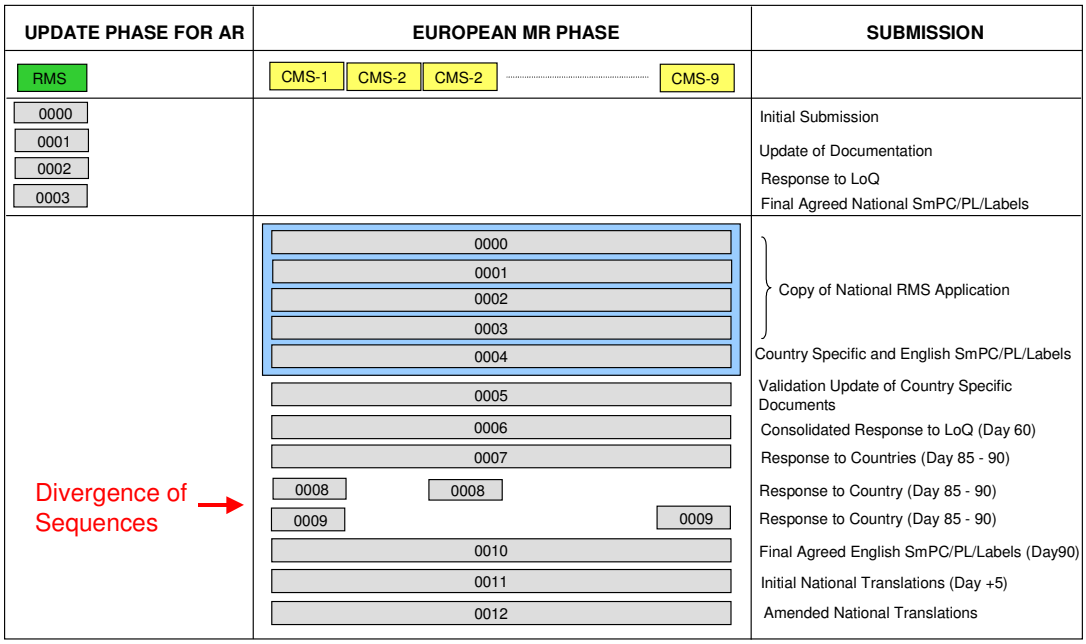
can be interpreted as a shortcoming of the eCTD standard having an effect upon the submission of the documentation within the MRP and DCP especially.

5.2 Submission Management

At the end of the dossier compilation process the documentation must be submitted following the timelines described in figure 1 and 2 relevant for the MRP and DCP, respectively. As shown in figure 9A after the initial submission of the dossier of the medicinal product “Prontofer” additional documentation in relation to validation issues, a list of questions at different time points, and national translations of SmPC, PL and labels must be provided by the applicant to each of the NCAs of interest within a MRP. Due to the fact that the EU Module specification supports easy access to country specific information of Module 1, only a single sequence covering all country specific updates can be submitted, if updated documentation is required for both common and country specific information of Module 1. Since the ICH Module 2-5 specification supports no country specific information, in contrast to Module 1, all country specific information resulting, for example, from different country specific answers to a list of questions in relation to Module 3 will lead to a divergence of sequences. This means country specific information of Module 2-5 can only be provided by means of different sequences as can be seen in figure 9 A.

Figure 9 B shows a potential scenario covering the submission management for the dossier of the medicinal product “Prontofer” which will be used for granting a marketing authorisation in 10 Member States following the DCP. In a second wave the MRP will be used for subsequent applications to an additional four Member States in relation to the same medicinal product “Prontofer”. This procedure is known as “Repeat Use”. Repeat Use CMSs must receive all generally applicable documentation from initial approval and lifecycle submissions. Additionally, country-specific documents will be sent to all Repeat Use CMSs. To provide all Repeat Use CMSs also with all lifecycle meta data it is necessary to send all initial assessment sequences and also all general lifecycle sequences representing a high diversity of sequences. This course of action is unavoidable, since the eCTD standard does not allow for merging of different sequences in consideration of all lifecycle meta information. The latter represents a shortcoming of the eCTD standard resulting from the fact that meta data, which are necessary for tracking of changes, are only implemented on document level, but not on module or dossier level. As a result, product related lifecycle management of dossiers based on reuse of different parts of documentation across sequences is not possible by means of the current eCTD standard.

A – MAA following the MRP



B – MAA following the DCP (Repeat Use)

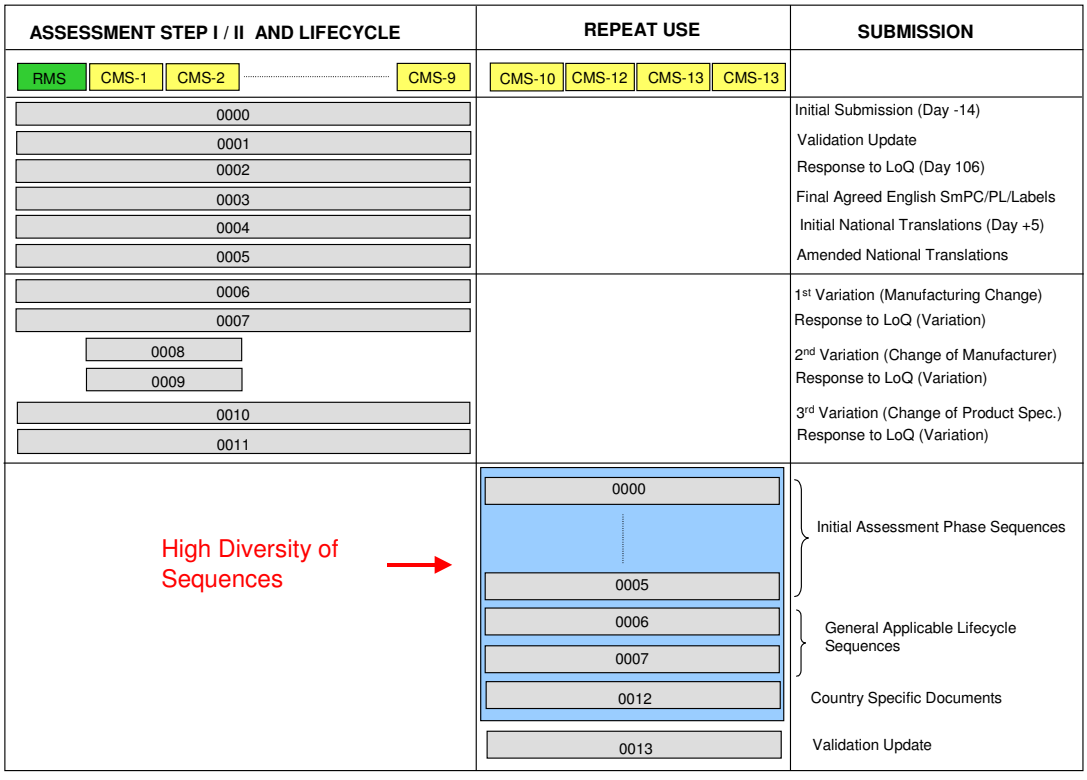


Figure 9: Overview submission management of a multi-national MAA.
A - MAA following the MRP; B - MAA following the DCP (Repeat Use).

5.3 Lifecycle Management

The eCTD standard allows for the submission of amendments and supplements subsequent to the original submission, so called lifecycle management. An important feature of the eCTD is that amendments/supplements are never incorporated directly into the original submission and each remains separate and discrete from previous submissions. Each amendment/supplement includes its own XML backbone file that defines the exact relationships between the new files being submitted and those submitted previously. This means the that eCTD standard is capable of spanning all regulatory activities including initial MAA, all variations, line extensions, renewals, and answering lists of questions. Consequently, the lifecycle management has to start at that point of time when the decision is made with regard to the overall marketing authorization strategy, i.e. before granting of the marketing authorization of the medicinal product “Prontofer” considering the following issues:

- Complexness of submission, especially in case of a multi-national MAA following the MRP or DCP.
- Lifecycle features are implemented within the eCTD standard only at document level and not at module or dossier level.
- Granularity of documentation influences effectiveness of lifecycle management.
- Navigation through the dossier may be corrupted by broken hyperlinks resulting from deletion or replacing of files.
- Differing Member State-specific implementation of eCTD/NEES specifications.

Taking these issues into account different lifecycle management concepts are available ranging from linear lifecycle management to parallel lifecycle management. In the case of linear lifecycle, one dossier exists for all trade names, strengths, and countries, meaning that the dossier is very complex and cannot be overviewed as a whole. On the other hand each sequence can be easily linked to its corresponding submission and all problems in relation to lifecycle management are reduced to one dossier. Alternatively, parallel lifecycle management can be used meaning that one dossier is used for separate trade names, strengths and countries. Each of these dossiers can be reviewed very easily, but the submission management of sequence numbers for each dossier is difficult. Each dossier has its own lifecycle leading to high granularity of documentation especially in case of a multi-national MAA following the MRP or DCP addressing several countries.

The outcome of this analysis indicates that the lifecycle management in accordance with the eCTD structure and granularity in support of a submission of a multi-national MAA following the MRP or DCP is a regulatory challenge, especially with NCAs using different viewing tools and at different stages of becoming eCTD compliant. To successfully navigate these waters it is important to know what the regulators expect from

an eCTD submission, how sequences should be related, how much hypertext linking is desirable, and when to replace, delete, append and submit new files. Detailed information on the values of the attribute “operation” is given in the annex.

6. Conclusion and Outlook

In keeping with efforts to rationalise and harmonise the regulations of medicinal products the ICH has developed standardised specifications for the CTD and the electronic version, the eCTD. The eCTD standard is now at Step 5 of the ICH process – implementation by the NCAs. The Member States are progressing with implementation at quite different rates. As a transition step, some NCAs are currently accepting electronic submissions following the CTD specification in lieu of, or in addition to the paper CTD. However, paper is currently the only legally recognised way to submit a marketing authorisation application for most EU Member States. The vast majority of submissions exchanged within the EU, more than 90%, are conducted through the national procedure underlying the importance of each single NCA for the uniform implementation of electronic-only submission in Europe. However, the complexity of the European landscape, with its many Member States, and the fact that a move away from paper as legally binding copy for submission requires a change in national archive law and the setup of adequate electronic workflows at the NCAs in each Member State, delays the implementation process of the electronic-only submission in Europe. On the other hand it should be noted that future emphasis is specifically on electronic submission. The target date for full adoption of eCTD standard is currently the end of 2009.

The EMEA has clearly stated that eCTD submissions alongside paper are welcomed, because they enable applicants and the agency alike to gain experience in electronic submission processing and review, and to develop the expertise necessary for full implementation of the eCTD standard. Also more and more Member States are moving towards the eCTD standard by establishing electronic workflows normally capable of managing electronic-only submission of MAAs of all types - initial, variation and renewal. Unfortunately, some NCAs have followed an aggressive e-submission/eCTD implementation schedule and have already succeeded in having legislation changed to permit electronic-only submissions. These are not necessarily eCTDs, however. As detour to the eCTD standard NCAs such as MHRA (UK) and DGMP (Belgium) have implemented various national requirements representing no standard, but in fact individual procedures and acceptance criteria resulting from their bespoke e-submission processing system that accepts a variety of electronic submission types. The comparison of guidance from three Member States (UK, Belgium, and Netherlands) can be summarized as follows:

1. There is a range of acceptance of different types of non-eCTD electronic submissions.

2. Many areas of divergence revealed relatively small differences, capable of being overcome.
3. There is still a need in some instances for local statutory differences.
4. Harmonisation around eCTD was potentially more straightforward than with non-eCTD electronic submissions.
5. Some significant areas of eCTD are undefined.
6. A common European guidance document is missing with locally specific appendices restricted to statutory differences.
7. Following issues must be addressed: Validation rules for eCTD, eCTD versioning, application portals.

This comparison illustrates that the implementation of the electronic submission procedures in Europe is currently the object of individual courses of action at the NCAs resulting in different electronic submission requirements. The outcome of this comparison is also demanding for harmonization of electronic submission procedures across all Europe. The EMEA and Member States have also recognized the critical need for harmonisation, therefore forming a working group called the “EU Guidance Harmonisation Topic Group”. The first meeting of this group took place in November 2006.

Any electronic standard represents a so called “moving target” which is exposed to changes over time. This is also true for the ICH eCTD specification. The ICH eCTD M2 ESTRI working group is currently working on the next release of the ICH eCTD specification known as version 3.3.2. In this version a number of approved change requests were taken and incorporated into the specification. The most significant changes comprise the inclusion of the STF requirements into the XML backbone. Other minor changes will be: change of modified-file to modified-leaf, CTD numbering revision in Appendix 4, deletion of references to logical documents, update of references to websites and other external resources, update of references to regional style sheets and DTDs. Also approved change requests will be incorporated such as recommended resolution for scanning documents containing non-western characters, the preferred version of pdf, the increased maximum file size for pdf files and the removal of the redundant Appendix 9. Due to the fact that the ICH eCTD M2 ESTRI working group has decided to release this new version via an ICH step process, the regional implementation will be expected at the end of 2008 or at the beginning of 2009 in Europe. In contrast to the ICH eCTD specification, there are no plans at present for updates of the EU Module 1 specification. Therefore, version 3.3.2 of the ICH eCTD specification subsumes all most significant change requests, but overall it represents only a minor change in relation to the functionality of the eCTD standard. Unfortunately, issues such as:

- Communication from applicant to the NCA and vice versa,
- Implementation of country specific information in Module 2-5,

- Reuse of different parts of documentation across sequences in consideration of lifecycle meta data

are not addressed by this new version.

The solution for these shortcomings of the eCTD standard might be a new standard for electronic submission, the Regulated Product Submission (RPS). RPS is the American answer to European eCTD. Health Level Seven (HL7), a standard organisation similar to the International Organisation for Standardisation (ISO), has initiated it. RPS creates a regulated product submission message based on XML including meta data, which is general enough to handle all regulated products and which contains enough information to allow regulators to support structured review. It is intended that the RPS standard will be used worldwide for regulated products, including but not limited to foods, medical devices, human and veterinary medicinal products. The scope of the initial release of the RPS standard is to define the message for submitting information to regulatory authorities aligned to the current eCTD standard. This message includes the contents of a regulatory submission and all information needed to process the submission message. It must be flexible enough to be used for regulatory submissions for any regulated product. Subsequent releases of the standard will provide information about the submission, for example, information currently collected on application forms, in addition to information about the files in the submission, two-way communication, and linking to master files. RPS allows for document lifecycle, reuse of documents across applications, product/submission management, submission lifecycle, computer aided review, visibility into product/submission, and regional/product differences. Therefore, RPS might overcome the difficulties especially in support of MAAs following the MRP or DCP in Europe based on the current eCTD standard.

Finally, it should be noted that there is little doubt that a successful eCTD submission to agencies in Europe is attainable. But unfortunately, there is a period of transition meaning that the identification of precise criteria for a valid eCTD can be an elusive goal. Also, agency acceptance of an eCTD does not guarantee a perfect submission – problems may not be evident until a number of sequences have been submitted. The ICH M2 Implementation Working Group continues to address these issues through projects such as ETICS and through the sharing of observations and recommendations with applicants, vendors and agencies. In the mean time, those applicants wishing to make eCTD submissions can improve the likelihood of a trouble free submission by studying all relevant materials, and communicating with the agencies and with the eCTD tool vendors. All in all, electronic standards in the pharmaceutical industry have made significant progress in the last years, with both industry and regulatory bodies acknowledging the benefits. It can only be anticipated that these standards will continue to evolve and new standards will be proposed. Nevertheless, any standard should be designed with one ultimate goal – providing safe and effective healthcare to patients.

7. References

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8. Annex

8.1 Regional Permitted File Formats

The ICH eCTD Version 3.2 specification includes allowable file types and refers to regional guidance's for additional permitted or required file types. Table 1 shows file types by region adapted from literature [22]. Note – if a file type is ICH specified, it is permitted in all regions.

File Type	Extension	ICH	CA	EU	US
ASCII Text (SAS Programs, etc.)	txt				X
Data for Comparative Bioavailability Studies – information file	inf		X		
Data for Comparative Bioavailability Studies – data file	dat		X		
Graphics Interchange Format (CompuServe)	gif	X			
JPEG	jpg, jpeg	X			
Portable Document Format	pdf	X			
Portable Network Graphics	png	X			
Rich Text Format	rtf			X	
SAS Transport	xpt				X
Word	doc		X	X	X
WordPerfect	wpd		X		
XML	xml	X			
Compressed Tar	tar			X	
Zip	zip			X	

Table 1: Comparison chart – regional permitted file formats

8.2 Regional Differences

The chart below describes areas where regulatory authorities have requirements or preferences that are different from, or in addition to those in the eCTD specification and guidance (e.g. ICH M2 Q&A #36) adapted from literature [22].

	ICH	**CA**	**EU**	**US**
Organization of Modules 2-5	see specification	ICH	ICH	- datasets folder - crf location
File naming	allowable characters, name length, recommended names in specification	ICH	M1 file names follow detailed strict rules. See - M1 specification.	- STF file - SPL file - underscore allowed - M1 DTD naming – conflicting guidance
File size limit	100 MB	ICH	ICH	SAS files can be >100MB
Labelling	n/a (M1 issue)	-	PIM folder	SPL folder
Leaf Lifecycle interpretation	not specified	Implicit/Inheritance	Explicit	Mixed
Lifecycle target	same application (implied)	ICH	ICH	Can cross applications
M1 Sub-folders	n/a (M1 issue)	NOT PERMITTED	Extensive, complex, variable	No guidance
Node extensions	permitted	Accepted	Encouraged for study reports	DO NOT USE
Required folders	m1-m5, util, util/style, util/dtd, m1/rr	ICH	PIM folder in M1 util folder in M1	SPL in M1, datasets in M5
Root folder	left to region	Clear rule	Clear rule	Not clear
Sequence / related sequence	n/a (M1 issue)	Only one	Any number	Conflicting guidance
STF requirement	left to region	Ignored if present	Do not submit	Required
STF lifecycle	cumulative / accumulative	n/a	n/a	DO NOT USE CUMULATIVE
STF validvalues.xml	provided as ICH standard	n/a	n/a	Provided different version (new values)
Stylesheet	default ICH stylesheet provided but any stylesheet permitted	any	any	Only ICH default
3.2.a.1 attributes	name, manufacturer	ICH	ICH	2 of these: manufacturer, substance, dosageform and product-name
3.2.a.2 attributes	name, dosage form, manufacturer	ICH	ICH	3 of these: manufacturer, substance, dosageform and product-name

Table 2: Comparison chart – regional differences

8.3 eCTD Architecture (lifecycle management)

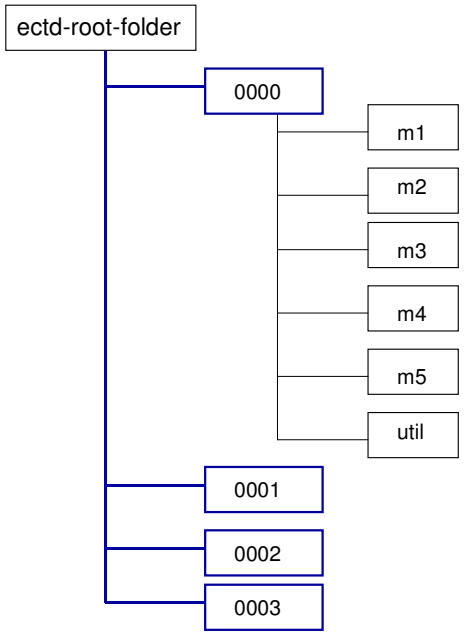

Figure 10: Lifecycle management within the eCTD standard

In figure 10 a general idea is given for the eCTD architecture in relation to lifecycle management. In this example, folder 0000 contains the initial submission. In addition, three subsequent supplements/amendments have been added as folders 0001, 0002 and 0003. Each of the sequentially numbered folders contains a file "index.xml" that containing the XML backbone that relates to that particular submission.

Folders 0001, 0002 and 0003 are unlikely to contain a full eCTD folder structure. Only those parts of the eCTD folder tree that are needed to hold new or replacement files will be included (any empty folders will have been deleted).

The XML backbone files provide descriptive information ("meta data") on every file that is affected by the submission, in the form of a "leaf element" for each file. Each leaf element has an "operation" attribute and a "modified-file" attribute.

The operation attribute gives the status of the new file (where applicable) in relation to what has been submitted previously, and it has the following possible values:

- "new" - the file in question is a new file unrelated to anything submitted previously;
- "append" - the file in question is being appended to a file submitted previously, at the location specified in the "modified-file" attribute;

- "replace" - a file that replaces a file submitted previously, at the location specified in the "modified-file" attribute;
- "delete" - a file submitted previously, at the location specified in the "modified-file" attribute, is being deleted without being replaced.

8.4 CTD and eCTD Structure

The CTD is divided into 5 modules. While it was originally intended to harmonize the content of Modules 2 to 5, in the meantime some regionally different requirements were established influencing the reusability of Module 2-5 in the different regions. In contrast Module 1, for administrative information, was right from the start left to each region to develop. It should be noted that in contrast to the CTD, the eCTD also accommodates the Module 1 of each region shown in figure 11, which was adapted from literature [21].

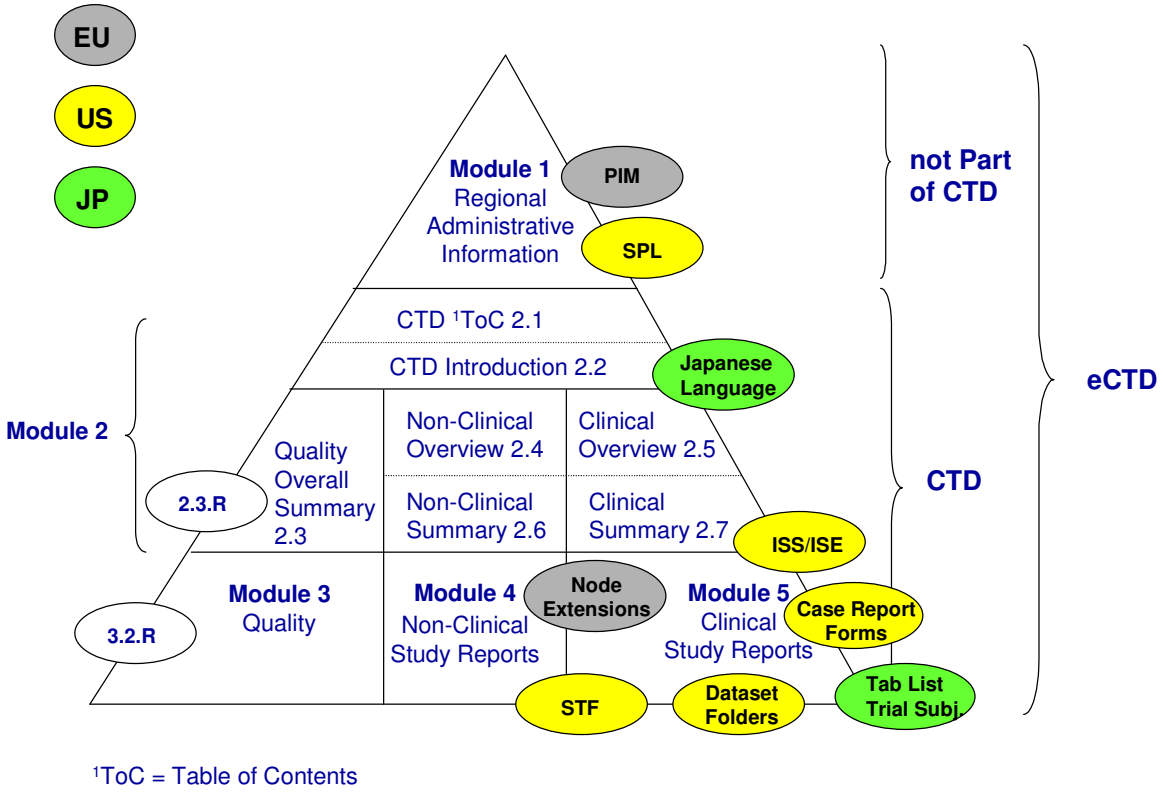

Figure 11: Assembling of CTD and eCTD structure

8.5 eCTD/NEES Specifications/Guidance Documents

Country/ Region	Agency	Topic	Item	Date
US	FDA	eCTD Guidance	Guidance for Industry Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications	Apr 2006
CA	Health Canada	eCTD Guidance	DRAFT GUIDANCE FOR INDUSTRY Preparation of Drug Submissions in eCTD Format	Jan 2006
EU	EMEA NCAs	eCTD Module 1 Specification	EU Module 1 Specification V1.2.1.	Dec 2006
EU	EMEA NCAs	Accompanying Paper submission	Practical guidance for the paper submission of regulatory information in support of a marketing authorisation application when using the Electronic Common Technical Document ("eCTD") as the source submission. V1.0	Feb 2006
EU	EMEA NCAs	CTD Submission	Presentation and format of the dossier. Common Technical Document (CTD)	Jun 2006
EU	EMEA NCAs	PIM	Data Exchange Standard Specification for Product Information in the European Union	Jul 2007
EU	EMEA NCAs	eAF	Electronic Application Form : New Application Specification V2.0	Jan 2006
ICH	EMEA FDA NCAs	eCTD Module 2-5 Specification	ICH M2 EWG - Electronic Common Technical Document Specification V3.2	Feb 2004
Portugal	Infarmed	e-submission	SUBMISSÃO DE PEDIDOS DE ALTERAÇÃO EM FORMATO ELECTRÓNICO MANUAL DE CARREGAMENTO	Oct 2007
Belgium	DGMP	e-submission	eSubmission Guidelines. New ways of working at DGMP	Aug 2006
UK	MHRA	e-submission	Special Mail 5 Guidelines on submission of applications to the MHRA	July 2006
UK	MHRA	e-submission	Special Mail 5 Frequently Asked Questions	Nov 2006
UK	MHRA	e-submission	UPDATE Special MAIL 5: Guidelines on Submission of Applications to the MHRA	Mar 2007
UK	MHRA	e-submission	Changes to applications for Manufacturer's Licences, Wholesale Dealer's Licences, inspection work and update on Sentinel system	Oct 2005
UK	MHRA	e-submission	Special MAIL 1	Apr 2005

			NEW WAYS OF WORKING AT MHRA	
Netherlands	MEB	e-submission	Guidance for Industry on Providing Regulatory Information in Electronic Format in the Netherlands:	Mar 2006
Germany	BfArm PEI	e-submission	Erläuterungen zum Vollzug der Verordnung über die Einreichung von Unterlagen in Verfahren für die Zulassung und Verlängerung der Zulassung von Arzneimitteln	Jul 2007
Denmark	Danish Medicines Agency	e-submission	Electronic applications for marketing authorisations for medicinal products	Jul 2007

Table 3: Survey current eCTD/NEES specifications/guidance documents

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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Unterschrift