EU Module 1 eCTD Specification

Version 3.1.1

June 2025

Approved by the eSubmission Expert Group, NICTAC and EU IT Directors group

Document Control

Change Record

Version	Date	Author(s)	Comments
0.1	July, 2001	Stan van Belkum	Draft
0.2	September, 2001	Stan van Belkum	Draft
0.3	October, 2001	Stan van Belkum	Draft
0.4	November, 2001	Stan van Belkum	Draft
0.5	February, 2002	Stan van Belkum	Draft
0.6	February, 2002	Stan van Belkum	Draft
0.7	March, 2002	Stan van Belkum	Draft
0.8	October, 2002	Stan van Belkum	Draft
0.9	November, 2002	Stan van Belkum	Draft
0.91	February, 2003	Stan van Belkum	Draft
0.92	July, 2003	Stan van Belkum	Draft
0.93	February 2004	M. Bley	Draft
0.95.1	May 2004	EMEA	Draft
0.95.2	28 May 2004	EMEA	Draft
0.95.3	23 June 2004	EMEA	Draft
1.0	July 2004	EMEA	Final
1.1	December 2005	EMEA	Integration of PIM
1.2	May 2006	EMEA	Structural changes from CTD
1.2.1	October 2006	EMEA	Alignment to CTD and Change Requests
1.3	May 2008	EMEA	Incorporation of paediatric requirements and Change Requests
1.4	August 2009	EMEA	Alignment to the New Variation Regulation and Change Requests
1.4.1	November 2011	EMA	Incorporation of Additional Change Requests and Q&A
1.4.2	December 2012	EMA	New Draft version including proposed DTD changes as requested by: CR 20120924 rev CR 20121119 CR 20091203 CR 20100408 CR 20101022-01 CR 20101214 CR 20110614
1.4.3	17 December 2012	EFPIA	EFPIA changes, added PDF 1.5, 1.6, edited file allowed formats, added common for CP, adjustments to agency codes
1.4.4	20 December 2012	EFPIA	Removed PIM, added HR to App 2.4, updated Spanish agency name in 2.4, removed 'AR' from App 2 codes, (p24), added –var to tracking table name, updated TOC
1.4.5	21 December 2012	M BLEY	Acceptable file formats in EU Module 1 (XML), use of « common » as country sub-directory for CAP, further examples of file naming convention,
2.0	27 February 2013	EFPIA/EMA/NCA/M BLEY	All accepted change requests implemented.
2.1	30.05.2015	K. Menges	Implementing accepted change requests: Update of agencies names, additional submission types, adding submission unit types and related term list, alignment of term lists with respective ETUCT CTL, additional samples and adjusting examples according to the above mentioned changes, adding EDQM to the list of receivers.
2.2	02.07.2015	A. J. Nixon	Modifications to improve consistency and English wording.
2.3	10.07.2015	K. Menges	Incorporating comments from eSub CMB, TEAB, HHMG in regard to additional explanations of technical aspects of the UUID, additional submission

			types, clarifications how to use new submission types and submission unit types.
2.4.1	29.09.2015	K. Menges	Reconciliation of comments from public consultation.
2.4.2	01.10.2015	K. Menges	Additional submission type 'rup', change of definition of submission unit type 'consolidating'
3.0	07.10.2015	K. Menges	Preparation of the clean version 3.0
3.0.1	12.05.2016	K. Menges	Correction of errors in the files 'eu-envelope.mod' , 'eu-regional.dtd' and 'eu-regional.xsl', correction of the submission type 'referral-53' into 'referral-5-3'
3.0.2	08.03.2017	K. Menges	Additional notes for submission types, submission number and procedure tracking numbers for clarification
3.0.2	02.05.2017	K. Gröndahl, K. Menges, K. Puusaari	Editorial change to correct the recommendation for PSUSA on page 10 which was not adapted to the statements on page 17 as it should have been.
3.0.3	07.11.2017	K. Menges	Editorial changes to explain how the envelope will be completed in case of a PSUFU procedure. Addition of the fixed file name for eAF and their annexes.
3.0.4	03.02.2021	K.Gröndahl, K.Puusaari	Editorial changes due to Brexit as well as to include information about the use of UUID, format related guidance and some other clarifications. Drafted within the Human Harmonisation Group (HHG).
3.1	18.06.2024	K. Puusaari, M.Pereteatcu	Added reference to an Annex on accepted Regional file formats Editorial changes to explain the use of authentication measures (electronic signatures) Clarifications added for: • General architecture for Module 1 • Example for Withdrawal • Example of the use of the Related Sequence and the Submission unit type elements: o Closing sequence o Related sequence Appendix 1: • Identifier: UUID typo fixed • New submission type added: Article 18 • New submission unit: re-examination • Submission unit: clarification added for "consolidating" type • Submission unit: extension to all procedure types for „closing" • Example of the use of the Related Sequence and the Submission Unit type elements: Clarification added Appendix 2: • Number 6: Clarification added for tracking table • Number 70: Clarification added for Additional data Appendix 2.1 • "xi" the destination code for UK Northern Ireland Appendix 2.2 • "ga" the language code for Irish Appendix 2.3 • Clarification added Appendix 2.4 • Proposed English versions of the Agency names (where missing) DTD updates: • New submission type added (Article-18) • New submission unit added (re-examination) • New language added: ga (Irish)

			• New country code added: xi (UK(NI)) Eu-regional.xls • Updated the names of the agencies
3.1.1	23.05.2025	Mihaela Pereteatcu Kristiina Puusaari	• Exception added for EDQM for the tracking table • Updated the examples for the Procedure numbers • Clarification added for the product number to be used in the pre-submission phase

Reviewers

Version	Name	Organisation
0.1-0.3	EU Regulators	EU Regulatory Authorities, EMEA
0.4	Interested parties	
0.5-0.6	EU Regulators	EU Regulatory Authorities, EMEA
0.7-0.8	Interested parties	
0.9	EU regulators	EU Regulatory Authorities, EMEA
0.91	EU Regulators ICH, EMEA	EU Regulatory Authorities, EMEA
0.92	EU regulators	EU Regulatory Authorities (members TIGes and NtA)
0.95.1	EU Regulators, interested parties	EU Regulatory Authorities (members TIGes and NtA), EFPIA, Pharma, other interested parties
0.95.2	EU Regulators, interested parties	EU Regulatory Authorities (members TIGes and NtA), EFPIA, Pharma, other interested parties
0.95.3	EU Regulators, interested parties	EU Regulatory Authorities (members TIGes and NtA), EFPIA, Pharma, other interested parties
1.1		
1.2		
1.2.1		
1.3	EU Regulators, interested parties	EU Regulatory Authorities (members TIGes and NtA), EFPIA, Pharma, other interested parties
1.4	EU Regulators, interested parties	EU Regulatory Authorities (members TIGes and NtA), EFPIA, EGA, other interested parties
1.4.1	EU Regulators, interested parties	EU Regulatory Authorities (members TIGes and NtA), EFPIA, EGA, other interested parties
1.4.3	December 2012 EFPIA	EFPIA Review of EMA changes
2.0	EU Regulators, interested parties	EU Regulatory Authorities (members TIGes and NtA), EFPIA, EGA, other interested parties
2.1.5	eSubmission CMB	EU Regulatory Authorities (NCAs and EMA), EFPIA, EGA, other interested parties
2.1.5	TEAB	Telematic Enterprise Architecture Board (NCAs and EMA)
2.1.5	IT Directors	IT Directors of all NCAs
2.4	EU-Regulators, interested parties	Public consultation
2.4.1	EU-Regulators, interested parties	Review of reconciliation changes
3.0	EU-Regulators, interested parties	Implementers
3.0.2	EU-Regulators, interested parties	Human Harmonisation Maintenance Group
3.0.2 (corrected version)	EU-Regulators, interested parties	Human Harmonisation Maintenance Group
3.0.3	EU-Regulators, interested parties	Human Harmonisation Maintenance Group
3.0.4	EU-Regulators, interested parties	Human Harmonisation Group and eSubmission Expert group
3.1	EU-Regulators, interested parties	Human Harmonisation Group
3.1.1	EU-Regulators	Human Harmonisation Group

TABLE OF CONTENT

Glossary of Terms

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.
eCTD application or also known as a dossier	A collection of electronic 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 ***eCTD application*** may comprise a number of ***regulatory activities***. In the EU an eCTD application may comprise several dosage forms and strengths, all under one invented product name. This is understood to be equivalent to a Global Marketing Authorisation according to Art. 6 para 2 Dir. 2001/83/EC as amended.
Procedure	A Community registration procedure for the authorisation of medicinal products in the European Community. There are 4 types of procedure that operate within the EC – Centralised, Decentralised, Mutual Recognition and National.
Regulatory Activity	A ***single sequence or a collection of sequences*** covering the start to the end of a specific business process, e.g. an MA application or Type II variation. To allow a more precise handling, the regulatory activity will be classified using a controlled vocabulary (submission type or regulatory activity type) and a free text field for a short narrative description.
Sequence	A single set of information and / or electronic documents submitted at one particular time by the applicant as a part of, or the complete application***.*** Any collection of content assembled in accordance with the eCTD specification (ICH and EU) will be described using metadata as defined by the EU envelope. Sequences may be related to one another within one regulatory activity. The related sequence number should always be stated. In case of activities with only one sequence the same sequence number will be used.
Submission Type	The submission type describes the ***regulatory activity*** to which the content will be submitted.
Submission Unit Type	The submission unit type element of the envelope metadata set describes the content at a lower level (a "sub-activity") which is submitted in relation to a defined regulatory activity such as the initial submission, the applicant response to validation issues or list of questions or any other additional information.

Introduction

This document specifies Module 1 of the electronic Common Technical Document (eCTD) for the European Union ("EU").

This document should be read together with the ICH eCTD Specification to prepare a valid eCTD submission in the EU. The latest version of the ICH eCTD Specification can be found at: https://www.ich.org/page/electronic-standards-estri.

EU Module 1: Regional Information

The ICH Common Technical Document ("CTD") specifies that Module 1 should contain region-specific administrative and product information. The content and numbering of Module 1 for the EU is specified in the latest version of the *Notice to Applicants* that can be found at: http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

The following items listed in the Notice to Applicants should be included for an initial submission:

- a cover letter,
- a comprehensive table of contents (in eCTD the XML backbone acts as a 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,
- information relating to orphan market exclusivity (if required),
- information relating to pharmacovigilance,
- information relating to clinical trials (if required),
- information relating to paediatrics.

For eCTD the Module 1 should also include a tracking table.

In addition, other items such as answers to regulatory questions, rationale for variations and renewal documentation could also be included in Module 1.

It should be noted, that for subsequent submissions in the lifecycle of a medicinal product, e.g. for a variation, not all of the above-mentioned types of document need to be included in Module 1. Consult the various legal documents for guidance on the exact documents to be submitted in such a case.

This document describes only the region-specific information that is common to all submissions in the different Member States. However, at the same time the EU Module 1 Specification allows for country-specific information to be included in Module 1, if required.

The acronym 'EMEA' will remain in use in the Product Numbers, however it has been updated to EMA in the various technical texts.

Regional File Formats

Module 1

Generally, the recommended file format for content documents is PDF. All PDF files included in an eCTD (irrespective of the module) should be versions 1.4, 1.5, 1.6, 1.7, PDF/A-1 and PDF/A-2 except where there is an agency-specific requirement for a later version (e.g. for an application form).

For the latest acceptable file formats list, please refer to the document "EU Accepted File Formats for eCTD". Other formats (not specified in the document) for Module 1 content provided outside of the eCTD in the working-documents folder should be used as required by the receiving authority.

For data requested by authorities which needs to be provided in any other format than specified above, please follow the instructions given by requestor.

Use of electronic signatures

Electronic signatures are regulated in EU by Regulation (EU) No 910/2014 of the European Parliament and of the council of 23 July 2014 on electronic identification and trust services for electronic transactions in the internal market and repealing Directive 1999/93/EC. For applications of Marketing Authorisations including post-authorisation submissions, most NCAs and EMA do not require wet or digitally signed cover letters or application forms if submitted through a portal (e.g. CESP and EMA Gateway) with logon credentials. However, some NCAs still require additional signatures and might accept wet signatures, scanned signatures and/or electronic signatures as specified in the CMDh documents 'Requirements on submissions for New Applications within MRP, DCP or National procedures' and 'Requirements on submissions for Variations and Renewals within MRP and National procedures'.
For EMA submissions, in general, qualified and advanced electronic signatures as per the European Commission eIDAS regulation (Regulation (EU) No 910/2014) are accepted.
Please note, if digital signatures are requested in the eAF by a specific NCA, the signature needs to be included in a copy of the finalised eAF and be provided in addition to the original one.

It should be noted that documents that include digital signatures should normally be accepted.

Handling of Empty or Missing eCTD Sections

Placeholder documents highlighting 'no relevant content' should not be included in the eCTD. These files would create a document lifecycle for non-existent documents, and unnecessary complication and maintenance of the eCTD lifecycle. So, sections without information should be left empty and justified in the respective Module 2 document, as relevant.

The EU Module 1 is provided with a standard style-sheet that can be used to view the content. Note that the style-sheet has been designed to display the complete Module 1 table of contents (i.e. all the sections), irrespective of whether files are actually present in those sections or not.
Information about missing eCTD sections, specifically 'M1 sections/documents', should be justified in the "cover letter or notes to reviewer" as required.

Updating backbone attributes/metadata

It is not possible to update XML backbone attributes such as 'manufacturer' during the eCTD lifecycle, nor is it necessary to attempt workarounds such as deleting existing documents and resubmitting them with new attributes. The recommendation is to retain the obsolete entry and to rely on the document content to explain the current details.

Whilst the need for a change to the set of EU Module 1 XML attributes/metadata (this covers country, language and product information type) in the middle of the procedure is deemed to be very rare, it is recommended to contact the agency whether such change could be done during the procedure, along with other changes, or as part of an eCTD "reformat" submission.

General Architecture of Module 1

The EU Module 1 architecture is similar to that of Modules 2 to 5 of the eCTD, comprising a directory structure and a backbone with leaves. The backbone must be a valid XML document according to the EU Regional Document Type Definition (DTD). The backbone instance (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. The root element is "eu-backbone" and contains two elements: "eu-envelope" and "m1-eu".

The EU Regional DTD is modularised, i.e. the envelope and leaves are referenced from the main part of the DTD as external entities called respectively "**eu-envelope.mod**" and "**eu-leaf.mod** ". The EU "leaf" is identical to the leaf element described in the ICH eCTD DTD; reference is made to Table 6-8 of the ICH eCTD Specification. A full description of the EU Regional DTD can be found in Appendix 3 of this specification.

Examples of XML coding for a simple new application, specific regulatory activities and a submission for a National or Mutual Recognition Procedure are provided as an annex to this specification. Examples of XML coding that support the variation regulation are provided as well.

Files can be referred to across modules (e.g. from Module 1 to Module 2) or across sequences within the same eCTD application; note however that it is not possible to refer to files in sequences in other eCTD applications. When referring to files across modules or across sequences, the reference must always be relative, starting from the location of the XML file. For instance, a reference from within Module 1 of Sequence 0003 (e.g. 0003/m1/eu/eu-regional.xml) to a file located in Module 2 of Sequence 0000 (e.g. file "introduction.pdf" in folder 0000/m2/22-intro), would be encoded in the EU Module 1 as "../../../0000/m2/22-intro/introduction.pdf". (This example is not business-specific – it merely serves to demonstrate the principle).

While submitting future sequences during the Lifecycle management of the product, any file(s)/document(s) already submitted in previous sequences should not be added again in eCTD, to avoid complication and extra maintenance. Applicants are encouraged to provide cross reference/hyperlink across sequences to facilitate the dossier review.

Envelope

The "eu-envelope" element is designed to be used for all types of submissions (MAAs, variations, renewals, etc.) for a given medicinal product and will mainly be used for the first simple processing at EMA level. The envelope provides meta-data at the eCTD application and sequence level. A description of each "envelope" element is provided in Appendix 1 of this specification.

For Centralised Procedure submissions, the "eu-envelope" element should contain a single "envelope "element with the country attribute value set to 'EU-EMA'. For all other procedures, the "eu-envelope" element should contain a separate "envelope" element for each Member State involved in the procedure that is going to receive that particular sequence, and each envelope country attribute should be set to the country value of the receiving Member State. Note that the value 'common' cannot be used in the envelope. This is also applicable in case of PSUSA submissions submitted to the PSUR Repository (EMA), as the sequences for nationally authorised products are part of the product eCTD lifecycle in the relevant member state.

If a particular sequence is being sent to a CMS for information only (for example, if the concerned strength is not registered in that country), no "envelope" element should be created for this CMS. However, it should be clear from the cover letter which CMSs are concerned.

The envelope element submission 'mode' should only be used in variation, extension and workshare regulatory activities, and the value can be set to: 'single', 'grouping' or 'worksharing' (see examples in Appendix 1.1). An additional high-level submission number should also be provided in the envelope under the following circumstances:

- For worksharing submissions including PSUSA
  Here, the submission 'mode' value must be 'worksharing'. The high-level number should be the worksharing number. For PSUSA the high-level submission number field should be left empty.

- For submissions of grouped Type 1A variations that affect multiple marketing authorisations (super-grouping)

Here, the submission 'mode' will be '`grouping`' and the high-level number is group number/report' number. Please refer to the annex and associated guidance for further details of this high-level number. Examples of 'single', 'grouping' and 'worksharing' submissions are provided in the annex to this specification.

Such a high-level number, if appropriate, should be provided in addition to the usual product-specific procedure tracking numbers. If the high-level number is required but is not known (e.g. for the first submission of the procedure), this element should be populated with the value 'to be advised'. The relevant number will usually be provided by or obtained from the appropriate tracking system or regulatory agency. In the case of Centralised Procedure this number is always available on the Eligibility Confirmation Letter as 'Product Reference'.
At the time of editing this paragraph (May 2025), the Eligibility Confirmation Letter indicates, for example, product number H0002227. In this case, please eliminate first digit (0) from H0002227 to reflect H002227 in the envelope.
The use of Product Number H/C/xxxxxx is applicable after the Initial MAA has been submitted to the EMA.

Important note: There is a change planned for the format of the product number in the pre-submission phase, where the Eligibility Confirmation letter will indicate already the Product Number H/C/xxxxxx. The previously used format number H00XXXX (e.g. H002227) will not be applicable anymore.

In the case of Centralised Procedure, it is strongly recommended that when applying for a variation and the procedure number has not yet been allocated, then the term 'to be advised' should be used.
If the content of a sequence pertains to more than one submission type (e.g. parallel variations) the highest variation type should be selected as submission type. In this case there will be more than one related sequence. The value of submission unit type will be dictated by the content, e.g. "response".

For submissions to EDQM, the agency name EU-EDQM and the submission type 'CEP application' need to be selected. The submission unit type should be used as appropriate.

m-1-eu

The "`m1-eu`" element of the EU regional DTD is based on the same conceptual approach as the common part of the ICH eCTD DTD. It provides an XML catalogue with meta-data at the leaf level including pointers to the location of files in a directory structure. As for the ICH eCTD DTD, the "`m1-eu`" element maps to the directory structure. (There may at times be what is seen to be an apparently 'redundant' directory structure, but this is necessary in order to be able to use the same file / directory structure for all procedures.) Furthermore, as the same structure will be used during the lifecycle of the submission, the use of country directories even to place a single file in one submission is justified because it could be used to house several files in a subsequent submission, and in doing so the structure would not change. A tabular overview of the directory structure explaining where to place country and language-specific files is provided in Appendix 2 of this specification.

Directory / File Structure

The EU Module 1 Specification provides a directory and file structure that is strongly recommended:

- The same high-level directory structure is used for all 4 procedures (Mutual Recognition, , Decentralised, National and Centralised Procedures). This is possible, despite the fact that files for the Mutual Recognition, Decentralised and National Procedures are usually country-specific, whereas files for the Centralised Procedure are usually language-specific.
- Country directories are named according to Appendix 2.1.
- Language directories are named according to Appendix 2.2.
- The recommended directory structure for the use of country and language identifiers is described in Appendix 2. In general, Modules 1.0, 1.2, 1.3.2, 1.3.3, 1.3.4, 1.3.5, 'Additional Data' and 'Responses' have country subdirectories. Module 1.3.1 (Product Information) has both country and language subdirectories.
    - For the Centralised Procedure, the country subdirectory is always named either "ema" or "common", irrespective of whether it contains "common" or country folders; language subdirectories in Module 1.3.1 have the appropriate language identifier.

- For Mutual Recognition, Decentralised and National Procedures:
  - Documents for each country are placed in an appropriately named subdirectory. The folder name "common" should only be used for documents potentially applicable to all EU countries, irrespective of whether they are currently involved in the procedure or not.
  - In Module 1.3.1, every document should be placed in an appropriately named language subdirectory, even if the country only has one official language. Where a country has more than one official language (e.g. Belgium) separate language subdirectories should be used for each set of documents in a different language.
  - Should a country have documents in more than one language in a Module other than 1.3.1, then it is recommended to use the VAR (variable) part of the filename to identify the language of the document.

Node Extensions

Node extensions are a way of providing extra organisational information to the eCTD. The node extension should be visualised as an extra heading in the CTD structure and should be displayed as such when the XML backbone is viewed.

However, the **use of node extensions should be limited to those areas where it is critical**. Consideration should be given regarding the impact of the view for the reviewer since the inconsistent use of node extensions can lead to unanticipated effects in the cumulative view of a submission.

The following rules govern the use of node extensions in the EU:

- Node extensions must not be used where ICH-specified sub-headings already exist (e.g. indication, manufacturer, drug substance and drug product are all-ICH specified node extensions).
- Node extensions must only be used at the lowest level of the eCTD structure (e.g. a node extension can be used at the level 5.3.5.1 but must not be used at the level 5.3).
- Node extensions are mainly to be used to group together documents made up of multiple leaf elements (e.g. a clinical study made up of separate files for the synopsis, main body and individual appendices could be grouped together under a node extension with the Study Identifier as its Title attribute).
- Node extensions must be maintained over the entire life of the eCTD lifecycle (e.g. if a node extension is used in Sequence 0000 to group files for a study report in Module 5.3.5.1, then any files submitted in a later sequence must also be placed under a node extension, even if only one file is submitted).
- Node extensions may be nested as this is allowed by the eCTD DTD. However, as noted in Bullet 2, the first node extension must be at the lowest level in the eCTD structure (e.g. in Module 5.3.7 a node extension may be added to group together files with the Study Identifier as Title attribute). Further node extensions may be added as children of the Study Identifier node, separating CRFs from individual patient listings.
- The content associated with a node extension can be placed in a separate sub folder in the submission; this is recommended for studies in Module 5 where study reports are provided as multiple files. However, there is no specific requirement for an additional subfolder. For example, if node extensions are used to further define ‘m1-responses’, additional folders under ‘m1/eu/responses/cc’ are not recommended. Instead, for navigational support the variable part of the file name can be used as outlined in the next section.

File Naming Convention

File names in Module 1 follow one of two conventions.

Country-specific items in sections *1.0; 1.2; 1.3; m1-responses* and *m1-additional-data* have the general structure CC-FIXED-VAR.EXT, where CC is a country code used in some CTD modules, FIXED is a defined component of the filename based on the CTD section and VAR is an additional optional variable component. EXT represents the file extension. Components are separated by a hyphen (except the dot

for the file extension). No spaces should be used within each component but hyphens can be used in the variable part to separate several words.

Fixed components are highly recommended. The variable component is optional and should be used as appropriate to further define these files. The variable component, if used, should be a meaningful concatenation of words with the option of hyphens for separators and should be kept as brief and descriptive as possible to avoid exceeding the maximum path length. File extensions in line with this specification should be applied as applicable.

The first component in a file name should be the country code, as per Appendix 2.1, except when the document is valid for all countries in all procedures, as per Appendix 2. The second component should be the document type code, as per Appendix 2 and 2.3. The third component if necessary should be the variable component. In cases where differentiation is needed (e.g. between 1.5mg and 15mg) the word 'point' written in full (i.e. '1point5mg') or a hyphen can be used (i.e.'1-5mg').

There are no recommendations for variable components in this specification. The format of the file is indicated by the file extension. File names should always be in lowercase, in line with the ICH eCTD specification.

Examples:

fr-cover.pdf
be-form-eaf.pdf
it-form-annex-01.pdf
pt-form-annex-proofpayment.pdf
se-outer-tablet10mg.pdf
ema-combined-tablet1-5mg.pdf
ema-combined-tablet10mgannotated.pdf
nongmo.pdf

In m1-responses/cc, the recommendation is to use cc-responses-<regulatory activity type identifier>-<timeline identifier>-<content identifier>.pdf, using the -var component of the filename to define the content. It is recommended to use the variable component of the filename and the leaf title, to present the information clearly to the assessor.

Examples:

common-responses-maa-d106-clin.pdf Leaf title: Day 106 Clinical Responses, MAA
common-responses-var05-d59-qual.pdf Leaf title: Day 59 Quality Responses, Var 05

Non-country specific items in Sections *1.4; 1.5; 1.6; 1.7; 1.8; 1.9 and 1.10* have fixed file names, as defined in Appendix 2.

Folder and File Name Path Length

The overall folder and file name path length starting from the sequence number should not exceed 180 characters, for any file in any module. This is an EU regional requirement, and it is acknowledged that this is less than the ICH agreed overall path length.

Business Protocol

It is clear that the detailed business process between industry and a regulatory agency in the EU cannot be completely harmonised due to the differences in organisation and processes. The exact description has to be provided by the EMA, EDQM or the individual Member States. However, a few common steps can be identified and will be detailed in the Harmonised Technical Guidance for eCTD Submissions in the EU. The EDQM and most national agencies are unable to provide positive feedback of technically valid submissions. However, if there is any problem experienced during the upload of the sequence, agencies will promptly inform the applicants. Please note that the EMA provides automated feedback

(acknowledgement) of technical validation for submissions received via their eSubmission Gateway and Web Client.

Universal Unique Identifier (UUID)

In the EU, although the eCTD envelope contains several pieces of information about the eCTD application that the sequence belongs to, such as the procedure number and the trade name, there have been instances when an eCTD sequence has been loaded into the wrong application by the receiving agency. For this reason, all eCTD sequences built in accordance with this specification must contain a(UUID, linking the sequence to the eCTD application to which it belongs.

The UUID is used by the authorities to facilitate archiving the sequence with the correct eCTD lifecycle and some authorities also use it for automated sorting of incoming eCTD submissions to the correct eCTD lifecycle. It is important that the UUID for each eCTD lifecycle is unique and it should therefore always be machine generated, i.e. be created by the eCTD building tool or, if not possible, by using an online UUID generator. Creating the UUID with uppercases or lowercases is not restricted but needs be kept as chosen during the full lifecycle.

The applicant should generate a UUID based on ISO/IEC 11578:1996 and ITU-T Rec X.667 | ISO/IEC 9834-8:2005. It is a hexadecimal number in the form of xxxxxxxx-xxxx-xxxx-xxxx-xxxxxxxxxxxx, showing 32 digits and 4 hyphens. The 'x' will be replaced by a number or a letter. It is recommended to use randomly generated sections (version 4 of UUID types). Such UUID would for example look like 4cc86cf0-9088-4a3c-9526-fa6320f4c469.

This structure guarantees uniqueness across applicants and applications. The UUID will be generated for the first time when creating the first sequence following the implementation of the UUID requirement in the specification and will be provided in the eCTD envelope. All subsequent sequences for that same eCTD lifecycle should contain the same UUID. In this way, sequences can be allocated automatically to the correct eCTD lifecycle by the receiving agency and it is therefore important that the UUID is kept for the eCTD for its entire lifecycle. The UUID should also be transferred to any new MAH and should also remain the same in cases where the procedure number changes due to an RMS change. Any independent application with its own life cycle should have its own UUID, e.g. CEP applications to the EDQM or referral stand-alone eCTD submissions not being part of an existing eCTD application
The only exceptions to the above are when the eCTD is split or merged (see Q&A) or the eCTD is fully re-baselined by submitting a new 0000 sequence for that eCTD (see details in section 2.12.3 of the Harmonised Technical Guidance for eCTD Submissions in the EU).

The backbones of previously submitted, technically valid, sequences not containing the UUID do not need updating. So, only eCTD sequence created since the introduction of the UUID into this specification must have a UUID, and this will be tested with the relevant validation criteria.

Beside the technical validation checking the correct UUID, some authorities can also check that the UUID is not the same as in another already existing eCTD lifecycle in the authority's eCTD repository. Although extremely unlikely, this has been experienced, probably by copying a UUID from an example given somewhere or from another eCTD. Since the UUID is used by some authorities in the automatic processing of eCTD sequences, it is important that each UUID in the eCTD repository is unique. Therefore, even if this is not part of the eCTD technical validation criteria, in such cases, the authority will contact the applicant/MAH and request an updated eCTD sequence with a new UUID. If this is not the first sequence of the eCTD lifecycle, the applicant/MAH must also update all previously submitted sequences in the eCTD lifecycle that have been assigned this same UUID. In case the eCTD lifecycle includes a large amount of sequences with this UUID, the NCA and the applicant/MAH might agree on a pragmatic solution to fix the problem. The updated eCTD sequence(s) should be submitted with a new UUID to all authorities concerned by the eCTD sequence/lifecycle using the same sequence number(s). A comment should be included in the CESP delivery file that the eCTD is a technically corrected sequence (corrected UUID) that is re-sent. The sequence(s) should not include any other changes to the earlier submitted sequence(s) than just the new UUID. Where the identical UUID would be the same as in another already existing eCTD lifecycle for eCTD sequences within the Centralised Procedures, EMA will contact the applicant/MAH with specific instruction of the handling, since this cannot be handled within the normal Gateway delivery.

Change Control

The EU Module 1 specification is likely to change with time. Factors that could affect the content of the specification include, but are not limited to:

- Change in the content of the Module 1 for the CTD, either through the amendment of information, at the same level of detail, or by provision of more detailed definition of content and structure
- Change to the regional requirements for applications that are outside the scope of the CTD
- Update of standards that are already in use within the eCTD
- Identification of new standards that provide additional value for the creation and/or usage of the eCTD
- Identification of new functional requirements
- Experience of use of the eCTD by all parties, in particular Module 1.

For any proposed changes to the eCTD v3.2.2 specification or the related validation rules, please raise a ticket via the EMA service desk.

Appendix 1: The EU Module 1 XML Submission

The EU Module 1 XML Submission contains an element for each Table of Contents entry of the Notice to Applicants Module 1. The following sections describe information that is captured within the Module 1 XML submission in an eCTD, but which is not captured within the Notice to Applicants Table of Contents for Module 1.

Appendix 1.1: Envelope Element Description

The "`eu-envelope`" element is the root element that defines meta-data of the submission. This element may contain several envelope entries, each related to a specific country.

The list of elements is provided in the SPOR portal Referentials Management Service (RMS).

The following table indicates a subset of data elements taken from different RMS controlled vocabularies (see references in the table) and describe the only allowed terms for usage in eCTD submissions.

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
eu-envelope		Root element that provides meta-data for the submission. This element may contain several envelopes, which are country specific.	N/A	**Mandatory**	**Unique**
envelope		Parent element for the submission meta-data. This element must be country-specific or in the case of the Centralised Procedure, '`ema`' and in the case of CEP applications '`edqm`'.	N/A	**Mandatory**	**Repeatable**
	country	The country to which the envelope applies (or '`ema`' or respectively' `edqm`').	**be**	**Mandatory**	**Unique**
identifier		A UUID as specified by ISO/IEC 11578:1996 and ITU-T Rec X.667 | ISO/IEC 9834-8:2005. The same UUID will be used for all sequences of an eCTD application	25635f23-a3a4-c4e0-b994-99c5f074960f	**Mandatory**	**Unique**
submission		Provides administrative information associated with the submission.	N/A	**Mandatory**	**Unique**

	type	The type of regulatory activity to which the content will be submitted. The following are the valid values (from RMS: 1000000155688 Application Submission Type): ▪ `maa` = Marketing Authorisation Application ▪ `var-type1a` = Variation Type IA ▪ `var-type1ain` = Variation Type IA_{IN} (This submission type should also be used in case of a grouped type IA variation where at least one variation type IA_{IN} is included.) ▪ `var-type1b` = Variation Type IB ▪ `var-type2` = Variation Type II ▪ `var-nat` = National variation (e.g. national variation to apply for a pack size that is already registered within an existing MRP/DCP authorisation) ▪ `extension` = Extension ▪ `rup` = Repeat Use Procedure in decentralised or mutual recognition procedures to include one or more additional member states ▪ `psur` = Periodic Safety Update Report (PSUR) which should only be used for PSURs outside of the PSUSA ▪ `psusa` = PSUR single assessment procedure ▪ `rmp` = Risk Management Plan (outside any procedure) ▪ `renewal` = Renewal (yearly or 5-yearly) ▪ `pam-sob` = Specific obligation related to a post-authorisation measure ▪ `pam-anx` = Annex II condition related to a post-authorisation measure ▪ `pam-mea` = Additional pharmacovigilance activity in the risk-management plan (RMP) or related to post-authorisation measures following PSUR observations (e.g. interim results of imposed/non-imposed interventional/non-interventional clinical or nonclinical studies) (PSUFU procedure) ▪ `pam-leg` = Legally binding measure related to a post-authorisation measures ▪ `pam-sda` = Cumulative review following a request originating from a PSUR or a signal evaluation related to a post-authorisation measure ▪ `pam-capa` = Corrective Action/Preventive Action related to a post-authorisation measure ▪ `pam-p45` = Paediatric submissions related to a post-authorisation measure ▪ `pam-p46` = Paediatric submissions related to a post-authorisation measure ▪ `pam-paes` = Submission of a post authorisation efficacy study ▪ `pam-rec` = Recommendation related to a post-authorisation measures e.g. quality improvement related to a post-authorisation measure ▪ `pass107n` = Submission of a post authorisation safety study protocol (according article 107n Dir. 2001/83/EC). This code should also be used for post authorisation safety study protocol according to Article 107oDir. 2001/83/EC	var-type2	**Mandatory**	**Unique**

		▪ pass107q = Submission of a post authorisation safety study report (according article 107q) ▪ asmf = Active Substance Master File ▪ pmf = Plasma Master File ▪ referral-20 = Referral under Article 20 Reg (EC) 726/2004 ▪ referral-294 = Referral under Article 29(4) Dir. 2001/83/EC. This code should also be used for Referral under Article 29(1) Dir 2001/83/EC and Referral under Article 13 Commission Reg (EC) 1234/2008 ▪ referral-29p = Referral under Article 29 paediatric Reg (EC) 1901/2006 ▪ referral-30 = Referral under Article 30 Dir 2001/83/EC ▪ referral-31 = Referral under Article 31 Dir 2001/83/EC ▪ referral-35 = Referral under Article 35 Dir 2001/83/EC ▪ referral-5-3 = Referral under Article 5(3) Reg (EC) 726/2004 ▪ referral-107i = Referral under Article 107i Dir 2001/83/EC ▪ referral-16c1c = Referral under Article 16c (1c) Dir 2001/83/EC ▪ referral-16c4 = Referral under Article 16c(4) Dir 2001/83/EC ▪ annual-reassessment = Annual Reassessment ▪ usr = Urgent Safety Restriction ▪ clin-data-pub-rp = Clinical data for publication – Redacted Proposal ▪ clin-data-pub-fv = Clinical data for publication – Final Version ▪ paed-7-8-30 = Paediatric submission related to a paediatric investigational plan according to article 7, 8 or 30 of the Reg (EC) 1901/2006 ▪ paed-29 = Paediatric submission post approval once a paediatric investigational plan has been performed, according to article 29 of the Reg (EC) 1901/2006 ▪ paed-45 = Paediatric submission according to article 45 of the Reg (EC) 1901/2006 ▪ paed-46 = Paediatric submission according to article 46 of the Reg (EC) 1901/2006 ▪ article-58 = Article 58 Reg (EC) 726/2004 (to be used for an initial application) ▪ notification-61-3 = Notification 61(3) Dir 2001/83/EC ▪ transfer-ma = Transfer of a marketing authorisation ▪ lifting-suspension = Lifting of a suspension ▪ withdrawal = Withdrawal of a marketing authorisation in regard to a strength or form or entirely. This submission type shall not be used to withdraw a regulatory activity. ▪ cep = Submission that applies to an application on a Certificate of suitability CEP application (EDQM only). ▪ none = In the exceptional case of reformatting the application no regulatory activity is allowed. Therefore, 'none' must be stated. The submission application unit will			

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
		identify the sub-activity related to the product. In the submission description some information can be provided to e.g. highlight specific modules being reformatted. ▪ `Article-18` = For the review of the available scientific data on medicinal products which have the potential to be used to address the public health emergency (Regulation - 2022/123 - EN - EUR-Lex (europa.eu))			
		N.B. Officially, Roman numerals are used for variations, e.g. Type IA, Type II – the elements must remain Arabic, however.			
	mode	The high-level handling of the information submitted as part of variation(s) and extension applications. The mode should only be used in variation or line extension regulatory activities and must be included in every sequence of that activity. The following are the valid values (from RMS 100000155553 Submission Mode): ▪ `single` = a single regulatory activity (e.g. a Type II variation) ▪ `grouping` = a grouped activity (e.g. several variations grouped into a single submission, or a report of type IA variations applicable to one or more marketing authorisations) ▪ `worksharing` = an activity subject to a worksharing agreement (e.g. a Type II variation) and should also be used for all PSUSA submissions even if only one product is covered. This information should be identical with the information provided/ticked in the application form.	Single	**Optional** *(note that this element must be populated for sequences in variation and line extension activities)*	**Unique**
number		This is the high-level submission number, either a 'worksharing' number, or the high-level submission number to be used when grouping Type IA variations for multiple marketing authorisations (super-grouping). In case of a grouping concerning only one single marketing authorisation or for any PSUSA submissions, this number field should be left empty. (Note that for submissions affecting multiple MAs, the 'xxxx' used in the submission number is a permanent placeholder, as a single product number cannot be provided). If the Applicant did not obtain the sequential number from the relevant Authorities in advance of their application this field should be populated as "xxxx". For centrally authorised products this number must always be obtained in advance by sending an email to PA-BUS@ema.europa.eu.	For worksharing: **EMA/VR/xxxxxxxxxx** **For grouped IAs (super-grouping):** **EMA/VR/xxxxxxxxxx**	**Optional**	**Unique**
procedure-tracking		Provides administrative information associated with the application.	N/A	**Mandatory**	**Unique**

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
	number	This is any number, used by an agency or the applicant to track the submission, in any procedure, in relation to a particular product. This could be one or more of the following: • an MRP/DCP number (e.g. `DE/H/0126/001/MR`), • a national procedure number (e.g. `2131577`), • the EMA application number (e.g. `EMEA/H/C/000123` or **EMA/VR/xxxxxxxxxx** or in case of sequences after 'initial', (e.g. '`response`' or '`additional-info`'), **EMA/VR/xxxxxxxxxx**), • an authorisation or licence number, (e.g. `EU/1/00/44/0003 – 0004`), • any other number used by an agency to track a submission, (e.g. `PL01234/0003-0004`)	For examples, see bullet points in the column on the left-hand side	**Mandatory**	**Repeatable**

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
		• a number used by the applicant to manage the submission within their company (e.g. `Pharmacompany123`) There must be at least one tracking number identified from the regulators and, in addition, the applicant can choose to include an internal tracking number. In the case of Centralised Procedure, it is strongly recommended that when applying for a variation and the procedure number has not yet been allocated, then the term 'to be advised' should be used (no internal number from the applicant should be used). However, if the full procedure number including the suffix for the variation is known, it must be added in this field to allow an appropriate display in the Central Repository, e. g. **EMA/VR/xxxxxxxxxx**. For details of number allocation for the centralised procedure, see the relevant guidance here, under the section, "4.7 How is an EMA application/procedure number attributed?". In the case of Decentralised and Mutual Recognition Procedures the numbering schema is available here, under section "7. Numbering System for the Procedures for Mutual Recognition and Decentralised Procedure". It is suggested that if the procedure number has not yet been allocated by the agency then the term 'to be advised' should be used. Applicants should consult national guidance for further information. In case of worksharing or grouped Type IA variations applying to more than one MA, a separate eCTD submission must be built for each MA covered by the variation. In the envelope of each of the eCTD submissions, the high-level submission number will be the same, but the individual tracking numbers listed here should be specific to the MA in question, e.g.: For worksharing, for grouped variations (including super-grouping): • **EMA/VR/xxxxxxxxxx** In case of PSUSA • `PSUSA/00123456/201709` (no individual procedure numbers are required) Please ensure that these WS/super-grouping numbers are always mentioned in the case of additional information or corrigendum otherwise the Agency might not be able to process your submission correctly.			

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
submission-unit		Submission unit type describes the content at a lower level (a “sub-activity”) which is submitted in relation to a defined regulatory activity. The following are the valid values (from RMS: 100000155046 Applicants Submission Unit Type): ▪ `initial` = Initial submission to start any regulatory activity ▪ `validation-response =` For rectifying business validation issues. ▪ `response` = submission unit type that contains the response to any kind of question, out-standing issues information requested by the agency ▪ `additional-info` = Other additional Information (could include, for example, missing files) and should only be used, if `validation-response` or `response` is not suitable ▪ `closing` = Submission unit type that provides the final documents in all procedure types (centralised, mutual recognition, decentralised, national) following the decision of the European Commission ▪ `consolidating` = Submission unit type that consolidates the application after several information in the MRP or DCP handled outside the eCTD but that need to be integrated thereafter to maintain the life cycle properly. This submission unit type should also be used for national, MRP/DCP or CAPs when consolidating the dossier as a result of withdrawing or rejecting a single regulatory activity (not in case of the withdrawal of the entire application). ▪ `corrigendum =` Correction to the published annexes in the centralised procedure (usually shortly after approval) ▪ `reformat` = Intended to support the reformatting of an existing submission application from any format to eCTD, i.e. a baseline eCTD submission containing no content change and which will not be subject to review (see example below). This type will always be used together with the submission type ‘`none`’ ▪ `re-examination` = Used for requesting a re-examination of a CHMP opinion (applicable for MAA, extension, type II variation, renewal, annual re-assessment, referrals)	response	**Mandatory**	**Unique**
applicant		The name of the company submitting the eCTD.	**PharmaCompany Ltd.**	**Mandatory**	**Unique**
agency		Parent element for the identification of the receiving agency.	N/A	**Mandatory**	**Unique**
	code	The identification of the receiving agency (see Appendix 2.4).	**EU-EMA**	**Mandatory**	**Unique**
procedure		Defines the procedure in use with the submission	N/A	**Mandatory**	**Unique**

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
	type	The type of procedure for the submission. The following are the valid values (from RMS 100000154442 EU Regulatory Authorisation Procedure): ▪ `centralised` = Centralised Procedure ▪ `national` = National Procedure ▪ `mutual-recognition` = Mutual Recognition Procedure ▪ `decentralised` = Decentralised Procedure	**Centralised**	**Mandatory**	**Unique**
invented-name		The name of the medicinal product.	**WonderPill**	**Mandatory**	**Repeatable**
inn		International Non-proprietary Name, used to identify pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A non-proprietary name is also known as a generic name.	**Pioglitazone hydrochloride**	**Optional**	**Repeatable**
sequence		This is the sequence number of the submission – this should start at 0000 for the initial submission, and then increase incrementally with each subsequent submission related to the same product e.g. `0000, 0001, 0002, 0003` etc.	**0000**	**Mandatory**	**Unique**
related-sequence		This is the sequence number of previous submission(s) to which this submission relates e.g. the responses to questions to a particular variation. In the case of submission unit types '`initial`' and '`reformat`' related sequence is identical to the sequence number.	**0001** see also annex document	**Mandatory**	**Repeatable**
submission-description		This element is used to provide a free text description of the submission. The list below provides additional examples for such a field: ▪ For an MAA: Original MAA Application for <Product X> ▪ For a Type II variation: Please quote the scope of variation from the Application Form ▪ For a Type IB variation: Please quote the scope of variation from the Application Form ▪ For an Annual Reassessment submission: 4th AR submission for <Product X> ▪ In case of a referral related submission: Referral under Article YY ▪ For responses: Response to validation questions / Response to D120 LOQ ▪ For supplementary information: Providing supplementary information regarding xx	**Response to D120 LOQ**	**Mandatory**	**Unique**

Example of the use of the Related Sequence and the Submission Unit type elements

The related-sequence element is used to identify sequences belonging to the same 'regulatory activity'. A 'regulatory activity' is a logical unit of submission activity (e.g., a Type II Variation) with a defined start and end point (e.g. initial submission to final approval). In eCTD, this will consist of all the sequences that together make up the lifecycle of that particular 'regulatory activity'. The Submission Unit type element describes the stage within the regulatory activity, such as initial, response, consolidating.

For new regulatory activities ("initial") and for "reformat", the related-sequence attribute should always be equal to the sequence number. When submitting lifecycle sequences within an existing activity, the related-sequence attribute should be populated with the sequence number the regulatory activity has been started with.
Therefore, **when submission unit = initial or submission_unit = reformat, then the related sequence number always = sequence number and vice versa, when the submission unit ≠ initial or the submission_unit ≠ reformat , the related sequence always < sequence number**. See below for some illustrative examples.

The submission unit type should be populated with the respective term describing the content of the sequence to be filed at that point in time. See below for some illustrative examples.

It is generally expected that there is usually just one related sequence, but there are occasions where more than one related sequence should be provided: e.g. there are two post authorisation measures (sequence 0050 and sequence 0060) and a single response (sequence 0070) is produced that relates to both post authorisation measures. If more than one different category of activities (submission Types) are referred to (as related sequence), then the "highest category" should be used in the envelope attributes. If any of the related variations were grouped, then 'grouping' should be used. For any of the submission types (regulatory activities) an initial and any of the additional submission unit types can be used, e.g. 'response' in case of responses to list of questions or out-standing list of issues. The post authorisation measure may have an initial and additional-info submission unit type. The submission description may describe details if this content is related to e.g. an earlier defined obligation or to which day in the procedure the response is assigned to.

Special attention should be paid to the correct use of the related-sequence element when the regulatory activity is a variation that covers more than one Marketing Authorisation. An example is given in the Annex.

Sequence	Submission description	Submission type	Related sequence	Submission unit type	Comment
0000	Original MAA application	maa	0000	initial	This is the beginning of a new regulatory activity and so the submission unit type is 'initial'. The related sequence will be identical with the sequence number (i.e. 0000 in this example).
0001	Day 121 Responses to questions on the original application	maa	0000	response	This is a continuation of the regulatory activity 'maa' initiated in 0000 and so the related sequence points to the beginning of that activity. The submission unit type describes the actual contribution 'response' being submitted within maa regulatory activity

0002	Day 181 Responses to further questions on the original application	maa	0000	response	This is a continuation of the regulatory activity ‘maa’ initiated in 0000 and so the related sequence points to the beginning of that activity The submission unit type describes the actual contribution ‘response’ being submitted within maa regulatory activity
0003	Letter of Undertaking (submission unit type: additional info)	maa	0000	additional-info	This is a continuation of the regulatory activity initiated in 0000 and so the related sequence points to the beginning of that activity. The submission unit describes the actual contribution ‘additional-info’ being submitted within maa regulatory activity
0004	Type II variation for ‘Treatment of Pain’ indication	var-type2	0004	initial	This is the beginning of a new regulatory activity ‘var-type2’ and so the submission unit is ‘initial‘. The related sequence will be identical with the sequence number 0004.
0005	Type II variation for a change in manufacturing site (Westferry)	var-type2	0005	initial	This is the beginning of another new regulatory activity ‘var-type2’ and so the submission unit is ‘initial‘. Again, the related sequence will be identical with the sequence number 0005.
0006	Responses to questions on Type II variation for ‘Treatment of Pain’ indication	var-type2	0004	response	This is a continuation of the regulatory activity initiated in 0004 and so the related sequence points to the beginning of that activity. The submission unit type ‘response’ indicates that this is a response to questions.
0007	Responses to questions on Type II variation for change in manufacturing site (Westferry)	var-type2	0005	response	As above, but this is a continuation of the regulatory activity initiated in 0005
0008	Extension to introduce a new dosage form (iv solution) that amends information provided in the original application and the manufacturing change variation	extension	0008	initial	This is the beginning of a new regulatory activity and so the submission unit type is ‘initial’, The related sequence will be identical with the sequence number 0008.
0009	Updated, agreed, product information taking into account new indication (‘Treatment of Pain’)	var-type2	0004	response	This is the completion of the new indication (‘Treatment of Pain’) activity, the related sequence points to the sequence which was ‘initial’ for this activity, and submission unit indicates that this is a response to questions.
0010	Updated, agreed product information for the iv formulation	extension	0008	consolidating or closing	This is the completion of the new dosage form (iv solution) extension, and so the related sequence is the sequence that started the activity. Submission unit type ‘consolidating’ indicates that further lifecycle ‘fixes’ have been applied in the sequence. If only the final product information text version will be submitted, the submission unit type ‘closing’ will be appropriate.

For a new regulatory activity, the appropriate submission type should be used. Applicants should refer to the submission type descriptions in the EU Module 1 specification. For the submission unit type that initiates a regulatory activity the term ‘initial’ should always be used. For subsequent sequences within that regulatory activity the respective terms should be selected from the submission unit type values in the EU M1 specification. The related sequence will be maintained as another way to describe relationships and will be especially meaningful in case of parallel variations.

After the Regulatory Activity has concluded a consolidation of the application may be necessary as in the late phase of the procedure direct exchange of draft documents and interim communication has happened. Final decision, final assessment reports and final versions of the product information texts should be submitted within a consolidating sequence. If only the final product information text version is being submitted the submission unit type ‘closing’ should be chosen. The submission type ‘corrigendum’ should only be used in exceptional circumstances to correct information, typically for the product information annexes to be provided in the centralised procedure.

Tables 1, 2 and 3 provide examples of this convention.

Table 1: Example of a MAA in the Centralised Procedure

Sequence number	**Submission Description**	**Submission Type**	**Related Sequence**	**Submission Unit Type**
0000	MAA	maa	0000	initial
0001	Validation update	maa	0000	validation-response
0002	Day 121 responses	maa	0000	response
0003	Day 181 responses	maa	0000	response
0004	Day 210 Agreed English product information	maa	0000	response
0005	Day 215 – translated product information	maa	0000	response
0006	Final translations of product information for Decision after closing the procedure	maa	0000	response
0007	Correction of errors in Danish product information after Decision	maa	0000	corrigendum

Table 2: Example of a MAA in the Decentralised Procedure

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit Type
0000	MAA	maa	0000	initial
0001	Validation update	maa	0000	validation-response
0002	Day 106 responses	maa	0000	response
0003	Day 180 responses	maa	0000	response
0004	Day 210 Agreed English product information	maa	0000	response*
0005	consolidation after closure of procedure	maa	0000	consolidating**

* If only the final product information text version is necessary to be submitted the submission unit type 'closing' should be chosen.

** In case not all outstanding consolidation has been done by sequence 0004 this additional sequence 0005 is required.

Table 3: Example of a Variation

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit Type
0008	Variation for new indication of COPD	var-type2	0008	initial
0009	Validation update	var-type2	0008	validation-response
0010	Responses to questions	var-type2	0008	response

Example of the use of the submission type 'referral-31'

Referrals according to article 31 are covering in many cases applications from different procedures. For these procedures, creating a specific stand-alone eCTD is recommended and the eCTD envelope should then reflect all the products included in the referral i.e. this single submission would cover all concerned nationally authorised products (NP, MRP, DCP) as applicable. However, if any CAPs are included in the referral procedure, separate eCTD sequences should be submitted as per product lifecycle and if preferred by the applicant, lifecycle sequences per NP, MRP or /DCP product would also be accepted. The envelope should indicate the referral procedure number in the Procedure-Tracking Number(s)..

Envelope for EMA	
UUID	c3ac0ae6-f07e-4ead-8f35-403429361d5b
Submission:	Type: Referral-31
Submission:	Mode: worksharing
Number	EMEA/H/A-31/1234 [optional, the referral procedure number or empty]
Procedure-Tracking Number(s):	EMEA/H/A-31/1234 [This is the referral procedure number]
Submission Unit	Type: initial
Applicant:	Miracle Pharmaceuticals, Inc.
Agency:	EMA - European Medicines Agency (EU-EMA)
Procedure:	Centralised Procedure [As the referral procedure is centralised.]
Invented Name:	Ibuprofen referral
INN:	Ibuprofen
Sequence:	0000 [The sequence number will be the first one due to the separate referral life cycle].
Related-Sequence:	0000
Submission Description:	Referral under Article 31 evaluating hemorrhagia risk

In case of only one product concerned by a referral (in relation to an MRP or DCP) the submission mode should be set to single and the Number should not be filled. The procedure type should remain MRP or DCP and the sequence number must reflect the next free number of the eCTD lifecycle:

Envelope for CZ	
UUID	111954d7-a702-46b0-bc6b-483a38a63d50
Submission:	Type: Referral-31
Submission:	Mode: single
Number	
Procedure-Tracking Number(s):	PT/H/9999/001-002 [This is the original MRP number which will serve to allocate the application correctly. In this case no high level procedure number is needed in addition.]
Submission Unit	Type: initial
Applicant:	Miracle Pharmaceuticals, Inc.

Agency:	CZ – State Institute for Drug Control (CZ-SUKL) [Receiving Member State]
Procedure:	Mutual Recognition Procedure (MRP) [As the referral procedure remains non-centralised even if coordinated by EMA.]
Invented Name:	Proprietary-Wonderdrug
INN:	Ibuprofen
Sequence:	0004 [The sequence number needs to be the next available sequence number within the product life cycle].
Related-Sequence:	0004 [The related sequence number will be identical to sequence number in this case].
Submission Description:	Referral under Article 31 evaluating hyper-sensitivity reactions

Any variation application required as a result of a referral outcome should be submitted in eCTD format per concerned product as for other variations.

Example of the use of the submission unit type 'reformat'

The submission unit type 'reformat' should be used for each baseline submission. (Note: the submission unit type 'additional-info' should not be used for the second reformat submission.) Related sequence should be equal to the sequence number.
An example is given below.

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit Type
0000	Baseline of Modules 4 & 5	none	0000	reformat
0001	Variation for new indication of COPD	var-type2	0001	initial
0002	Baseline of Module 3	none	0002	reformat
0003	Extension for 8mg tablet	extension	0003	initial

Example of how to use the submission type 'withdrawal' and how to indicate the withdrawal of a single regulatory activity or a strength or pharmaceutical form

If a regulatory activity (e.g. variation) needs to be withdrawn or was rejected by agency, the sequence needs to re-establish the previous status of the dossier. Submitted documents justifying the regulatory activity (e.g. variation) need to be deleted or replaced by the previous version of a document. Therefore, the submission unit type of that sequence is 'consolidating'.

The submission description should state the intention of withdrawing the regulatory activity (e.g. variation) number (sequence 0007 from first example above). The related sequence points to the sequence number used for the initial submission of the regulatory activity (e.g.variation) as mentioned.

In case a strength or form will be withdrawn (but not the entire product) a new sequence must be created to delete from the dossier all documents that are no longer valid. Although this sequence will consolidate the dossier, the withdrawal of a strength is a variation and need to be handled as a new regulatory activity.

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit Type
0011	Withdrawal of variation to change manufacturing site 'Westferry'	var-type2	0007	consolidating
0012	Variation for new indication of back pain	var-type2	0012	initial
0013	Response to clinical questions	var-type2	0012	response
0014	Final product information texts	var-type2	0012	closing
0015	Withdrawal of strength 200 mg	var-type1b	0015	initial

In case of withdrawing the entire MA application or the already authorised product (i.e. the full eCTD dossier) the withdrawal submission sequence needs to state this in a simple way (using submission description text field). This is considered as a regulatory activity, the submission type is 'withdrawal', the submission unit type 'initial' and the related sequence will be identical with the sequence number.

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit Type
0016	Withdrawal of the MA application (entirely)	withdrawal	0016	initial

For more information on the withdrawal process, please consult the Variations in eCTD format Q&A document.

Appendix 1.2: Country-Specific Elements

A number of the elements that represent NtA Module 1 TOC headings possess the child element "`specific`", which allows country-specificity of content to be explicitly indicated.

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
specific		Parent element for identifying the receiving country for a document or documents.	N/A	Mandatory	Repeatable
	country	The receiving country for the document(s) (or "common") (see Appendix 2.1 for full list of allowable values)	se	Mandatory	Unique

Module 1 elements that have "specific" child elements can therefore contain multiple documents, each with content for review by a different country. These elements are listed below:

- `m1-0-cover` (1.0 Cover Letter)
- `m1-2-form` (1.2 Application Form)
- `m1-3-2-mockup` (1.3.2 Mock-Up)
- `m1-3-3-specimen` (1.3.3 Specimen)
- `m1-3-4-consultation` (1.3.4 Consultation with Target Patient Groups)
- `m1-3-5-approved` (1.3.5 Product Information Already Approved in the Member States)
- `m1-responses` (Responses to Questions)
- `m1-additional-data` (Additional Data)

Appendix 1.3: Product Information Element Description

The "`m1-3-1-spc-label-pl`" corresponds to the Notice to Applicants heading 1.3.1 SPC, Labelling and Package Leaflet. This element can have multiple child "`pi-doc`" elements that allow identification of product information language, document type and applicable country as described below.

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
pi-doc		Parent element for identification of the type, language and country of one or more product information documents.	N/A	Mandatory	Repeatable
	xml:lang	The language that the product information is written in (see Appendix 2.2 for allowable values).	fr	Mandatory	Unique
	type	The type of product information document (see Appendix 2.3 for allowable values).	combined	Mandatory	Unique
	country	The receiving country for the product information (or "common") (see Appendix 2.1 for full list of allowable values)	be	Mandatory	Unique

Appendix 2: Directory / File Structure for Module 1

The directory / file structure is defined in this appendix as a table containing the following information:

Sequential number		Each item in the table has a unique sequentially assigned reference number. These reference numbers can change with each version of this appendix.
	Number	CTD section number
	Title	CTD title
	Element	Element name in the EU Backbone
	File/Directory	File/Directory name from m1/eu – should be relative path from eu/m1 e.g. 12-form/fr-form.pdf. This is consistent with ICH standards. The file extension corresponds to the file type; i.e. the "pdf" extension is only illustrative.
	Comment	Comments

Where the following conventions are used:

Codes*	**Definition**
CC	Country Code, also referred to as the destination code as per Appendix 2.1
LL	Local Language code as per Appendix 2.2
EXT	File extension.
PIDOC	Product Information Document identifier as per Appendix 2.3
VAR	Variable component of the filename.
DDDD	A sequence number made of 4 digits (e.g. 0000)

* = The names of the actual files and directories used should be presented in lower case in accordance with the eCTD specification. The use of upper case for codes is for illustrative purposes only to show differentiation between the variable parts and the fixed part of the name.

1	Number	
	Title	Module 1 EU
	Element	m1-eu
	Directory	m1/eu
	Comment	Top level directory for the EU Module 1as per ICH eCTD Specification
2	Number	
	Title	
	Element	
	File	m1/eu/eu-regional.xml
	Comment	The EU Regional XML instance including the envelope information. Note that the operation attribute for the eu.regional.xml should always be set to ‘new’.
3	Number	1.0
	Title	Cover Letter
	Element	m1-0-cover
	Directory	m1/eu/10-cover
	Comment	
4	Number	
	Title	
	Element	
	Directory	m1/eu/10-cover/*CC*
	Comment	Always use the country directory at this level for all procedures even when only one file is submitted to only one country during the lifecycle of the submission.

5	Number	
	Title	
	Element	
	File	m1/eu/10-cover/*CC*/*CC*-cover-*VAR*.*EXT*
	Comment	Filename for the Cover Letter composed of a fixed component "*CC*", a fixed component "cover" and an optional variable component if required (e.g. fr-cover-variationrationale.pdf). When only the cover letter is submitted in this directory the file name should be *CC*-cover.pdf. Single document correspondences e.g. Letter of Undertakings should be placed here.
6	Number	
	Title	
	Element	
	File	*m1/eu/10-cover/CC/CC-tracking-VAR.EXT*
	Comment	A tracking table should always be included in addition to the cover letter for submissions within all procedures, except for EDQM submissions. The file should be named cc-tracking-var.pdf and be placed in /XXXX/m1/eu/10-cover/cc (e.g. ema-tracking-var.pdf for a CP, common-tracking-var.pdf in an MRP/DCP, or be-tracking-var.pdf in a NP.)
7	Number	1.2
	Title	Application Form
	Element	m1-2-form
	Directory	m1/eu/12-form
	Comment	The Application Form refers to any form (new applications, applications for variations or renewals).
8	Number	
	Title	
	Element	
	Directory	m1/eu/12-form/*CC*
	Comment	Always use the country directory at this level for all procedures even when only one file is submitted to only one country during the lifecycle of the submission.
9	Number	
	Title	
	Element	
	File	m1/eu/12-form/CC/CC-form-eaf-VAR.EXT

	Comment	Filename for the Application Form composed of a fixed component “CC”, a fixed component “form-eaf” (*there could be country specific exceptions to this file naming, e.g. national forms*) and an optional variable component to be used if required (e.g. fr-form-eaf-tablet.pdf). When only the application form is submitted in this directory the file name should be CC–form-eaf.pdf.
10	Number	
	Title	
	Element	
	File	m1/eu/12-form/CC/CC-form-annex-VAR.EXT
	Comment	Filenames for the Annexes to the Application Form composed of a fixed component “CC”, a fixed component “form-annex” and an optional variable component to be used if required (e.g. fr-form-annex-01.pdf, fr-form-annex-proofpayment.pdf). Annexes that potentially apply to all EU countries should be placed in the ‘common’ sub-directory (e.g. common-form-annex-12.pdf, common-form-annex-pheurcertificate.pdf). The variable component, if used, should be a logical name and should be added without spaces Supportive documents, which are not part of any M2-5 section or Response to Questions, should be placed here. Any updates to documents originating from M2-5 should replace the outdated version in its original location in M2-5. Supportive documents submitted as answers to questions should be placed in Module 1 Responses to Questions (see line 67-69).
11	Number	1.3
	Title	Product Information
	Element	m1-3-pi
	Directory	m1/eu/13-pi
	Comment	General placeholder for Product Information
12	Number	1.3.1
	Title	SmPC, Labelling and Package Leaflet
	Element	m1-3-1-spc-label-pl
	Directory	m1/eu/13-pi/131-spclabelpl
	Comment	General placeholder for SmPC, Labelling, Package Leaflet or Combined PI
13	Number	
	Title	
	Element	
	Directory	m1/eu/13-pi/131-spclabelpl/*CC*
	Comment	Always use the country directory at this level for all procedures even when only one file is submitted to only one country during the lifecycle of the submission.
14	Number	

	Title	
	Element	
	Directory	m1/eu/13-pi/131-spclabelpl/*CC*/*LL*
	Comment	Always use a language directory at this level during the lifecycle of the submission. See Row 13 for an example.
15	Number	
	Title	
	Element	
	File	m1/eu/13-pi/131-spclabelpl/*CC*/*LL*/*CC-PIDOC-VAR.EXT*
	Comment	Filename for the spc-label-pl document composed by a fixed component "*CC*", a fixed component "PIDOC" as per table of Appendix 2.3 and an optional variable component to be used if needed (e.g. m1/eu/13-pi/131-spclabelpl/ema/de/ema-combined-tablet10mgde.pdf). For centralised procedure, please also refer to the EMA *User guide on how to generate PDF versions of the product information and other annexes*.
16	Number	1.3.2
	Title	Mock-up
	Element	m1-3-2-mockup
	Directory	m1/eu/13-pi/132-mockup
	Comment	
17	Number	
	Title	
	Element	
	Directory	m1/eu/13-pi/132-mockup/*CC*
	Comment	Always use the country directory at this level for all procedures even when only one file is submitted to only one country during the lifecycle of the submission.
18	Number	
	Title	
	Element	
	File	m1/eu/13-pi/132-mockup/*CC*/*CC*-mockup-*VAR.EXT*
	Comment	Filename for the mock-up document composed by a fixed component "*CC*", a fixed component "mockup" and an optional variable component to be used if needed. (e.g. fr-mockup-tablet10mgouter.pdf).

19	Number	1.3.3
	Title	Specimen
	Element	m1-3-3-specimen
	Directory	m1/eu/13-pi/133-specimen
	Comment	
20	Number	
	Title	
	Element	
	Directory	m1/eu/13-pi/133-specimen/*CC*
	Comment	Always use the country directory at this level for all procedures even when only one file is submitted to only one country during the lifecycle of the submission.
21	Number	
	Title	
	Element	
	File	m1/eu/13-pi/133-specimen/CC/*CC*-specimen-*VAR.EXT*
	Comment	Filename for the list of physical specimens provided with the submission composed by a fixed component "*CC*", a fixed component "specimen" and an optional variable component to be used if needed. (e.g. fr-specimen.pdf).
22	Number	1.3.4
	Title	Consultation with Target Patient Groups
	Element	m1-3-4-consultation
	Directory	m1/eu/13-pi/134-consultation
	Comment	
23	Number	
	Title	
	Element	
	Directory	m1/eu/13-pi/134-consultation/*CC*
	Comment	Always use the country directory at this level for all procedures even when only one file is submitted to only one country during the lifecycle of the submission.

24	Number	
	Title	
	Element	
	File	m1/eu/13-pi/134-consultation/*CC*/*CC*-consultation-*VAR*.*EXT*
	Comment	Filename for the results of assessments carried out in cooperation with target patient groups on the package leaflet, composed by a fixed component "*CC*", a fixed component "consultation" and an optional variable component to be used if needed. (e.g. be-consultation-tablet10mgpl.pdf).
25	Number	1.3.5
	Title	Product Information already approved in the Member States
	Element	m1-3-5-approved
	Directory	m1/eu/13-pi/135-approved
	Comment	
26	Number	
	Title	
	Element	
	Directory	m1/eu/13-pi/135-approved/*CC*
	Comment	Always use the country directory at this level for all procedures even when only one file is submitted.
27	Number	
	Title	
	Element	
	File	m1/eu/13-pi/135-approved/*CC*/*CC*-approved-*VAR*.*EXT*
	Comment	Filename for the approved Product Information document composed by a fixed component "*CC*", a fixed component "approved" and an optional variable component to be used if needed. The "CC" prefix should be used for the country receiving the submission, not the country where the product information is already approved (e.g. when submitting an application in France, where Product Information has been approved in Poland, the file name would be (e.g. fr-approved-poland.pdf or fr-approved-polandmanumber.pdf).
28	Number	1.3.6
	Title	Braille
	Element	m1-3-6-braille
	Directory	m1/eu/13-pi/136-braille
	Comment	

29	Number	
	Title	
	Element	
	File	m1/eu/13-pi/136-braille/braille-*VAR*.*EXT*
	Comment	Filename for the Braille information is composed by a fixed component “braille” and an optional variable component to be used if needed. (e.g. braille.pdf).
30	Number	1.4
	Title	Information about the Experts
	Element	m1-4-expert
	Directory	m1/eu/14-expert
	Comment	General placeholder for Expert Information.
31	Number	1.4.1
	Title	Quality
	Element	m1-4-1-quality
	Directory	m1/eu/14-expert/141-quality
	Comment	General placeholder for quality information.
32	Number	
	Title	
	Element	
	File	m1/eu/14-expert/141-quality/quality-*VAR*.*EXT*
	Comment	Filename for the quality expert document composed by a fixed component “quality” and an optional variable component to be used if needed. (e.g. quality.pdf).
33	Number	1.4.2
	Title	Non-Clinical
	Element	m1-4-2-non-clinical
	Directory	m1/eu/14-expert/142-nonclinical
	Comment	General placeholder for non-clinical information.

34	Number	
	Title	
	Element	
	File	m1/eu/14-expert/142-nonclinical/nonclinical-*VAR*.*EXT*
	Comment	Filename for the non-clinical expert document composed by a fixed component “nonclinical” and an optional variable component to be used if needed. (e.g. nonclinical.pdf).
35	Number	1.4.3
	Title	Clinical
	Element	m1-4-3-clinical
	Directory	m1/eu/14-expert/143-clinical
	Comment	General placeholder for clinical information.
36	Number	
	Title	
	Element	
	File	m1/eu/14-expert/143-clinical/clinical-*VAR*.*EXT*
	Comment	Filename for the clinical expert document composed by a fixed component “clinical” and an optional variable component to be used if needed. (e.g. clinical.pdf).
37	Number	1.5
	Title	Specific Requirements for Different Types of Applications
	Element	m1-5-specific
	Directory	m1/eu/15-specific
	Comment	General placeholder for Specific Information.
38	Number	1.5.1
	Title	Information for Bibliographical Applications
	Element	m1-5-1-bibliographic
	Directory	m1/eu/15-specific/151-bibliographic
	Comment	General placeholder for bibliographical applications.

39	Number	
	Title	
	Element	
	File	m1/eu/15-specific/151-bibliographic/bibliographic-*VAR*.*EXT*
	Comment	Filename for the specific bibliographic submission information composed by a fixed component “bibliographic” and an optional variable component to be used if needed. (e.g. bibliographic.pdf).
40	Number	1.5.2
	Title	Information for Generic, ‘Hybrid’ or Bio-similar Applications
	Element	m1-5-2-generic-hybrid-biosimilar
	Directory	m1/eu/15-specific/152-generic-hybrid-bio-similar
	Comment	General placeholder for generic, ‘hybrid’ or bio-similar applications.
41	Number	
	Title	
	Element	
	File	m1/eu/15-specific/152-generic-hybrid-bio-similar/generic-*VAR*.*EXT* or m1/eu/15-specific/152-generic-hybrid-bio-similar/hybrid-*VAR*.*EXT* or m1/eu/15-specific/152-generic-hybrid-bio-similar/biosimilar-*VAR*.*EXT*
	Comment	Filename for the specific generic, hybrid or bio-similar submission information composed by a fixed component “generic” or “hybrid” or “biosimilar”, and an optional variable component to be used if needed (e.g. generic.pdf).
42	Number	1.5.3
	Title	(Extended) Data/Market Exclusivity
	Element	m1-5-3-data-market-exclusivity
	Directory	m1/eu/15-specific/153-data-market-exclusivity
	Comment	General placeholder for (extended) data/market exclusivity.
43	Number	
	Title	
	Element	
	File	m1/eu/15-specific/153-data-market-exclusivity/datamarketexclusivity-*VAR*.*EXT*
	Comment	Filename for the data / market exclusivity composed of a fixed component “datamarketexclusivity” and an optional variable component to be used if needed (e.g. datamarketexclusivity.pdf).

44	Number	1.5.4
	Title	Exceptional Circumstances
	Element	m1-5-4-exceptional-circumstances
	Directory	m1/eu/15-specific/154-exceptional
	Comment	General placeholder for marketing authorisation granted under exceptional circumstances.
45	Number	
	Title	
	Element	
	File	m1/eu/15-specific/154-exceptional/exceptional-*VAR*.*EXT*
	Comment	Filename for marketing authorisation granted under exceptional circumstances, composed of a fixed component “exceptional” and an optional variable component to be used if needed (e.g. exceptional.pdf).
46	Number	1.5.5
	Title	Conditional Marketing Authorisation
	Element	m1-5-5-conditional-ma
	Directory	m1/eu/15-specific/155-conditional-ma
	Comment	General placeholder for conditional marketing authorisation.
47	Number	
	Title	
	Element	
	File	m1/eu/15-specific/155-conditional-ma/conditionalma-*VAR*.*EXT*
	Comment	Filename for conditional marketing authorisation, composed of a fixed component “conditionalma” and an optional variable component to be used if needed (e.g. conditionalma.pdf).
48	Number	1.6
	Title	Environmental Risk Assessment
	Element	m1-6-environrisk
	Directory	m1/eu/16-environrisk
	Comment	General placeholder for Environmental Risk Assessment.

49	Number	1.6.1
	Title	Non-GMO
	Element	m1-6-1-non-gmo
	Directory	m1/eu/16-environrisk/161-nongmo
	Comment	General placeholder for non-GMO.
50	Number	
	Title	
	Element	
	File	m1/eu/16-environrisk/161-nongmo/nongmo-*VAR.EXT*
	Comment	Filename for the environmental risk assessment non-GMO composed by a fixed component “nongmo” and an optional variable component to be used if needed. (e.g. nongmo.pdf). Only one of the 2 folders 1.6.1 or 1.6.2 can have content when sending a sequence.
51	Number	1.6.2
	Title	GMO
	Element	m1-6-2-gmo
	Directory	m1/eu/16-environrisk/162-gmo
	Comment	General placeholder for GMO.
52	Number	
	Title	
	Element	
	File	m1/eu/16-environrisk/162-gmo/gmo-*VAR.EXT*
	Comment	Filename for the environmental risk assessment GMO-composed by a fixed component “gmo” and an optional variable component to be used if needed (e.g. gmo.pdf). Only one of the 2 folders 1.6.1 or 1.6.2 can have content when sending a sequence.
53	Number	1.7
	Title	Information relating to Orphan Market Exclusivity
	Element	m1-7-orphan
	Directory	m1/eu/17-orphan
	Comment	General placeholder for Orphan Market Exclusivity information.

54	Number	1.7.1
	Title	Similarity
	Element	m1-7-1-similarity
	Directory	m1/eu/17-orphan/171-similarity
	Comment	General placeholder for information on similarity with authorised orphan product.
55	Number	
	Title	
	Element	
	File	m1/eu/17-orphan/171-similarity/similarity-*VAR.EXT*
	Comment	Filename for the information on similarity composed by a fixed component “similarity” and an optional variable component to be used if needed.
56	Number	1.7.2
	Title	Market Exclusivity
	Element	m1-7-2-market-exclusivity
	Directory	m1/eu/17-orphan/172-market-exclusivity
	Comment	General placeholder for information on market exclusivity.
57	Number	
	Title	
	Element	
	File	m1/eu/17-orphan/172-market-exclusivity/marketexclusivity-*VAR.EXT*
	Comment	Filename for information on market exclusivity composed by a fixed component “marketexclusivity” and an optional variable component to be used if needed.
58	Number	1.8
	Title	Information relating to Pharmacovigilance
	Element	m1-8-pharmacovigilance
	Directory	m1/eu/18-pharmacovigilance
	Comment	General placeholder for information on pharmacovigilance.

59	Number	1.8.1
	Title	Pharmacovigilance System
	Element	m1-8-1-pharmacovigilance-system
	Directory	m1/eu/18-pharmacovigilance/181-phvig-system
	Comment	General placeholder for information on pharmacovigilance system.
60	Number	
	Title	
	Element	
	File	m1/eu/18-pharmacovigilance/181-phvig-system/phvigsystem-*VAR.EXT*
	Comment	Filename for information on pharmacovigilance system composed by a fixed component “phvigsystem” and an optional variable component to be used if needed.
61	Number	1.8.2
	Title	Risk-management System
	Element	m1-8-2-risk-management-system
	Directory	m1/eu/18-pharmacovigilance/182-riskmgt-system
	Comment	General placeholder for information on risk management system.
62	Number	
	Title	
	Element	
	File	m1/eu/18-pharmacovigilance/182-riskmgt-system/riskmgtsystem-*VAR.EXT*
	Comment	Filename for information on pharmacovigilance system composed by a fixed component “riskmgtsystem” and an optional variable component to be used if needed.
63	Number	1.9
	Title	Information relating to Clinical Trials
	Element	m1-9-clinical-trials
	Directory	m1/eu/19-clinical-trials
	Comment	General placeholder for information on clinical trials.

64	Number	
	Title	
	Element	
	File	m1/eu/19-clinical-trials/clinicaltrials-*VAR*.*EXT*
	Comment	Filename for information on clinical trials composed by a fixed component “clinicaltrials” and an optional variable component to be used if needed.
65	Number	1.10
	Title	Information relating to Paediatrics
	Element	m1-10-paediatrics
	Directory	m1/eu/110-paediatrics
	Comment	General placeholder for information on paediatrics.
66	Number	
	Title	
	Element	
	Directory	m1/eu/110-paediatrics/paediatrics-*VAR*.*EXT*
	Comment	Filename for information on paediatrics composed by a fixed component “paediatrics” and an optional variable component to be used if needed.
67	Number	
	Title	Responses to Questions
	Element	m1-responses
	Directory	m1/eu/responses
	Comment	
68	Number	
	Title	
	Element	
	Directory	m1/eu/responses/*CC*
	Comment	Always use the country directory at this level for all procedures even when only one file is submitted to only one country during the lifecycle of the submission.

69	Number	
	Title	
	Element	
	File	m1/eu/responses/*CC*/*CC*-responses-*VAR*.*EXT*
	Comment	Filename for responses to questions composed by a fixed component "*CC*", a fixed component "responses" and an optional variable component to be used if needed (e.g. be-responses.pdf).
70	Number	
	Title	Additional Data
	Element	m1-additional-data
	Directory	m1/eu/additional-data
	Comment	The 'Additional Data' section should only be used for information required for National, MR and Decentralised Procedures; it is therefore not generally applicable for the Centralised Procedure, other than for justifications for active substances. This section is not intended for including already submitted documents. Any information/file which was already submitted in a previous sequence should **not** be submitted again in eCTD. For already submitted documents, a reference/hyperlink/cross-link to the existing file should be created. This helps to avoid multiple lifecycles and repetitions of the files.
71	Number	
	Title	
	Element	
	Directory	m1/eu/additional-data/*CC*
	Comment	Always use the country directory at this level for all procedures even when only one file is submitted to only one country during the lifecycle of the submission.
72	Number	
	Title	
	Element	
	File	m1/eu/additional-data/*CC*/*CC*-additionaldata-*VAR*.*EXT*

	Comment	Filename for additional information requested composed by a fixed component "*CC*", a fixed component "additionaldata" and an optional variable component to be used if needed (e.g. be-additionaldata-yellowpink.pdf). Supporting data for variations should be not be placed in this section; wherever possible they should be placed in the relevant CTD section, primarily within Module 3 'Quality' and Module 1 (1.3.1) 'Summary of Product Characteristics, Labelling and Package Leaflet'. Where documents cannot be assigned to specific CTD-defined locations, then they should be attached to the 1.2 Application Form. The same approach should be used for renewals. Additionally see comments in row no 9. The 'Additional Data' section should only be used for information required for country specific information/documentation for National, MR and Decentralised Procedures; it is not applicable for the Centralised Procedure, other than for justifications for active substances.
73	Number	
	Title	
	Element	
	Directory	m1/eu/util
	Comment	Additional folder to hold utility files used in EU Region only.
74	Number	
	Title	
	Element	
	Directory	m1/eu/util/dtd
	Comment	Additional folder to hold DTD files used in EU Region only.
75	Number	
	Title	
	Element	
	Directory	util/dtd
	Comment	ICH specified location for eCTD DTD files.
76	Number	
	Title	
	Element	
	Directory	util/style

	Comment	ICH specified location for eCTD style-sheet files. The style-sheet to be used should be the most recent version, which is always published as part of the specification package for download. Note that the XML instance can only point to one style-sheet and that referencing a customised style-sheet will effectively prevent the agency using the official one. It is therefore recommended not to submit customised style-sheets.

Appendix 2.1: Destination Codes

In most cases the destination code is an ISO-3166-1-alpha-2 code usually called “country code” or “*CC*” in this specification.

Code	Destination	Comment
at	Austria	ISO-3166-1-alpha-2 code
be	Belgium	ISO-3166-1-alpha-2 code
bg	Bulgaria	ISO-3166-1-alpha-2 code
common	All countries	This is not an ISO code, but should be used to identify documents that are potentially applicable to all EU countries, irrespective of whether they are participating in the procedure or not
cy	Cyprus	ISO-3166-1-alpha-2 code
cz	Czech Republic	ISO-3166-1-alpha-2 code
de	Germany	ISO-3166-1-alpha-2 code
dk	Denmark	ISO-3166-1-alpha-2 code
edqm	EDQM	This is not an ISO code, but should be used as per guidance for application forms provided by EDQM
ee	Estonia	ISO-3166-1-alpha-2 code
el	Greece	This is not an ISO code, but should be used as per guidance for application forms in the Notice to Applicants
ema	EMA	This is not an ISO code, but should be used for files that apply to all countries in the Centralised Procedure.
es	Spain	ISO-3166-1-alpha-2 code
fi	Finland	ISO-3166-1-alpha-2 code
fr	France	ISO-3166-1-alpha-2 code
hr	Croatia	ISO-3166-1-alpha-2 code
hu	Hungary	ISO-3166-1-alpha-2 code
ie	Ireland	ISO-3166-1-alpha-2 code
is	Iceland	ISO-3166-1-alpha-2 code
it	Italy	ISO-3166-1-alpha-2 code
li	Liechtenstein	ISO-3166-1-alpha-2 code
lt	Lithuania	ISO-3166-1-alpha-2 code
lu	Luxembourg	ISO-3166-1-alpha-2 code
lv	Latvia	ISO-3166-1-alpha-2 code
mt	Malta	ISO-3166-1-alpha-2 code
nl	Netherlands	ISO-3166-1-alpha-2 code
no	Norway	ISO-3166-1-alpha-2 code
pl	Poland	ISO-3166-1-alpha-2 code
pt	Portugal	ISO-3166-1-alpha-2 code
ro	Romania	ISO-3166-1-alpha-2 code
se	Sweden	ISO-3166-1-alpha-2 code
si	Slovenia	ISO-3166-1-alpha-2 code
sk	Slovakia	ISO-3166-1-alpha-2 code
uk	*United Kingdom*	*Not to be used anymore*
xi	United Kingdom	This country code should be used for UK Northern Ireland UK(NI) until a new major version of the EU eCTD M1 specification is released that will include the correct term.

Appendix 2.2: Language Codes (RMS: 100000072057 Language)

Code	Language
bg	Bulgarian
cs	Czech
da	Danish
de	German
el	Greek
en	English
es	Spanish
et	Estonian
fi	Finnish
fr	French
ga	Irish
hr	Croatian
hu	Hungarian
is	Icelandic
it	Italian
lt	Lithuanian
lv	Latvian
mt	Maltese
nl	Dutch
no	Norwegian
pl	Polish
pt	Portuguese
ro	Romanian
sk	Slovakian
sl	Slovenian
sv	Swedish

Appendix 2.3: SPC, Labelling and Package Leaflet File Name Identifiers

PI DOC	Description
spc	Summary of Product Characteristics
annex2	Annex II
outer	Outer Packaging
interpack	Intermediate Packaging*
impack	Immediate Packaging
other	Other product information
pl	Package Leaflet
combined	Single text file incorporating the following documents: spc + annex2 + outer + interpack + impack + other + pl, in this sequence as applicable for the Centralised Procedure. Only one file per language is required. 'Combined' means presented as one document.

* = When labelling documents (Outer and Immediate Packaging) are submitted as a single file, the type 'interpack' should be used

Appendix 2.4: Agency Codes and Names

The table below provides the list of Agencies as identified on the Heads of Medicines Agency website, i.e. http://www.hma.eu. The Agency Code is the value to use from within the EU Module 1 XML file.

RMS: 100000160680 EU Territorial Authority

Country	Agency Code	Human/Vet (H/V)*	Agency Name
Austria	AT-BASG	H/V	Austria - Austrian Federal Office for Safety in Health Care / Austrian Medicines and Medical Devices Agency
Belgium	BE-FAMHP	H/V	Belgium - Federal agency for medicines and health products
Bulgaria	BG-BDA	H	Bulgaria - Bulgarian Drug Agency
Croatia	HR-HALMED	H	Croatia – Agency for Medicinal Products and Medical Devices of Croatia
Cyprus	CY-PHS	H/V	Cyprus - Pharmaceutical Services, Ministry of Health
Czech Rep.	CZ-SUKL	H	Czech Rep - State Institute for Drug Control
Denmark	DK-DKMA	H/V	Denmark - Danish Medicines Agency
Estonia	EE-SAM	H/V	Estonia - State Agency of Medicines
EU	EU-EDQM	H/V	EDQM – European Directorate for the Quality of Medicines & HealthCare
EU	EU-EMA	H/V	EMA - European Medicines Agency
Finland	FI-FIMEA	H/V	Finland - Finnish Medicines Agency
France	FR-ANSM	H	France - National Agency for the Safety of Medicines and Health Products
Germany	DE-BFARM	H	Germany - BfArM - Federal Institute for Drugs and Medical Devices
	DE-PEI	H/V	Germany – PEI – Federal Institute for Vaccines and Biomedicines
Greece	EL-EOF	H/V	Greece - Greek National Organization for Medicines
Hungary	HU-OGYI	H	Hungary - National Center for Public Health and Pharmacy
Iceland	IS-IMCA	H/V	Iceland - Icelandic Medicines Agency
Ireland	IE- HPRA	H/V	Ireland - The Health Products Regulatory Authority
Italy	IT-AIFA	H	Italy - Italian Medicines Agency
Latvia	LV-ZVA	H/V	Latvia - State Agency of Medicines of Latvia

Liechtenstein	LI-LLV	H/V	Liechtenstein - Office of Health / Department of Pharmaceuticals
Lithuania	LT-SMCA	H	Lithuania - State Medicines Control Agency of Lithuania
Luxembourg	LU-MINSANT	H/V	Luxembourg - Ministry of Health
Malta	MT-MEDAUTH	H	Malta - Medicines Authority
Netherlands	NL-MEB	H/V	Netherlands - Medicines Evaluation Board
Norway	NO-NOMA	H/V	Norway - Norwegian Medical Products Agency
Poland	PL-URPL	H/V	Poland - Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Portugal	PT-INFARMED	H/V	Portugal - National Authority of Medicines and Health Products
Romania	RO-ANMMD	H/V	Romania- National Agency for Medicines and Medical Devices
Slovak Rep.	SK-SIDC	H	Slovak Rep - State Institute for Drug Control
Slovenia	SI-JAZMP	H/V	Slovenia - Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
Spain	ES-AEMPS	H/V	Spain - Spanish Agency for Medicines and Health Products
Sweden	SE-MPA	H/V	Sweden - Medical Products Agency
United Kingdom	UK-MHRA	H	UK - Medicines and Healthcare products Regulatory Agency (The agency code UK-MHRA refers to UK Northern Ireland when included in an EU eCTD submission.)

*eCTD apply only for Marketing Authorisation applications for medicinal products for human use.

Appendix 3: Modularised DTD for EU Module 1

eu-regional.dtd

```
<!--
PUBLIC "-//EU//DTD eCTD EU Backbone 3.1//EN"
In the eCTD File Organisation: "util/dtd/eu-regional.dtd"

August 2009

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February 2013

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June 2015

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May 2016

Contributors:
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May 2024

Contributors:
EMA (Mihaela Pereteatcu)

Meaning or value of the suffixes:
? : element must appear 0 or 1 time
* : element must appear 0 or more time
+ : element must appear 1 or more times
<none>: element must appear once and only once
-->

<!-- General declarations, external modules
references..................... -->
<!ENTITY % countries
"(at|be|bg|common|cy|cz|de|dk|edqm|ee|el|es|ema|fi|fr|hr|hu|ie|is|it
|li|lt|lu|lv|mt|nl|no|pl|pt|ro|se|si|sk|uk|xi)">
<!ENTITY % languages
"(bg|cs|da|de|el|en|es|et|fi|fr|ga|hr|hu|is|it|lt|lv|mt|nl|no|pl|pt|
ro|sk|sl|sv)">

<!ENTITY % leaf-node "(( leaf | node-extension )*)">

<!ENTITY % envelope-module SYSTEM "eu-envelope.mod" >
%envelope-module;

<!ENTITY % leaf-module SYSTEM "eu-leaf.mod" >
%leaf-module;
```

```
<!ELEMENT specific (
%leaf-node;
)>
<!ATTLIST specific
country %countries; #REQUIRED
>
<!ELEMENT pi-doc (
%leaf-node;
)>
<!ATTLIST pi-doc
xml:lang %languages; #REQUIRED
type (spc|annex2|outer|interpack|impack|other|pl|combined) #REQUIRED
country %countries; #REQUIRED
>

<!-- Root element
..................................................... -->
<!ELEMENT eu:eu-backbone (
eu-envelope,
m1-eu
)>

<!ATTLIST eu:eu-backbone
xmlns:eu CDATA #FIXED "http://europa.eu.int"
xmlns:xlink CDATA #FIXED "http://www.w3c.org/1999/xlink"
xml:lang CDATA #IMPLIED
dtd-version CDATA #FIXED "3.1"
>

<!--
.....................................................................
-->
<!ELEMENT m1-eu (
m1-0-cover,
m1-2-form?,
m1-3-pi?,
m1-4-expert?,
m1-5-specific?,
m1-6-environrisk?,
m1-7-orphan?,
m1-8-pharmacovigilance?,
m1-9-clinical-trials?,
m1-10-paediatrics?,
m1-responses?,
m1-additional-data?
)>

<!--
.....................................................................
-->
<!ELEMENT m1-0-cover (
specific+
)>
```

```
<!--
.....................................................................
-->
<!ELEMENT m1-2-form (
specific+
)>

<!--
.....................................................................
-->
<!ELEMENT m1-3-pi (
m1-3-1-spc-label-pl?,
m1-3-2-mockup?,
m1-3-3-specimen?,
m1-3-4-consultation?,
m1-3-5-approved?,
m1-3-6-braille?
)>

<!ELEMENT m1-3-1-spc-label-pl (
pi-doc+
)>
<!ELEMENT m1-3-2-mockup (
specific+
)>
<!ELEMENT m1-3-3-specimen (
specific+
)>
<!ELEMENT m1-3-4-consultation (
specific+
)>
<!ELEMENT m1-3-5-approved (
specific+
)>
<!ELEMENT m1-3-6-braille (
%leaf-node;
)>

<!--
.....................................................................
-->
<!ELEMENT m1-4-expert (
m1-4-1-quality?,
m1-4-2-non-clinical?,
m1-4-3-clinical?
)>

<!ELEMENT m1-4-1-quality %leaf-node;>
<!ELEMENT m1-4-2-non-clinical %leaf-node;>
<!ELEMENT m1-4-3-clinical %leaf-node;>

<!--
.....................................................................
-->
<!ELEMENT m1-5-specific (
m1-5-1-bibliographic?,
```

```
m1-5-2-generic-hybrid-bio-similar?,
m1-5-3-data-market-exclusivity?,
m1-5-4-exceptional-circumstances?,
m1-5-5-conditional-ma?
)>

<!ELEMENT m1-5-1-bibliographic %leaf-node;>
<!ELEMENT m1-5-2-generic-hybrid-bio-similar %leaf-node;>
<!ELEMENT m1-5-3-data-market-exclusivity %leaf-node;>
<!ELEMENT m1-5-4-exceptional-circumstances %leaf-node;>
<!ELEMENT m1-5-5-conditional-ma %leaf-node;>

<!--
.....................................................................
-->
<!ELEMENT m1-6-environrisk (
(m1-6-1-non-gmo | m1-6-2-gmo)?
)>
<!ELEMENT m1-6-1-non-gmo %leaf-node;>
<!ELEMENT m1-6-2-gmo %leaf-node;>

<!--
.....................................................................
-->
<!ELEMENT m1-7-orphan (
m1-7-1-similarity?,
m1-7-2-market-exclusivity?
)>
<!ELEMENT m1-7-1-similarity %leaf-node;>
<!ELEMENT m1-7-2-market-exclusivity %leaf-node;>

<!--
.....................................................................
-->
<!ELEMENT m1-8-pharmacovigilance (
m1-8-1-pharmacovigilance-system?,
m1-8-2-risk-management-system?
)>
<!ELEMENT m1-8-1-pharmacovigilance-system %leaf-node;>
<!ELEMENT m1-8-2-risk-management-system %leaf-node;>

<!--
.....................................................................
-->
<!ELEMENT m1-9-clinical-trials %leaf-node;>
<!--
.....................................................................
-->

<!ELEMENT m1-10-paediatrics %leaf-node;>

<!--
.....................................................................
-->
<!ELEMENT m1-responses (
specific+
```

```
)>

<!--
.....................................................................
-->
<!ELEMENT m1-additional-data (
specific+
)>
```

eu-envelope.mod

```
<!--
In the eCTD File Organisation: "util/dtd/eu-envelope.mod"

Version 1.4
August 2009

Contributors:
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Version 2.0
February 2013

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Version 3.0
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Version 3.0.1
May 2016

Contributors:
BFARM (Klaus Menges)

Version 3.1
May 2024

Contributors:
EMA (Mihaela Pereteatcu)-->

<!--
.....................................................................
-->
<!ELEMENT eu-envelope (
     envelope+
)>

<!ELEMENT envelope (
     identifier,
        submission,
        submission-unit,
     applicant,
     agency,
     procedure,
     invented-name+,
     inn*,
     sequence,
     related-sequence+,
     submission-description
```

```
)>

<!--
.....................................................................
-->
<!ELEMENT identifier            ( #PCDATA )>
<!ELEMENT submission            ( number?, procedure-tracking )>
<!ELEMENT procedure-tracking    ( number+ )>
<!ELEMENT number           ( #PCDATA )>
<!ELEMENT submission-unit  EMPTY>
<!ELEMENT applicant             ( #PCDATA )>
<!ELEMENT agency     EMPTY>
<!ELEMENT procedure             EMPTY>
<!ELEMENT invented-name    ( #PCDATA )>
<!ELEMENT inn                 ( #PCDATA )>
<!ELEMENT sequence         ( #PCDATA )>
<!ELEMENT related-sequence      ( #PCDATA )>
<!ELEMENT submission-description ( #PCDATA )>

<!--
.....................................................................
-->
<!ATTLIST submission
type (maa | var-type1a | var-type1ain | var-type1b | var-type2 |
var-nat | extension | rup | psur | psusa | rmp | renewal | pam-sob |
pam-anx | pam-mea | pam-leg | pam-sda | pam-capa | pam-p45 | pam-p46
| pam-paes | pam-rec | pass107n | pass107q | asmf | pmf | referral-
20 | referral-294 | referral-29p | referral-30 | referral-31 |
referral-35 | referral-5-3 | referral-107i | referral-16c1c |
referral-16c4 | annual-reassessment | usr | clin-data-pub-rp | clin-
data-pub-fv | paed-7-8-30 | paed-29 | paed-45 | paed-46 | article-58
| notification-61-3 | transfer-ma | lifting-suspension | withdrawal
| cep | article-18 | none) #REQUIRED
mode ( single | grouping | worksharing ) #IMPLIED
>

<!--
.....................................................................
-->
<!ATTLIST submission-unit
type (initial | validation-response | response | additional-info |
closing | consolidating | corrigendum | reformat | re-examination )
#REQUIRED
>

<!--
.....................................................................
-->
<!ATTLIST agency
code ( AT-BASG | BE-FAMHP | BG-BDA | CY-PHS | CZ-SUKL | DE-BFARM |
DE-PEI | DK-DKMA | EE-SAM | EL-EOF | ES-AEMPS | FI-FIMEA | FR-ANSM |
HR-HALMED | HU-OGYI | IE-HPRA | IS-IMCA | IT-AIFA | LI-LLV | LT-SMCA
| LU-MINSANT | LV-ZVA | MT-MEDAUTH | NL-MEB | NO-NOMA | PL-URPL |
PT-INFARMED | RO-ANMMD | SE-MPA | SI-JAZMP | SK-SIDC | UK-MHRA | EU-
EMA | EU-EDQM ) #REQUIRED>
```

```
<!--
.....................................................................
-->
<!ATTLIST procedure
 type (
   centralised
 | national
 | mutual-recognition
 | decentralised
 ) #REQUIRED
>

<!--
.....................................................................
-->
<!ENTITY % env-countries
"(at|be|bg|cy|cz|de|dk|edqm|ee|el|ema|es|fi|fr|hr|hu|ie|is|it|li|lt|
lu|lv|mt|nl|no|pl|pt|ro|se|si|sk|uk|xi)">

<!--
.....................................................................
-->
<!ATTLIST envelope country %env-countries; #REQUIRED >

<!-- +++ -->
```

eu-leaf.mod

```
<!--
In the eCTD File Organisation: "util/dtd/eu-leaf.mod"

Version 1.4
August 2009

Contributors:
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This is based on ich-ectd-3-2.dtd;

If the ich-ectd.dtd is modularized, this one could be replaced.
Hence, one is certain that the common and EU leaf are the same.
-->

<!-- ============================================================= -
->
<!ELEMENT node-extension (title, (leaf | node-extension)+)>
<!ATTLIST node-extension
     ID ID #IMPLIED
     xml:lang CDATA #IMPLIED
>

<!-- ============================================================= -
->
<!ENTITY % show-list " (new | replace | embed | other | none) ">
<!ENTITY % actuate-list " (onLoad | onRequest | other | none) ">
<!ENTITY % operation-list " (new | append | replace | delete) ">
<!ENTITY % leaf-element " (title, link-text?) ">
<!ENTITY % leaf-att '
 ID                  ID                  #REQUIRED
 application-version CDATA               #IMPLIED
 version             CDATA               #IMPLIED
 font-library        CDATA               #IMPLIED
 operation           %operation-list;    #REQUIRED
 modified-file       CDATA               #IMPLIED
 checksum            CDATA               #REQUIRED
 checksum-type       CDATA               #REQUIRED
 keywords            CDATA               #IMPLIED
 xmlns:xlink         CDATA               #FIXED
"http://www.w3c.org/1999/xlink"
 xlink:type          CDATA               #FIXED    "simple"
 xlink:role          CDATA               #IMPLIED
 xlink:href          CDATA               #IMPLIED
 xlink:show          %show-list;         #IMPLIED
 xlink:actuate       %actuate-list;      #IMPLIED
 xml:lang            CDATA               #IMPLIED
 '>

<!ELEMENT leaf %leaf-element;>
<!ATTLIST leaf
     %leaf-att;
```

```
>
<!ELEMENT title (#PCDATA)>
<!ELEMENT link-text (#PCDATA | xref)*>

<!ELEMENT xref EMPTY>
<!ATTLIST xref
      ID ID #REQUIRED
      xmlns:xlink CDATA #FIXED "http://www.w3c.org/1999/xlink"
      xlink:type CDATA #FIXED "simple"
      xlink:role CDATA #IMPLIED
      xlink:title CDATA #REQUIRED
      xlink:href CDATA #REQUIRED
      xlink:show %show-list; #IMPLIED
      xlink:actuate %actuate-list; #IMPLIED
>

<!-- +++ -->
```