EU Module 1 eCTD Specification

Version 2.~~0~~4 – Draft

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Comment [HHMG1]: The version number will become 3.0 once finalised.

Document Control

Change Record

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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 filenaming 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 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.

22 # 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

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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	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~~sequences~~***. 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. Some review tools describe such a collection as a ~~dossier~~application (a term which will not be used in this document).
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 collection of ***sequences*** covering the start to the end of a specific business process, e.g. a~~n initial~~ MA application or Type II variation~~. It is a concept used in some review tools to group together several business related sequences.~~
~~Submission or~~ Sequence	A single set of information and / or electronic documents ~~supplied~~submitted at one particular time by the applicant as a part of, or the complete, ***~~eCTD~~ Application.*** ~~In~~.Any collection of content assembled in accordance with the ~~context of eCTD, this is equivalent to a **sequence**~~eCTD specification (ICH and EU) will be described using metadata as defined by the EU envelope.
Submission Type	The submission type describes the ***regulatory activity*** to which the content will be submitted.
Submission Unit	The submission unit 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: http://estri.ich.org/eCTD.

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[1],
- 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.

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. Country-specific information could relate to the details of the business process applied (e.g. specifying the number and names of those parts for which a paper copy is still requested) and local preferences for file formats.

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

Regional File Formats

Module 1

The file formats that can be included in Module 1 are given in Table 1. In addition to the common format PDF, as defined by the ICH eCTD Specification Document, XML and image formats are also accepted on an ad hoc basis. Note that all PDF files included in an eCTD (irrespective of the module) should be v1.4, v1.5, v1.6 or v1.7 (see ICH Q&A for further detail re PDF version acceptability), except where there is an agency-specific requirement for a later version (e.g. for an application form). Although the use of the file formats defined in Table 1 are mandatory, regulatory authorities and applicants could agree on the use of other formats for Module 1 content provided outside of the eCTD

[1] TOC not required for eCTD as the XML backbone acts as a table of contents

in the working-documents folder. For example, proprietary format MS Word is requested by some agencies for Product Information documents in Section 1.3. These documents, if requested, should not be referenced in the eCTD backbone, and should normally be provided in addition to the PDF versions (Note: Track changed Product Information provided in Word format is not required to be provided in PDF format within the eCTD, An exception to this rule is in the provision of either product labelling or risk management plan documentation in the Centralised Procedure, where the tracked changes version of the document in PDF format should be placed inside the eCTD, alongside the clean, non-tracked version.). Guidance should be referred to regarding the provision of MS Word and other requested documents (e.g. the ~~TIGes harmonised~~Harmonised Technical Guidance for eCTD ~~guidance~~Submissions in the EU).

Table 1 Acceptable file formats for Module 1

Document	File Format	Remark
Cover letter	XML*, PDF	PDF preferably generated from electronic source.
Administrative forms: • Application form and its annexes • Variation application form incl. background for the variation • Renewal form and its annexes	 XML*, PDF XML*, PDF XML*, PDF	Documents should be generated from electronic source documents, any signature may be embedded as a graphic file in the PDF text if desired, although this is not always necessary as the hard paper copy, if required by the receiving agency, contains the legally binding signature. The use of eAF is mandatory for Centralised Procedure applications (MAA, variation, renewal) from 1 July 2015 and for MRP/DCP/National from 1 January 2016. After these dates the paper forms will no longer be accepted.
Product Information: • Product information text** • Packaging mock-ups • Reference to specimens	 XML*,PDF PDF PDF	If a higher resolution is necessary for the mock-ups, use JPEG, GIF, PNG or SVG on a case-by-case basis.
Other	XML*, PDF	PDF preferably generated from electronic source.

* =XML format could replace PDF format whenever a structured EU exchange standard exists for the content in the specific CTD location
** = SmPC, Package Leaflet and labelling

Modules 2 to 5

No additional file formats are defined for Modules 2 to 5 other than those mentioned in the ICH eCTD Specification Document~~.~~.

Use of Electronic Signatures

~~The use of advanced electronic signatures (digital signatures) will be crucial in achieving pure electronic communication between the pharmaceutical industry and regulatory agencies, particularly for authentication of electronic submissions and documents contained therein. The EU is therefore developing a long-term strategy to implement digital signatures.~~ Currently ~~however~~, the use of digital signatures for electronic submissions within the EU is not fully supported ~~and digital signatures should therefore not be used.~~. ~~On the other hand side s~~Some agencies ~~have still~~continue to request wet signed documents and others will accept the log-in credentials for portals as a sufficient authentification. Please refer to the ~~TIGes~~ Harmonised ~~eCTD~~Technical Guidance for eCTD Submissions in the EU for information on the use of electronic signatures.

Handling of Empty or Missing eCTD Sections

For new applications (including generic applications), detailed statements justifying the absence of data or specific CTD sections should be provided in the relevant Quality Overall Summary and/or Non-Clinical/Clinical Overviews (Module 2.3, 2.4, 2.5). Note that placeholder documents highlighting 'no relevant content' should not be placed in the eCTD structure, as these would create a document lifecycle for non-existent documents, and unnecessary complication and maintenance of the eCTD.

For a generic application, there is no need to provide a justification for content that is typically absent.

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.

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. The sole exception to this rule is the EU envelope "submission type" attribute, which can be updated to support a mid-lifecycle change in submission type from one variation type to another (under the variation regulation~~). As the submission type is likely to change in any case with each submission (e.g. from 'initial-maa' to 'supplemental information' etc), this *particular* significant change in submission type should be further signalled using the free-text "submission description" envelope element.~~).

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, supplemental information 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 new 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).

Envelope

The "eu-envelope" element is designed to be used for all types of submissions (~~initial~~MAAs, variations, renewals, etc.) for a given medicinal product and will mainly be used for the first simple processing at the agency level. The envelope provides meta-data at the ~~submission~~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.

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

- For worksharing submissions including PSUSA and referrals
  Here, the submission 'mode' value will be 'worksharing' and the high-level number is a worksharing number, the PSUSA number or referral number;

- For submissions of grouped Type 1A variations that affect multiple marketing authorisations
  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~~Confirmation Letter as 'Product Reference'. E.g. if the Eligibility Confirmation ~~letter~~Letter indicates Product number H0002227 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.

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 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 should be used as appropriate.

~~Examples of 'single', 'grouping' and 'worksharing' submissions are provided in the annex to this specification.~~

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 (MR, National, Decentralised and Centralised Procedures). This is possible, despite the fact that files for the MR, 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 MR, 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, 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. 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.xml
it-form-annex1.pdf
pt-form-proofpayment.pdf
uk-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~~, taking into consideration that for some period of time the exchange of regulatory information~~ and will ~~take place through exchange of physical media like CD-Rs:~~

~~1. The actual submission of the physical media on which the application is contained should~~ be ~~accompanied by a signed paper copy of the cover letter where required by the local agency. The content of this cover letter is defined~~detailed in the ~~ICH~~ Harmonised Technical Guidance for eCTD ~~Specification Document Appendix 5, as is the packaging of the media units.~~

~~Most~~Submissions in the EU. The EMA, EDQM and most national agencies ~~and the EMA~~ are unable to provide positive feedback of technically valid ~~CD/DVD~~ 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~~Submission Gateway and Web Client.

~~A unique identifier of the submission is necessary and there could be different procedures for agencies to assign such a number. Either the applicant could request it of the relevant agency before submission, or, after receipt of the first submission, the agency could send it to the applicant (e.g. through an email connection for all related subsequent submissions). Relevant national guidelines should be consulted.~~

Universal Unique Identifier

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 revised specification must contain a universal unique identifier (UUID), linking the sequence to the eCTD application to which it belongs.

The UUID will be built 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-Axxx-yxxx-xxxxxxxxxxxx, showing 32 digits and 4 hyphens. The 'x' will be replaced by a number or a letter, 'A' will be replaced by a capital character and 'y' will be replaced by a lower case. It is recommended to use randomly generated sections (version 4 of UUID types). Such UUID is represented or example as: 25635f23-a3a4-C4e0-b994-99c5f074960f.

This structure guarantees uniqueness across applicants and application without further control, accepting a risk of duplication close to zero. The UUID will be generated when creating the first sequence built using this version of the specification, and will be provided in the eCTD envelope. All subsequent sequences for that same application will contain the same UUID. In this way, sequences can be allocated automatically to the correct eCTD application by the receiving agency. The UUID will be transferred to a new MAH and will remain the same also in cases 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 or referrals or PIP applications. Instead, redacted clinical study reports or post authorisation measures will relate to an existing application of which the UUID need to be used.

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.

Details of the change control process and a current Electronic Submission Change Request/Q&A Form are available on the EU eSubmission website.

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.

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`' rsp. `edqm`).	~~**Be**~~**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 596	**Mandatory**	**Unique**
submission		Provides administrative information associated with the submission.	N/A	**Mandatory**	**Unique**

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
	type	The type of regulatory activity to which the content will be submitted.. The following are the valid values: ▪ maa = Marketing Authorisation Application ▪ var-type1a = Variation Type IA ▪ var-type1ain = Variation Type IA_{IN} ▪ 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 ▪ 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 related to a post-authorisation measures (RMP) (e.g. interim results of imposed/non-imposed interventional/non-interventional clinical or nonclinical studies) ▪ 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-cada = 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) ▪ pass107q = Submission of a post authorisation safety study report (according article 107q)	var-type2	**Mandatory**	**Unique**

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
	type	The type of submission material sent to the regulatory agency. The following are the valid values: • initial-maa = Initial Marketing Authorisation Application • var-type1a = Variation Type IA • 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 • psur = Periodic Safety Update Report (PSUR) • rmp = Risk Management Plan (outside any procedure) • renewal = Renewal (yearly or 5-yearly) • supplemental-info = Supplemental Information (could include, for example, response to validation issues, response to questions or letter of undertaking) • fum = Follow-Up Measure (includes post-approval commitments for national MAs) • specific-obligation = Specific Obligation ▪ asmf = Active Substance Master File ▪ pmf = Plasma Master File ▪ referral-20 = Referral under Article 20 ▪ referral-294 = Referral under Article 29, (4) ▪ referral-29p = Referral under Article 29 paediatric ▪ referral-30, = Referral under Article 30 ▪ referral-31, = Referral under Article 31 ▪ referral-35 or 36= Referral under Article 35 ▪ referral-53 = Referral under Article 53 ▪ referral-107i = Referral under Article 107i ▪ referral-16c1c = Referral under Article 16c (1c)i ▪ referral-16c4 = Referral under Article 16c(4) ▪ 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 Regulation ▪ paed-29 = Paediatric submission, Article 29 post approval once a paediatric investigational plan has been performed ▪ paed-article 46-45= Paediatric submission, Article 46 according to article 45 of the Regulation ▪ paed-46= Paediatric submission according to article 46 of the Regulation ▪ article-58 = Article 58 (to be used for an initial application) ▪ notification-61-3 = Notification 61(3) ▪ transfer-ma = Transfer of a marketing authorisation	var-type2	Mandatory	Unique

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
	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: ▪ `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, referral procedures or a PSUSA applicable to more than one marketing authorisation) 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. It can also be the PSUSA number or the Referral number. (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" as well. For centrally authorised products and Referrals this number must always be obtained in advance by sending an email to PA-BUS@ema.europa.eu. The PSUSA number can be found from the EURD list	For worksharing: **EMEA/H/xxxx/WS/001** For grouped IAs: **EMEA/H/C/xxxx/IG/xxxx** For PSUSA **PSUSA/00xxxxx/201xxx** For Referral: EMEA/H/A-xx/xxxx	**Optional**	**Unique**
procedure tracking		Provides administrative information associated with the application.	N/A	**Mandatory**	**Unique**

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
~~number~~	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 EMEA/H/C/000123/II/tba (to be advised), or in case of ~~Supplemental Information,~~ sequences after 'initial', (e.g. 'response' or 'supplemental-info'), EMEA/H/C/000123/II/14~~-~~ ~~),~~), • 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) • 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). 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: • EMEA/H/C/000123/WS005/ In case of PSUSA • ~~•~~ ~~PSUSA/0000000X/123456~~ In case of Referral procedure • EMEA/H/A-xx/1234 For grouped type 1A variations across multiple MAs: • EMEA/H/C/000123/IG003/ Please ensure that these WS/IG numbers are always mentioned in the case of	See column left	**Mandatory**	**Repeatable**

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
submission unit		Submission unit 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: ▪ `initial` = Initial submission to start any regulatory activity ▪ `validation-response` = For rectifying business validation issues. ▪ `response` = submission unit that contains the response to any kind of question, validation issues out-standing 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 that provides the final documents in the centralised procedure following the decision of the European Commission ▪ `consolidating` = submission unit 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. ~~▪ `withdrawal` = Withdrawal of a marketing authorisation (during any assessment use “additional-info”)~~ ▪ `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`’	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**
	type	The type of procedure for the submission. The following are the valid values: ▪ `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**

Comment [KM2]: This term is changed to 'additional-info' to avoid confusing people or maintaining use as previously although the intent has changed..

Element	Attribute	Description/Instructions	Example	Constraint	Occurrence
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. It should never be used together with the submission unit '`initial`' or '`reformat`'	**0001** see guidance below on use and the annex	**Optional**	**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> / Response to D120 LOQ ▪ 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 ▪ Response to validation questions ▪ Providing supplementary information ▪ Dxxx translations	**Response to D120 LOQ**	**Mandatory**	**Unique**

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

The ~~Related Sequence number~~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 the eCTD world, this will consist of all the sequences that together make up the lifecycle of that particular 'regulatory activity'. The Submission Unit element describes the stage within the regulatory activity, such as initial, response, consolidating.

The related sequence attribute should always be left blank for new applications or new regulatory activities ~~(e.g. variations, PSURs).~~where the submission unit type is 'initial'. When submitting lifecycle sequences within an existing activity, the related sequence attribute should be populated with the sequence number ~~of the first sequence in the activity, regardless of how many sequences make up the activity. The related sequence attribute should be considered independent of any modified file attributes in a submission. For example, if a sequence 0010 modifies files (leaves) in sequence 0008 and 0009, the entry for related sequence in sequence 0010 should be the sequence number that started the regulatory activity that 0010 falls within, which will not necessarily be sequence 0008 or 0009.~~the regulatory activity has been started with. The submission unit 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~~related sequence, but there are occasions where more than one ~~Related Sequence~~related sequence should be provided: e.g. there are two ~~FUMs~~ PAMs (sequence 0050 and sequence 0060) and a single response (sequence 0070) is produced that relates to both ~~FUMs~~PAMs. 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~~, and if any of the related variations were grouped, then 'grouping' should be used~~. 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. 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~~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	Comment
0000	Original MAA application	maa	<none>	initial	This is the beginning of a new regulatory activity and so the submission unit is 'initial'. The related sequence should never be used together with the submission unit type 'initial'
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 describes the actual contribution 'response' being submitted within maa regulatory activity
0002	Day 181 Responses to further questions on the	maa	0000	response	This is a continuation of the regulatory activity 'maa' initiated in 0000 and so the ~~related~~elated sequence points to the beginning of that

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	original application				activity The submission unit describes the actual contribution 'response' being submitted within maa regulatory activity
0003	Letter of Undertaking (submission type: supplemental information)	maa	0000	supplemental-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 'supplemental-info' being submitted within maa regulatory activity
0004	Type II variation for 'Treatment of Pain' indication	var-type2	<none>	initial	This is the beginning of a new regulatory activity ~~and~~'var-type2'and so ~~no~~the submission unit is ,initial'.The related sequence ~~is included~~should be left blank.
0005	Type II variation for a change in manufacturing site (Westferry)	var-type2	<none>	initial	This is the beginning of ~~a~~another new regulatory activity 'var-type2' and so ~~no~~the submission unit is ,initial'.Again, the related sequence ~~is included~~should be left blank.
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 '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	~~This~~As above, but this is a continuation of the regulatory activity initiated in 0005 ~~and so the related sequence points to the beginning of that activity~~
0008	Extension to introduce a new dosage form (iv solution) that amends information provided in the original application and the manufacturing change variation	extension	<none>	initial	This is the beginning of a new regulatory activity and so ~~no~~the submission unit is 'initial', No related sequence is included.
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.
00010	Updated, agreed product information for the iv formulation	extension	0008	consolidating	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 'consolidating' indicates that further lifecycle 'fixes' have been applied in the sequence.

For a new ~~Regulatory Activity~~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 ~~sequence~~ submission unit that initiates a ~~Regulatory Activity 'supplemental-info' and 'corrigendum'~~regulatory activity the term 'initial should ~~not~~always be used. ~~These should only be used for~~For subsequent sequences within that ~~Regulatory Activity~~regulatory activity the

respective terms should be selected from the submission unit 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.

~~The submission type 'supplemental info' should be routinely used for all subsequent sequences until the conclusion of the Regulatory Activity.~~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.. The submission type 'corrigendum' should only be used in exceptional circumstances to correct information, typically for the product information~~, after the Regulatory Activity has concluded~~ annexes to be provided in the centralised procedure.

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

Table 1: Example of ~~an initial~~a MAA in the Centralised Procedure

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit
0000	~~Initial~~ MAA	~~initial~~ maa	none	initial
0001	Validation update	~~supplemental info~~maa	0000	response
0002	Day 121 responses	maa~~supplemental info~~	0000	response
0003	Day 181 responses	~~supplemental info~~maa	0000	response
0004	Day 210 Agreed English product information	~~supplemental info~~maa	0000	response
0005	Day 215 – translated product information	~~supplemental info~~maa	0000	response
0006	Final translations of product information for Decision after closing the procedure	~~supplemental info~~maa	0000	response
0007	Correction of errors in Danish product information after Decision	maa	0000	corrigendum

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Table 2: Example of an initial MAA in the Decentralised Procedure

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit
0000	~~Initial~~ MAA	~~initial~~ maa	none	initial
0001	Validation update	~~supplemental info~~maa	0000	response
0002	Day 106 responses	~~supplemental info~~maa	0000	response
0003	Day 180 responses	~~supplemental info~~maa	0000	response
0004	Day 210 Agreed English product information	~~supplemental info~~maa	0000	response
0005	consolidation after closure of procedure	maa	0000	consolidating

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Table 3: Example of a Variation

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit
0008	Variation for new indication of COPD	var-type2	none	none
0009	Validation update	~~supplemental info~~var-type2	0008	response
0010	Responses to questions	~~supplemental info~~var-type2	0008	response

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Table 4 provides details of which submission unit types should never have a related sequence and which should always have a related sequence

Table 4: List of Submission ~~Types~~Unit and the Use of Related Sequence

Submission ~~Type~~Unit	Should Never Have A Related Sequence	Should Always Have A Related Sequence
initial ~~maa~~	Yes	
~~var-type1a~~ validation-response	~~Yes~~	Yes
~~var-type1b~~response	~~Yes~~	Yes
additional-info		Yes
withdrawal		Yes
closing		Yes
consolidating		Yes
corrigendum		Yes
reformat	Yes	
~~var-type2~~	~~Yes~~	

~~var-nat~~	~~Yes~~	
~~extension~~	~~Yes~~	
~~psur~~	~~Yes~~	
~~renewal~~	~~Yes~~	
~~supplemental-info~~		~~Yes~~
~~fum-withdrawal~~	~~Yes~~	~~Yes~~
~~specific-obligation-closing~~	~~Yes~~	~~Yes~~
~~asmf-consolidating~~	~~Yes~~	~~Yes~~
~~pmf~~	~~Yes~~	
~~referral~~	~~Yes~~	
~~annual-reassessment~~	~~Yes~~	
~~usr~~	~~Yes~~	
~~paed-article-29~~	~~Yes~~	
~~paed-article-46~~	~~Yes~~	
~~article-58~~	~~Yes~~	
~~notification-61-3~~	~~Yes~~	
~~transfer-ma~~	~~Yes~~	
~~lifting-suspension~~	~~Yes~~	
~~withdrawal~~	~~Yes~~	

Example of the use of the submission type ‘referral-31’

Referrals according to article 31 are covering in many cases applications from different procedures. So the completing of metadata seems to be difficult and causes inconsistencies. The eCTD envelope will reflect the products involved. For a pharmacovigilance issue impacting multiple products the referral is run as a centralised procedure. The envelope should indicate the referral procedure number as well as the MR/DC procedure number the submitted sequence relates to.

Envelope for EMA	
UUID	25635f23-a3a4-Wce0-r994-99c5f074960f
Submission:	Type: Referral-31
Submission:	Mode: worksharing
Number	EMEA/H/A-31/9999 [This is the referral procedure number]
Procedure Tracking Number(s):	PT/H/9999/001-002 [This is the original MRP number which will serve to allocate the application correctly]
Submission unit	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:	
Submission Description:	Referral under Article 31

In case of only one product concerned (but authorised on the European level) the submission mode will turn to single and the submission number will not be filled. The procedure type will also remain MRP and the sequence number must reflect the next free number:

Envelope for CZ	
UUID	g578w301-a3a4-Vce0-a004-99g5f07T960f
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	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..]
Invented Name:	Proprietary-Wonderdrug
INN:	Ibuprofen
Sequence:	4444 [The sequence number needs to be the next available sequence number within the product life cycle].
Related Sequence:	
Submission Description:	Referral under Article 31

Example of the use of the submission type 'reformat'

The submission type 'reformat' should be used ~~in~~for each ~~case~~baseline submission. (Note: the submission type 'supplemental-info' should not be used for the second reformat submission.) Related sequence should not be used.
An example is given below.

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

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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~~Appendix 2.1 for full list of allowable values)	uk	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	Note that the tracking table required with MPR/DCP submissions should be located within a 'common' directory, with the filename 'common-tracking-var.pdf' In case of submissions of other procedure types the respective country code should be used, e.g. ema-tracking-var.pdf in case of a centralised procedure or de-tracking-var.pdf in case of a national procedure with BfArM or PEI.
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-VAR.EXT
	Comment	Filename for the Application Form composed of a fixed component “CC”, a fixed component “form” and an optional variable component to be used if required (e.g. fr-form-annex01.pdf, fr-form-proofpayment.pdf). When only the application form is submitted in this directory the file name should be CC -form.pdf. Annexes that potentially apply to all EU countries should be placed in the ‘common’ sub-directory (e.g. common-form-annex12.pdf, common-form-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 66-68).
10	Number	1.3
	Title	Product Information
	Element	m1-3-pi
	Directory	m1/eu/13-pi
	Comment	General placeholder for Product Information
11	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
12	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.
13	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.

14	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).
15	Number	1.3.2
	Title	Mock-up
	Element	m1-3-2-mockup
	Directory	m1/eu/13-pi/132-mockup
	Comment	
16	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.
17	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).

18	Number	1.3.3
	Title	Specimen
	Element	m1-3-3-specimen
	Directory	m1/eu/13-pi/133-specimen
	Comment	
19	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.
20	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).
21	Number	1.3.4
	Title	Consultation with Target Patient Groups
	Element	m1-3-4-consultation
	Directory	m1/eu/13-pi/134-consultation
	Comment	
22	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.

23	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. consultation-tablet10mgpl.pdf).
24	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	
25	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.
26	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 a ~~dossier~~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).
27	Number	1.3.6
	Title	Braille
	Element	m1-3-6-braille
	Directory	m1/eu/13-pi/136-braille
	Comment	

28	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).
29	Number	1.4
	Title	Information about the Experts
	Element	m1-4-expert
	Directory	m1/eu/14-expert
	Comment	General placeholder for Expert Information.
30	Number	1.4.1
	Title	Quality
	Element	m1-4-1-quality
	Directory	m1/eu/14-expert/141-quality
	Comment	General placeholder for quality information.
31	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).
32	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.

33	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).
34	Number	1.4.3
	Title	Clinical
	Element	m1-4-3-clinical
	Directory	m1/eu/14-expert/143-clinical
	Comment	General placeholder for clinical information.
35	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).
36	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.
37	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.

38	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).
39	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.
40	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).
41	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.
42	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).

43	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.
44	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).
45	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.
46	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).
47	Number	1.6
	Title	Environmental Risk Assessment
	Element	m1-6-environrisk
	Directory	m1/eu/16-environrisk
	Comment	General placeholder for Environmental Risk Assessment.

48	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.
49	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).
50	Number	1.6.2
	Title	GMO
	Element	m1-6-2-gmo
	Directory	m1/eu/16-environrisk/162-gmo
	Comment	General placeholder for GMO.
51	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).
52	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.

53	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.
54	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.
55	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.
56	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.
57	Number	1.8
	Title	Information relating to Pharmacovigilance
	Element	m1-8-pharmacovigilance
	Directory	m1/eu/18-pharmacovigilance
	Comment	General placeholder for information on pharmacovigilance.

58	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.
59	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.
60	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.
61	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.
62	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.

63	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.
64	Number	1.10
	Title	Information relating to Paediatrics
	Element	m1-10-paediatrics
	Directory	m1/eu/110-paediatrics
	Comment	General placeholder for information on paediatrics.
65	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.
66	Number	
	Title	Responses to Questions
	Element	m1-responses
	Directory	m1/eu/responses
	Comment	
67	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.

68	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).
69	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..
70	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.
71	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.

72	Number	
	Title	
	Element	
	Directory	m1/eu/util
	Comment	Additional folder to hold utility files used in EU Region only.
73	Number	
	Title	
	Element	
	Directory	m1/eu/util/dtd
	Comment	Additional folder to hold DTD files used in EU Region only.
74	Number	
	Title	
	Element	
	Directory	util/dtd
	Comment	ICH specified location for eCTD DTD files.
75	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	This is not an ISO country code, but should be used as per guidance for application forms in the Notice to Applicants

Appendix 2.2: Language Codes

Code	Language
bg	Bulgarian
cs	Czech
da	Danish
de	German
el	Greek
en	English
es	Spanish
et	Estonian
fi	Finnish
fr	French
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 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.

Country	Agency Code	Human/Vet (H/V)*	Agency Name
Austria	AT-~~AGES~~BASG	H/V	Austria - BASG-Austrian Federal Office for Safety in Health Care ~~(AGES PharmMed LCM)~~/ Austrian Medicines and Medical Devices Agency
Belgium	BE-FAMHP	H/V	Belgium - Agence Fédérale des Médicaments et des Produits de Santé
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-DHMA	H/V	Denmark - Danish Health and Medicines Authority
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 - ANSM - Agence nationale de sécurité du médicament et des produits de santé
Germany	DE-BFARM	H	Germany - BfArM - Bundesinstitut für Arzneimittel und Medizinprodukte
	DE-PEI	H/V	Germany – PEI - Paul-Ehrlich Institut, Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Greece	EL-EOF	H/V	Greece - EOF - National Drug Organisation
Hungary	HU-OGYI	H	Hungary - National Institute of Pharmacy
Iceland	IS-IMCA	H/V	Iceland - Icelandic Medicines Control Agency
Ireland	IE-~~IMB~~ HPRA	H/V	Ireland - ~~Irish Medicines Board~~The Health Products Regulatory Authority
Italy	IT-AIFA	H	Italy - Agenzia Italiana del Farmaco
Latvia	LV-ZVA	H/V	Latvia - State Agency of Medicines

Liechtenstein	LI-LLV	H/V	Liechtenstein - Kontrollstelle für Arzneimittel beim Amt für Lebensmittelkontrolle und Veterinärwesen
Lithuania	LT-SMCA	H	Lithuania - State Medicines Control Agency
Luxembourg	LU-MINSANT	H/V	Luxembourg - Direction de la Santé Villa Louvigny Division de la Pharmacie et des Medicaments
Malta	MT-MEDAUTH	H	Malta - Medicines Authority Divizjoni Tas-Sahha Bezzjoni Ghar-Regolazzjoni Tal-Medicini
Netherlands	NL-MEB	H/V	Netherlands - College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board
Norway	NO-NOMA	H/V	Norway - The Norwegian Medicines Agency
Poland	PL-URPL	H/V	Poland - Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Portugal	PT-INFARMED	H/V	Portugal - INFARMED - Instituto Nacional da Farmácia e do Medicamento Parque da Saúde de Lisboa
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 - Javna agencija Republike Slovenije za zdravila in medicinske pripomočke
Spain	ES-AEMPS	H/V	Spain - Agencia Española de Medicamentos y Productos Sanitarios
Sweden	SE-MPA	H/V	Sweden - Medical Products Agency
United Kingdom	UK-MHRA	H	Medicines and Healthcare products Regulatory Agency

*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 ~~2~~3.0//EN"
In the eCTD File Organisation: "util/dtd/eu-regional.dtd"

August 2009

Contributors:
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February 2013

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June 2015

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      BFARM (Klaus Menges)

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)">
<!ENTITY % languages
"(bg|cs|da|de|el|en|es|et|fi|fr|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   "2.03.0"
>

<!--
.....................................................................
-->
<!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

February 2009

Contributors:
   ANSM (Aziz Diop)
   EMA (Laurent Desqueper)
   MEB (C.A. van Belkum)

Version 2.0
February 2013

Contributors:
     EMA (Antonios Yfantis)

Version 3.0
July 2015

Contributors:
     BFARM (Klaus Menges)

-->

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

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

<!--
.....................................................................
-->
<!ELEMENT submission              ( identifier          (
#PCDATAnumber?, tracking )  >
<!ELEMENT submission              ( number?, procedure tracking )  >
```

```
<!ELEMENT procedure tracking          ( number+ )>
<!ELEMENT number                    ( #PCDATA )>
<!ELEMENT submission-unit           ( #PCDATA )>
<!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 (~~initial~~maa | var-type1a | var-type1ain | var-type1b | var-type2
| var-nat | extension | psur | psusa | rmp | renewal | ~~supplemental-
info | fum | specific-obligation~~pam-sob | pam-anx | pam-mea | pam-
leg | pam-sda | pam-cada | 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-53
| referral-107i | referral-16c1c | referral-16c4 | annual-
reassessment | usr | clin-data-pub-rp | clin-data-pub-fv | paed-
~~article-~~7-8-30 | paed-29 | paed-~~article-46-~~45 | paed-46 | article-58
| notification-61-3 | transfer-ma | ~~corrigendum |~~ lifting-suspension
| withdrawal | ~~withdrawal | reformat | rmp~~ cep | none) #REQUIRED
 mode ( single | grouping | worksharing ) #IMPLIED
>

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

<!--
.....................................................................
-->
<!ATTLIST agency
code ( AT-~~AGES~~BASG | BE-FAMHP | BG-BDA | CY-PHS | CZ-SUKL | DE-BFARM
| DE-PEI | DK-~~DKMA~~DHMA | EE-SAM | EL-EOF | ES-AEMPS | FI-FIMEA | FR-
ANSM | HR-HALMED | HU-OGYI | IE-~~IMB~~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
```

```
935  >
936
937  <!--
938  ..................................................................
939  -->
940  <!ENTITY % env-countries
941  "(at|be|bg|cy|cz|de|dk|edqm|ee|el|ema|es|fi|fr|hr|hu|ie|is|it|li|lt|
942  lu|lv|mt|nl|no|pl|pt|ro|se|si|sk|uk)">
943
944  <!--
945  ..................................................................
946  -->
947  <!ATTLIST envelope country %env-countries; #REQUIRED >
948
949  <!-- +++ -->
```

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
```

```
1005        %leaf-att;
1006    >
1007    <!ELEMENT title (#PCDATA)>
1008    <!ELEMENT link-text (#PCDATA | xref)*>
1009
1010    <!ELEMENT xref EMPTY>
1011    <!ATTLIST xref
1012        ID ID #REQUIRED
1013        xmlns:xlink CDATA #FIXED "http://www.w3c.org/1999/xlink"
1014        xlink:type CDATA #FIXED "simple"
1015        xlink:role CDATA #IMPLIED
1016        xlink:title CDATA #REQUIRED
1017        xlink:href CDATA #REQUIRED
1018        xlink:show %show-list; #IMPLIED
1019        xlink:actuate %actuate-list; #IMPLIED
1020    >
1021
1022    <!-- +++ -->
1023
```