

Guidance for Industry on Providing Regulatory Information in eCTD Format

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1 Glossary

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

| Term | Definition |
|--------------------------------------|---|
| Applicant | A pharmaceutical company or its agent submitting information in support of an application. |
| Application | A collection of documents compiled by a pharmaceutical company or its agent in compliance with Swiss legislation and guidelines in order to seek a marketing authorisation or any amendments thereof. An application may comprise a number of submissions or sequences. |
| Application Number | The Application Number is assigned to the application by Swissmedic. It tracks the Application at the agency level. |
| Regulatory Activity | Used to group together several related sequences of an application. |
| Dossier | Several pharmaceutical forms and strengths may be comprised under one medicinal product name. This is considered a Dossier. |
| eCTD backbone | XML, file and folder structure including technical files |
| eCTD identifier | An eCTD identifier is a name, code or number used as the directory name in the top-level directory. This can be a proposed trade name, a company internal project code, or the Marketing Authorisation Number. |
| eCTD submission or sequence | A single set of information and/or documents in eCTD format supplied by the applicant as a partial or complete application. |
| Marketing Authorisation Number (MAN) | The Marketing Authorisation Number is the unique identifier for the medicinal product and the dosage form for the Swiss market. (Swissmedic Number) |

2 List of Abbreviations

| | |
|----------|--|
| CTD | Common Technical Document |
| eCTD | electronic Common Technical Document |
| DMF/ASMF | Drug Master File / Active Substance Master File |
| DTD | Document Type Definition |
| EMA | European Medicines Agency |
| EWG | Expert Working Group |
| FO | Form |
| ICH | International Council on Harmonisation |
| IfP | Information for Professionals |
| INN | International Non-Proprietary Name |
| LCM | Life Cycle Management |
| LoQ | List of Questions |
| MAH | Marketing Authorisation Holder |
| MAN | Marketing Authorisation Number |
| NeeS | Non-eCTD Electronic Submission |
| OCR | Optical Character Recognition |
| OSS | Swissmedic division Operational Support Services |
| PDF | Portable Document Format |
| PI | Product Information |

| | |
|------------|---|
| PMF | Plasma Master File |
| PSUR/PBRER | Periodic Safety Update Report / Periodic Benefit-Risk Evaluation Report |
| RMP | Risk Management Plan (E2E) |
| Q&A | Questions and Answers document |
| ToC | Table of Contents |
| TPA | Therapeutic Product Act (Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, SR 812.21) / Loi fédérale du 15 décembre 2000 sur les médicaments et les dispositifs médicaux (Loi sur les produits thérapeutiques, LPT _h ; RS 812.21) |
| VAM | Ordinance of 21 September 2018 on Therapeutic Products (Therapeutic Products Ordinance, TPO) (SR 812.212.21) / Ordonnance du 21 septembre 2018 sur les médicaments (OMéd; RS 812.212.21) |
| XML | Extensible Markup Language |
| WL | Wegleitung / information sheet |

3 Introduction

This document aims to provide guidance on submitting regulatory information in eCTD format to the Swiss Agency for Therapeutic Products (Swissmedic). It reflects the current situation and will be updated regularly to implement changes in national legislation and/or ICH regulations.

The preparation and filing of submissions as well as sending additional information in eCTD format is encouraged but remains optional. The same timelines apply for both paper and electronic submissions. Applicants who choose to file a submission in the eCTD format must comply with the requirements as described in this document. Submissions and additional information in electronic format that do not comply with these requirements, for example NeeS, will be rejected.

Applicants are also encouraged to consult other guidance documents published by Swissmedic, EMA and ICH. A non-exhaustive list can be found in Appendix 1 (chapter 10.1) for more information.

4 Purpose and scope

The purpose of this guidance document is to integrate the eCTD format into the Swissmedic registration framework by describing the electronic format requirements for drug submissions filed pursuant to the Therapeutic Product Act (TPA) and all relevant ordinances.

Information on the use of the Swissmedic eGov portal is not part of this guidance document. Please refer to the *Swissmedic eGov Portal – Standard functions information* document for more information.

4.1 Types of products/submissions

This guidance document applies to pharmaceuticals, biologicals and vaccines, blood and blood derivatives as well as products pertaining to complementary medicines for human use.

The eCTD format is also encouraged for the drug component of drug and device combinations, where the primary mechanism of action is drug-related.

It does not apply to:

- veterinary medicinal products
- medical devices and drug device combinations where the medical product combination is classified as a device
- notification procedure for complementary medicine
- notification applications for clinical trials.

4.2 Additional information and subsequent applications

Once an applicant files an application in the eCTD format, all additional information for the application and subsequent applications for the same medicinal product have to be filed in the eCTD format (“Once eCTD, always eCTD”). Applicants must not revert to a paper-based format for subsequent applications for the same medicinal product. However, applications that have been submitted before the transition to eCTD must be completed in paper format. (Please refer to chapter 7.7 for further information).

4.3 Filing formats of submissions in eCTD format

eCTD is considered to be an electronic only format. For legal reasons, however, certain documents of Module 1 have to be sent in addition as signed paper documents (wet signature required). The current Swissmedic practices have to be taken into account to define which documents are needed for each submission type, and the documents detailed in Appendix 2 should be provided where applicable.

Please refer to the TPA and related ordinances and Swissmedic’s website for the latest information, including the *WL Formal requirements*.

It is possible to submit eCTDs via the Swissmedic eGov portal. In doing so, it will not be necessary to submit any accompanying paper documents or discs by post, including wet signature documents. For more information on the portal, please refer to the Information sheet *Swissmedic eGov Portal – Standard functions*.

5 Structure and content of submissions in eCTD format

5.1 Structure

The content of information required for submissions in eCTD format is the same as for paper-based submissions. However, the location of files may differ from the location of the paper documents. The XML backbone reflects the eCTD structure. It can be viewed in any XML editor. Figures 1 and 2 illustrate part of the eCTD structure, as seen when using a review tool or a file explorer.

Figure 1: Example eCTD Structure in an eCTD review tool

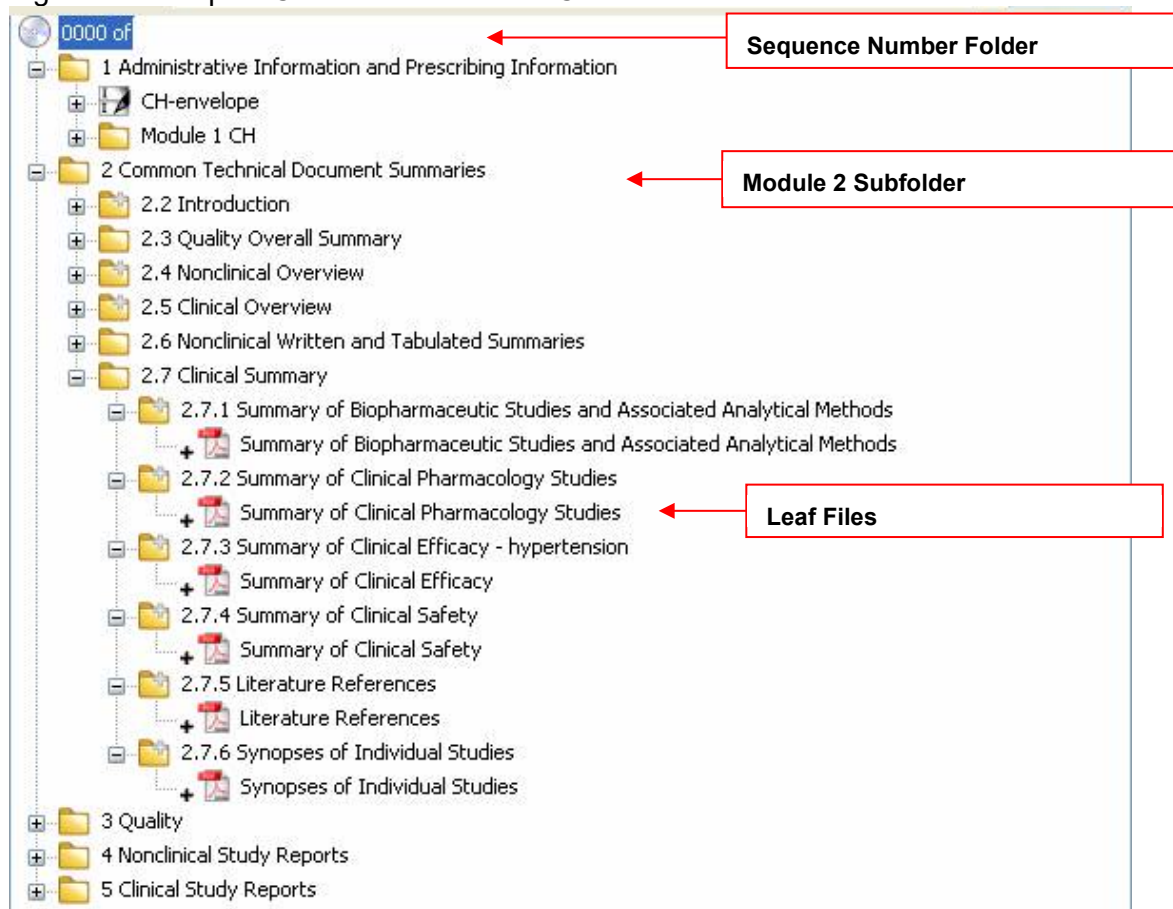
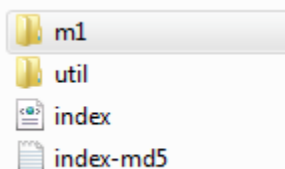


Figure 2: Example eCTD structure in file explorer view



The structure of an eCTD will affect the life cycle management of the eCTD over time, and therefore the structure of the first eCTD for a product or product range needs careful consideration. For example: An eCTD is built to cover 100mg and 200mg tablets, and common documents are submitted for both strengths. Over time, a 150mg tablet is added (line extension). Consequently, in Module 1, all 100/200mg documents should be replaced with 100/150/200mg documents. In Module 2 and 3, a new 23p and 32p section should be introduced to the existing eCTD life cycle. Alternatively, if the line extension results in a new brand name, the applicant should build an entirely different and new eCTD dossier for the 150mg tablets.

5.1.1 eCTD Identifier

There is no requirement to use an identifier for the directory name in the top-level directory. However, in order to facilitate the handling of submissions, Swissmedic recommends using the proposed trade name or a company internal project code as an identifier. Once defined, it should remain unchanged during the whole life cycle.

5.1.2 Sequence number folder

All files and folders in a submission in eCTD format are to be placed under the sequence number folder, as described in the *ICH Electronic Common Technical Document Specification, File Names and Directory Structure*.

The sequence number folder includes an m1 subfolder, m2–m5 subfolders (optional), and a *util* subfolder (see Figure 1). The eCTD backbone file (index.xml), the checksum file (index-md5.txt) and the util subfolder have to be placed in the sequence number folder as well. This sequence number folder must be named using a four-digit number, where for the first submission 0000 must be used. Subsequent submissions have to be provided using an incremental number, unique for each new sequence. Gaps between sequence numbers or disordered submissions should be avoided, i.e. sequence 0001 should be followed by 0002 and 0003 etc.

If a submission fails technical validation due to a technical error, the sequence number does not change when the submission is filed again (replacement sequence). If the submission passes technical validation, but has content deficiencies, resolving these deficiencies requires a new submission with a new sequence number (correctional sequence).

If one of several sequences simultaneously submitted fails technical validation, Swissmedic accepts the correct sequences and asks for replacement of the invalid sequences, provided that no life cycle issues are present. This is subject to Swissmedic's assessment on a case by case basis.

5.1.3 util and dtd subfolders

The *util* folder contains a *dtd* subfolder as well as a style folder and they must only contain the files that are mentioned in the Swiss Module 1 Specification which define the regional module 1 backbone file. The *dtd* subfolder located in the root folder must only contain the ICH eCTD DTD that defines the eCTD backbone file. The style folders must contain the relevant style sheet information.

5.1.4 Module 1 subfolder

The content of the Module 1 is described in detail in the *Swiss M1 Specification for eCTD* document.

5.1.5 Modules 2 to 5 subfolders

The structure and content of the modules 2 to 5 subfolders (m2–m5) are defined in the *ICH Electronic Common Technical Document Specification*.

The following requirements are to be considered:

- Node extensions are allowed, but should only be used where necessary
- Node extensions are necessary for each clinical study report. The leaf title for the node extension should serve as study identifier, containing study number and appropriate study title. If clinical study reports consist of several PDF files, the leaf title of each file should indicate its content (e.g. “study number_synopsis”, “study number_main body” and “study number_individual appendice”)
- The use of Study Tagging Files (STF) is not accepted and an eCTD containing STFs must be reworked for a submission in Switzerland. The only exceptions are applications according to Article 13 TPA, where STFs in the reference dossier and also in the consolidation sequence are accepted.

5.2 eCTD Envelope

The metadata provided by the applicant with the eCTD are important, since they indicate relationships between individual sequences for effective life cycle management of the application. The particular envelope elements used by the review tool for display and management of submissions are listed in the *Swiss Module 1 Specification for eCTD, Appendix 2*. Applicants must include and present metadata in a manner that unequivocally ties them to a submission (e.g. applicant name, INN). Over

the life cycle of a medicinal product, metadata may only be changed for legitimate reasons (e.g. change of MAH) and only if the change is technically supported. Consistency, quality and accuracy of metadata should always be assured.

In case the MAN is known, it should be included in the envelope.

The field *submission description* is a free text field with a maximum of 180 characters possible. It serves to link the application number to the application (in case of more than one application per eCTD Sequence).

Using the *submission description* element, submissions relating to multiple parallel variations can be easily identified and grouped together. The contents of the *submission description* element should therefore be concise but clearly indicative of the substance of the application in question.

The *submission description* can also serve to determine the differences between sequences where the same value for *application type* is used for multiple submissions. As an example, *new indication* as application type is not descriptive enough for the content and therefore the description should be supplemented by *application for new indication breast cancer* in the *submission description* field.

5.3 Metadata

The leaf attribute metadata provided by the applicant are considered important, since this information is displayed by review tools and is used for identifying documents and sections. The metadata become particularly important in managing the life cycle of the submission. For example, the *ICH eCTD Specification Document* describes six eCTD heading element attributes to structure the eCTD content. Five of these attributes can be found in Module 3:

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

These attributes correspond to elements in the eCTD that may be repeated, and are used to define specifically what each repeated section covers.

For example, in an eCTD submission covering two active ingredient manufacturing sites, the directory structure for the eCTD may be split into two paths which contain documents for the different sites. The XML should then be similarly structured (see *ICH eCTD Specification document*). The extent to which a single eCTD sequence can cover multiple substances, manufacturers, products and excipients, and the use of the respective attributes to describe what is being covered with, is left to the discretion of the applicant. eCTD sequences can be structured in various ways, affecting the presentation in the review tools and the repositories that are used to store the eCTD files and folder structure.

5.4 Inclusion of non-eCTD correspondence documentation

The term correspondence applies to all documents that are exchanged between the applicant and Swissmedic in the context of an authorisation procedure but which do not have a formal designated placeholder within the eCTD structure and/or are currently not supported in eCTD. For example, responses to authority questions are not classified as correspondence since the *Swiss M1 eCTD DTD* includes a designated section for such information.

Correspondence that is not directly relevant to the life cycle should be handled outside the life cycle, e.g.:

- announcing the timeline for when the sponsor will submit the responses to the List of Questions;
- requesting to extend a due date (e.g. for responses to List of Questions or to preliminary decisions);

However, any information that relates directly to the dossier content should be sent as an eCTD submission to Swissmedic. This includes all changes and all annexes to the dossier sent as additional information, as well as the acknowledgement of final changes to details submitted in the body of the dossier.

5.5 Cover Letter

The cover letter is located in section 1.0 of the Swiss Module 1. It has no life cycle and should therefore always be submitted with the document operation attribute *new*. As eCTD viewing tools display all *new* leaf elements in a current or cumulative view, it is recommended to place additional descriptive text in the leaf title to help identifying each cover letter leaf and the submission it is in. Some examples of possible leaf titles:

Cover Letter PSUR No 7
Cover Letter for New Indication AML
Cover Letter Label CDS 01-Jan-2001

The following statements must be included in the cover letter:

- “We confirm that the CD/DVD-burning session was closed and the submission was checked with an up-to-date and state-of-the art virus checker.”
 - “We confirm that the documents submitted in electronic form and the corresponding paper version of parts of module 1 are identical.”
- Please note that these statements are no longer necessary in case of a submission via Swissmedic eGov portal.

In case of a technical rejection, the original cover letter must be included alongside the new cover letter in the replacement sequence. The leaf titles of both cover letters should be named accordingly.

A tracking table in a tabular format should be included in or as an annex to the cover letter, as per the following example:

Figure 3: Tracking Table

| Date of submission | Sequence number | Related eCTD sequence | Regulatory activity / Type of claim | Regulatory status (submitted / approved / rejected / consolidated / withdrawn) |
|--------------------|-----------------|-----------------------|-------------------------------------|--|
| | | | | |

Note that a tracking table submitted as a separate document is a document with a life cycle and the life cycle operator on the document level should be *replace* in subsequent submissions.

If there are specificities concerning the eCTD submission the reviewers should be informed about, it is highly recommended to include a Reviewer’s Guide in or as an annex to the cover letter. This Reviewer’s Guide may contain the following sections, if applicable:

- Particularities relating to presentation and delivery of the eCTD
- Information on file sizes by module
- Data security/virus scan information
- Legacy documents and scanned pages details

- File formats (if any particularities to report)
- File size (if exceeding 200MB restriction)
- Files referenced at multiple locations within the backbone
- Specifications adhered to
 - Documents with relevance to more than one CTD module
 - Hyperlink appearance and strategy
 - Bookmarks
 - Particularities of module organisation
 - List of documents available on request

6 Technical requirements for submissions

6.1 Submission media

Swissmedic accepts media such as CD-ROMs, DVD-ROMs and Blu-Ray discs. Any other hardware such as laptops, desktops, hard drives, USB sticks etc. will not be accepted. The electronic information should be directly readable and usable on Swissmedic's hardware. It is the policy of Swissmedic to maintain desktop configurations and IT infrastructure in line with common office standards. When using re-writable disks, all applicants are advised to close open sessions before sending them to Swissmedic.

For very large submissions, Swissmedic prefers using a single disk to multiple smaller ones. Modules must not be split over multiple disks.

The submission media should be packed adequately to prevent damage. All the contained media units should be appropriately labelled with information as described below.

- The applicant's name
- The product (invented) name(s)
- The MAN (if available)
- The sequence number(s) of the eCTD submissions contained on the discs

For more information on the possibility to submit eCTDs using the Swissmedic eGov portal please refer to the *Information sheet Swissmedic eGov Portal – Standard functions*.

6.2 Compression and password protection/security settings

The applicant is required not to apply any compression to the submission or the files inside the submission.

One-time security settings or password protection of electronic submissions for security purposes are *not* acceptable during transportation from the applicant to Swissmedic. Applicants should also *not* apply any file level security settings or password protection to individual files in the eCTD. The file settings should allow printing, annotations to the documents, and selection of text and graphics.

The following requirements should be noted in relation to security:

- Encryption is not considered necessary when using a physical media. The applicant should assume all responsibility for the media until it is delivered to Swissmedic.
- Once received by Swissmedic, security and submission integrity is the responsibility of the agency.
- The md5 checksum allows the recipient of the eCTD to ascertain whether files in the submission have been modified since the checksum was generated by the applicant.

6.3 PDF files

The following requirements apply in relation to PDF files:

- Files should be created according to the latest EWG M2 Recommendations and should be legible with the Acrobat Reader or any other viewer. PDF files should be saved as *optimised* to reduce the size and allow faster opening.
- PDF v1.3 or earlier are not acceptable for technical reasons. No exceptions will be made.
- The use of additional software to navigate and work with the files is not acceptable.
- Documents in PDF/A format are accepted. Documents in PDF/X format are only accepted if they do not interfere with the review functionality since this format does not support hyperlinking or bookmarks. Please liaise with Swissmedic before including such PDF files.
- PDF files produced from an electronic source document are preferred to PDF files generated from scanned paper since these PDF files provide the maximum functionality to the reviewers in terms of search capabilities and copy & paste functionality. However, the PDF files of documents which bear an original signature on the paper version must be generated by scanning (e.g. cover letter, forms).
- Expert Reports and the Overviews/Summaries in Module 2 must be generated from an electronic source document.
- If scanning is unavoidable, readability and file size should be balanced; the following is recommended: resolution 300 dpi (photographs up to 600 dpi), avoid grayscale or colour where possible, use only lossless compression techniques.
- The maximum individual acceptable file size is approximately 200 MB. The file size should ensure clarity, speed of download and ease of review.
- All fonts used in a document should be embedded in the file.
- Adobe Portfolio files must not be used.

Additional details on PDF can be found in the *ICH eCTD Specification Document, App. 7*.

6.4 File naming conventions

It is recommended to adhere to the eCTD file naming conventions as described in the *ICH eCTD Specification Document*, the *Swiss Module 1 Specification* and the *Validation Criteria*.

If an applicant wishes to submit multiple files in one section where only one highly recommended name is available, this can be achieved using a suffix to the filename (e.g. *pharmaceutical-development-container.pdf*).

6.5 Hyperlinks and Bookmarks

In general, hyperlinks are encouraged within the eCTD to facilitate swift navigation within the dossier, but should not be overused. They are only to be included where considered necessary and where they add real value. It is important that eCTD titles (i.e. the backbone entries visible as the eCTD ToC) are used in consistency with how the documents themselves are referred to within other documents, for example summary documents. Hyperlinks are needed if the title presented by the review tool in the eCTD ToC and the reference in a summary document do not match and therefore the backbone cannot be used. The eCTD should be structured and links be provided in such a way as to ensure that the reviewer is constantly aware of the overall structure and narrative flow of the dossier.

For example, Module 3 is highly structured and defined to a relatively low level of granularity in the specification. Therefore, only minimal use of hyperlinks should be necessary. For example, when the same citation appears on a page more than once, it is recommended that a link only to the first instance of the citation per page be provided. Documents should be placed only once in the eCTD folder structure and referred to via hyperlinks.

In the nonclinical/clinical part of the eCTD, the structure is defined using a higher level of granularity. Within Modules 4 and 5, the localisation of studies and references may vary across submissions. For fast orientation purposes, linking from IfP to the respective part of the overviews and from overviews to Modules 4 and 5 is crucial (*two-click-strategy*). Hyperlinks from the nonclinical and clinical overviews to the references themselves can be provided directly from the text or from the list of references at the end of the document. Missing hyperlinks may lead to a formal objection.

Broken links are technically classified as best practice criteria (BP). Even though a submission is technically accepted, the submission may be objected due to formal reasons, if for example hyperlinks or bookmarks are not functional to a critical extent. As a general conclusion, broken links in a summary document (e.g. preclinical overview) are more critical than broken links in a study appendix due to different frequency these hyperlinks are used. References should not contain external links (e.g. links to websites).

Within Modules 2 to 5, bookmarks are needed for documents larger than 20 pages, except for literature references where bookmarks are not necessary. In general, for documents with a table of contents, bookmarks for each item listed in the table of contents should be provided including all tables, figures, publications, other references, and appendices. For further information regarding the use of bookmarks please refer to *ICH eCTD Specification Document, the Swissmedic Guidance for Industry, Verwaltungsverordnung Anleitung Anforderung an die Arzneimittelinformation von Humanarzneimitteln* and *WL Formal Requirements*.

6.6 md5 checksum

md5 checksums are used to verify the integrity of physical files in the submission. Both the XML backbone and each file in the sequence will be checked by using an individual checksum. Applicants must place a checksum file named *index-md5.txt* in the same directory as the XML eCTD instance.

A dated and signed hard copy of the checksum file as paper annex to the cover letter is mandatory. An invalid checksum will result in the rejection of the eCTD submission.

For users of the Swissmedic eGov portal it is not necessary to include the hard copy of the checksum file.

6.7 Additional files in Word format

Swissmedic requires Word files (.doc or .docx) for some documents in addition to the PDF for the purposes of review and document manipulation. Please refer to the *WL Formal requirements* for more information.

PDFs (and other accepted file formats) are only to be referenced in the eCTD XML backbone. Word documents must not be included in the eCTD backbone.

Word files should be placed on the same media, alongside the eCTD sequence, but not inside the actual sequence folder. The folder should be called *eCTD sequence-workingdocuments* (e.g. 0000-workingdocuments) with a substructure as follows:

- *eCTD sequence-Product information*
- *eCTD sequence-Forms*

For documents with several versions during the review process, a date of the version should be included in the file name for tracking purposes and the following naming convention could be applied (it would also be possible to use the same naming as the PDF in the eCTD life cycle):

- For the information to professionals:
prof_productname_submissiontype_date.doc (.docx)
- For the patient information:
patient_productname_submissiontype_date.doc (.docx)

6.8 Virus check

The applicant is responsible for checking the submission for viruses. Checking should be performed with an up-to-date virus checker.

Swissmedic will still perform an internal virus check after reception. A positive check will result in a rejection of the eCTD.

6.9 Technical validation before submission





Swissmedic requires applicants to use a validation tool that checks the submission for technical interoperability before submission.

It is at the discretion of the applicant to comment best practice criteria on the form *Technical Validation eCTD - Part1* available on the Swissmedic website. If submitted, the form technical validation is not part of the eCTD Module 1 and therefore must not be integrated in the eCTD but be submitted only as paper copy.

Further details on the validation are described in the document *Swiss eCTD Validation Criteria*.

6.10 Handling of thumbs.db files

It is possible that *thumbs.db* files are present among the eCTD files after having published the sequence. *thumbs.db* files are system files created by Microsoft Windows every time a file is opened and are often not displayed in the Windows Explorer. In the context of an eCTD submission such files are unreferenced in the XML backbone and will cause a validation error. These sequences will be rejected and a replacement sequence must be submitted.

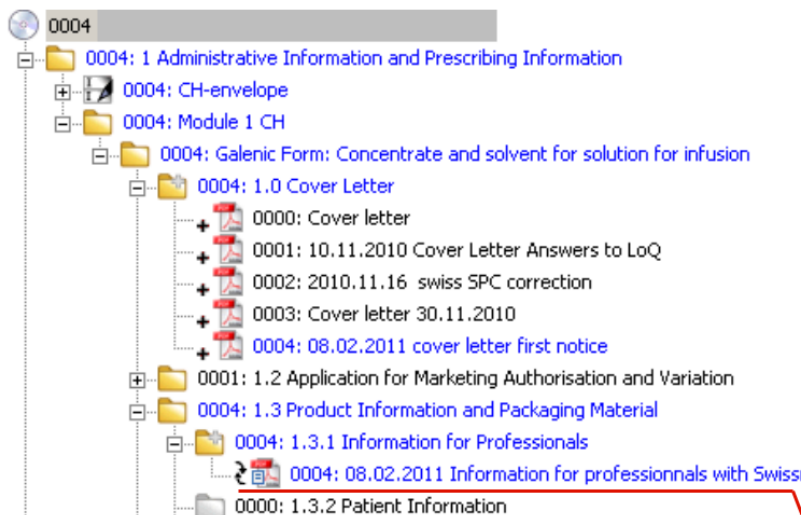
| Name | Änderungsdatum | Typ |
|---|------------------|----------------|
|  ch-cover-letter.pdf | 22.10.2014 12:16 | PDF-Datei |
|  ch-cover-summarychanges.pdf | 22.10.2014 12:16 | PDF-Datei |
|  ch-cover-tracking.pdf | 22.10.2014 12:16 | PDF-Datei |
|  Thumbs.db | 22.10.2014 13:12 | Data Base File |

To avoid creating thumbs.db files, the applicant is advised not to open files or folders after publishing and before burning the sequence on CD. It is possible to disable thumbs.db files in Microsoft Windows. Please liaise with your IT department for support.

7 Life cycle management

7.1 Benefits of the Life cycle

Maintaining a life cycle offers several benefits such as traceability and transparency. For the ease of review, changes to submissions and documents are placed in the context of previous submissions, which makes it easier to find and compare changes. Review tools allow a current view, which represents the current status of the medicinal product and all documents.



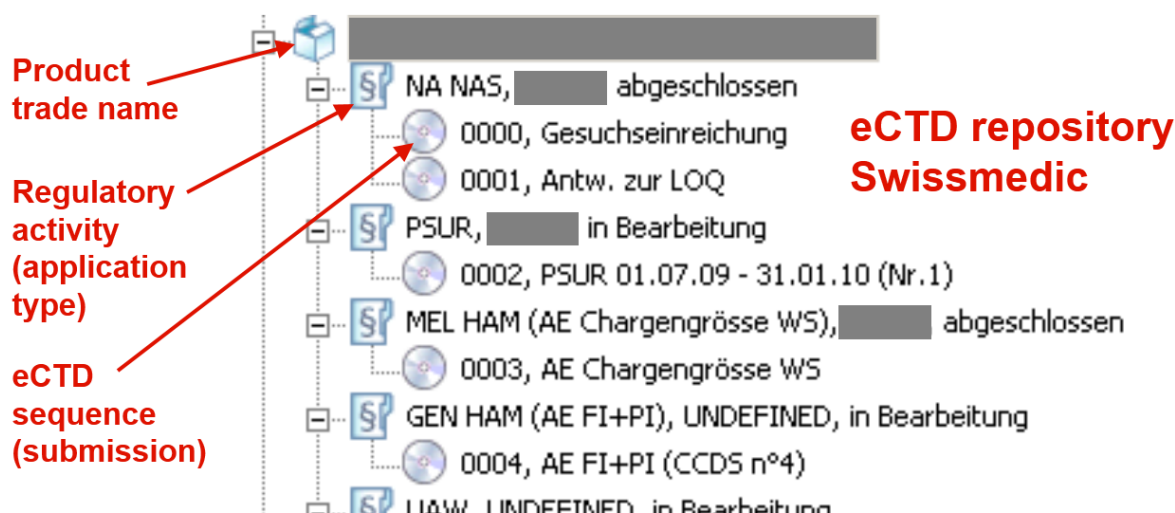
| | Opera... | Title | Sequence |
|----------------|----------|--|----------|
| + [new icon] | new | Swiss Information to Professionals Initial | 0000 |
| [replace icon] | replace | 2010.11.08 updated swiss SPC | 0001 |
| [replace icon] | replace | 2010.11.16 Swiss update SPC LoQ | 0002 |
| [replace icon] | replace | 2010.11.29 Updated Swiss SPC - Correction of the indication | 0003 |
| [replace icon] | replace | 08.02.2011 Information for professionals with Swissmedic corrections | 0004 |

7.2 Life cycle management at the drug product layer (i.e. eCTD application)

An initial filing usually has the sequence number 0000. There are some circumstances in which it might be filled with a sequence number other than 0000.

Each subsequent submission for the corresponding medicinal product will contain an incremental eCTD sequence number.

Swissmedic view of the drug product



Product trade name → NA NAS, [redacted] abgeschlossen

Regulatory activity (application type) → 0000, Gesuchseinreichung

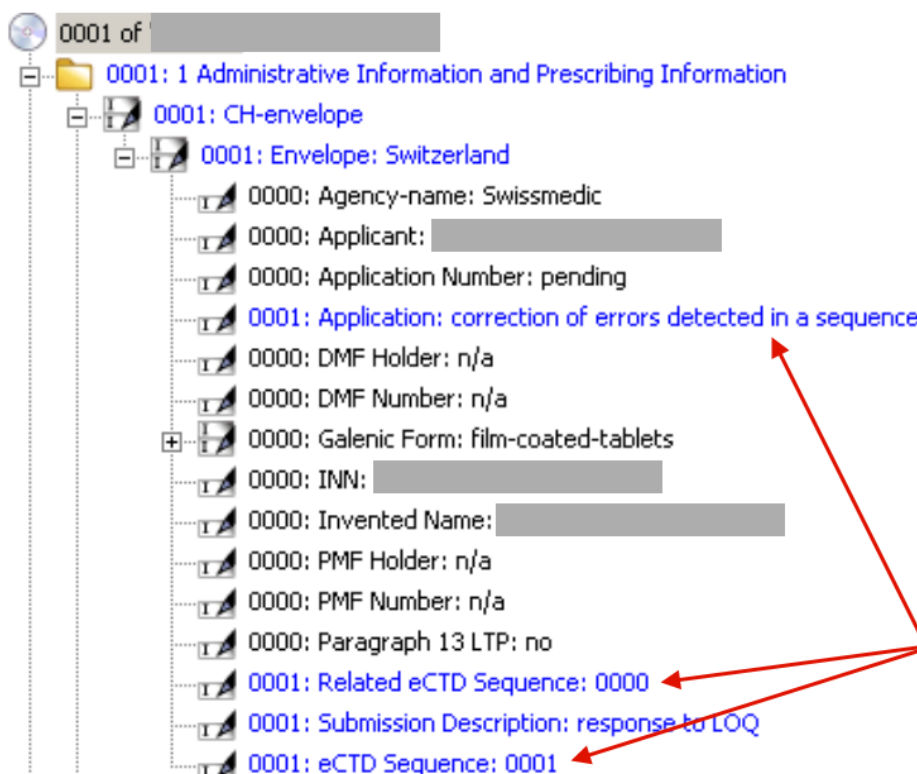
eCTD sequence (submission) → 0001, Antw. zur LOQ

eCTD repository Swissmedic

- PSUR, [redacted] in Bearbeitung
- 0002, PSUR 01.07.09 - 31.01.10 (Nr.1)
- MEL HAM (AE Chargengrösse WS), [redacted] abgeschlossen
- 0003, AE Chargengrösse WS
- GEN HAM (AE FI+PI), UNDEFINED, in Bearbeitung
- 0004, AE FI+PI (CCDS n°4)
- LAW UNDEFINED, in Bearbeitung

7.3 Life cycle management at the submission layer (i.e. eCTD sequence)

7.3.1 Metadata (Envelope)



Life Cycle related metadata

7.3.2 Related eCTD sequence

The related eCTD sequence number describes the relationship of additional information to the first sequence of a regulatory activity using the related sequence attribute in the envelope in ch-regional.xml. It allows sequences to be grouped together that make up an application or a regulatory activity.

For all new drug submissions types, the related eCTD sequence number in the envelope, in the cover letter and the tracking table should be *none*.

For subsequent submissions that are related to another eCTD sequence (submission type *supplemental info* or *corrigendum*), it is mandatory to include the related eCTD sequence as a four-digit number in the envelope. The related eCTD sequence number normally consists of only one single eCTD sequence number. Exceptions may apply.

For consolidation sequences the submission type *supplemental info* should be used as well. The related eCTD sequence depends on the type of the consolidation:

- In case an application is withdrawn or rejected after the review, the related sequence should match the initial sequence number of the regulatory activity concerned or the sequence number prior to the rejected or withdrawn application/variation, respectively.
- In case of an application according to Article 13 TPA, the related sequence is the initial Swiss eCTD sequence (0000) submitted according to Article 13 TPA
- In case regulatory activities have to be completed in paper format before including them in the eCTD life cycle, the related sequence should match the baseline sequence. If there is no baseline the related sequence should match the initial sequence number of the regulatory activity concerned

See *Example of the use of the Related Sequence* in Appendix 2 of Swiss Module 1 Specification for eCTD.

7.3.3 eCTDs with multiple galenic forms

Please note: In general, Swissmedic will now refer to the term galenic form as pharmaceutical form. For technical reasons the old term galenic form will still be used throughout this document and the technical files. There are no changes as to the handling of the term in the context of eCTD.

Several galenic forms (several MANs) of one medicinal product should be managed within a single eCTD life cycle. If the eCTD contains only one galenic form all documents are to be placed in the galenic form folder. In this case no common folder should exist.

If the eCTD covers more than one galenic form, documents for specific galenic forms have to be placed in the appropriate galenic form folder (which is named using the EU standard term of this galenic form, e.g. dispersible tablet) and documents applicable to all galenic forms of the eCTD have to be placed in the common folder.

If an eCTD initially covers one galenic form and, at a later stage in the life cycle, additional galenic forms are added, some of the documents may change their location from the specific galenic form folder into the common folder (e.g. common product information). In this case, the documents located in the specific galenic form folder should be deleted (operator is *delete*) and added in the common folder (operator is *new*). The applicant should explain in the cover letter or in the reviewer's guide which documents have been transferred. The cover letter must be placed either in the specific galenic form folder or the *common* folder.

Figure 4: eCTD Structure

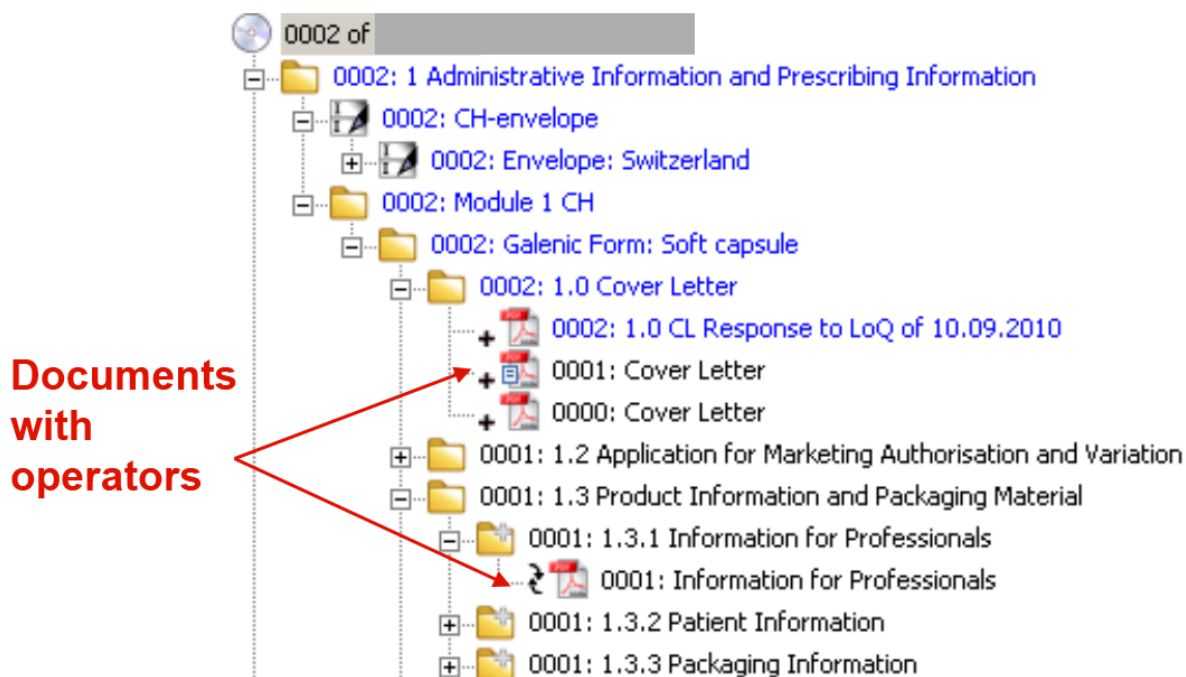


When submitting variations, the forms can be placed in the specific galenic form folder or in the *common* folder, if all galenic forms are covered by the variation.

Besides the remodelling of Module 1, an updated Module 2 and a new or updated section 3.2.P have to be provided. If section 3.2.P is combined for all previously existing galenic forms, an updated section should be provided, replacing existing documents where necessary.

If a separate section 3.2.P is provided for the additional galenic form to describe the extension, then all documents should have the operator *new*.

7.4 Life cycle management at the document layer (eCTD leaf)



7.4.1 Leaf life cycle operation attributes

The operation attribute describes the relationship between leaf files in submissions subsequent a specific submission and in additional information related to those submissions (For an initial submission only the operation attribute *new* is applicable).

The four LCM activities (operation attributes) provided by the ICH are *new*, *replace*, *delete* and *append*. The operation *append* should be avoided due to potential LCM issues.

Further information can be found in the *ICH Electronic Common Technical Document Specification*.

7.4.2 Specific requirements for documents

Some documents require special operation attributes, as described below. Please do also refer to *Swiss Module 1 Specification for eCTD, App. 1, Table 1* for further information.

For the PI (Information for Professionals, Patient Information, and elements of packaging materials) the following should be considered: When presenting new PI or variations of the PI please refer to the *WL Formal requirements*.

- The operator for the first submission of the PI is *new*.
- As the PI has a life cycle, each proposed PI document in the application process (sequence LoQ, sequence preliminary decision etc.) will be submitted as a replacement document for the previous version using the operator *replace*.
- The leaf title (-VAR) should be used to describe the variation (e.g. CCDS change or PSUR I).
- The approved version of the PI contains the new changes in addition to all previous changes, marked according to the requirements detailed in the *WL Formal requirements*.

7.5 Responses to the List of Questions

The document which lists all the questions with the corresponding narrative text response for each question should be placed in the *Responses to Swissmedic LoQ section* of M1. It is also possible to split this document into multiple documents, for example one for answers to quality, nonclinical, and clinical.

For responses which contain new or updated data/documents relating to Modules 3-5, such data/documents have to be placed in the relevant sections of these modules. This may also apply to Module 1 (e.g. revised product information), as well as to Module 2 in cases where extensive data/documents would require inclusion of the relevant summaries and/or overview sections.

If new or updated documents are required, hyperlinks from the consolidated LoQ document to the new or updated documents in the eCTD dossier should be included.

7.6 Consolidation Sequences

7.6.1 Consolidation sequence after a Baseline

See chapter 7.7 for more information.

7.6.2 Article 13

Please refer to the *Guidance on applications according to Article 13 TPA for eCTD applications* for further details.

7.6.3 Withdrawn, fully or partially rejected applications

These applications should not appear in the current view of the eCTD. If a submission is withdrawn or rejected, a consolidation sequence should be submitted to rebuild the approved status by removing eCTD documents associated with the rejected or withdrawn submission. The administrative documentation in Module 1 should be left unchanged (unless this documentation has an existing life cycle and is affected by the rejected or withdrawn variations). If you are unsure, please liaise with the responsible Case Manager.

The application type should be *supplemental information* and the *related sequence* should match the initial sequence number of the regulatory activity concerned or the sequence prior to the rejected or withdrawn application/variation, respectively.

7.6.4 Restructuring of Module 3

In case Swissmedic asks for restructuring of Module 3, the application type *supplemental information* should be used. *Related sequence* should be the baseline or the initial (0000) eCTD sequence.

7.7 Baseline submissions

7.7.1 General requirements

A baseline submission can mark the change from a paper based submission to an eCTD submission. It is **recommended, but not mandatory**, that such a submission is prepared in eCTD format for applications previously managed in paper or in eDok format. The marketing authorisation holder may provide Swissmedic with information reformatted as eCTD for their already authorised medicinal products. In particular for quality variations, Swissmedic encourages the submission of a baseline, in order to facilitate the handling of variations.

There is no requirement for a chronological or cumulative presentation of the dossier content. The baseline submission should reflect the most recently approved status. A signed declaration must also be submitted as an annex to the cover letter stating that the content of the submitted eCTD is identical to the current approved documents and that there have been no changes to the dossier content as a result of the provision of the eCTD submission. It is not acceptable to exclude any information from the original dossier unless it has been updated by a regulatory process (e.g. variation, line extension etc.).

The baseline should contain electronic source documents, but Swissmedic also accepts scanned documents where OCR has preferably been applied to.

Only a technical validation will be performed on the eCTD sequence. There is no content validation and no review process involved.

The envelope element *application type* for a baseline submission should be *reformat*.

A baseline always has always to be submitted as a separate sequence. It is possible to submit a baseline sequence as a separate sequence together with a variation.

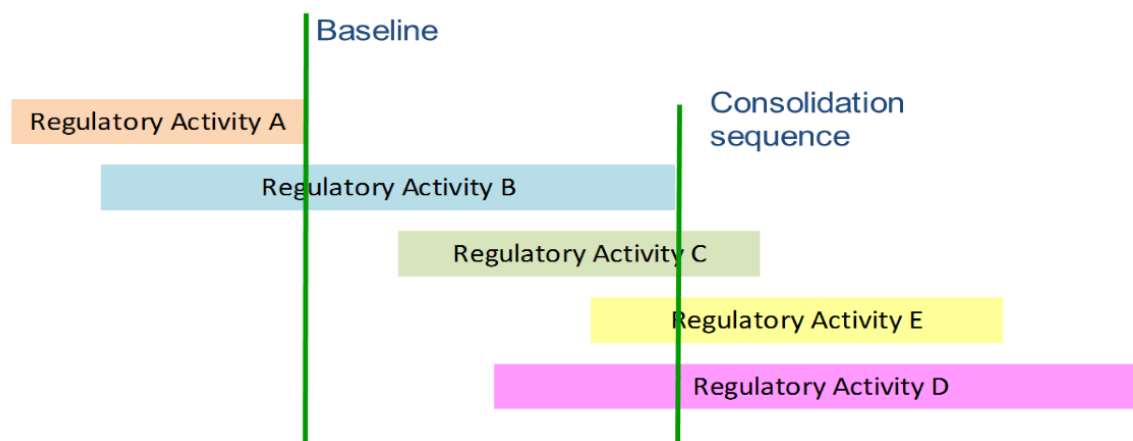
The following has to be considered when preparing a baseline submission:

1) Timing of the submission:

- Preferred option: At the beginning of the transition from paper to electronic as sequence 0000
- For medicinal products with variations planned for Module 3
- Before or with a new variation (of e.g. Module 3 update) but **always** as a separate sequence
- **Outside** an ongoing application, exception see figure 5.

2) Navigation (Hyperlinks): see Chapter 6.5, but normally, no hyperlinking is necessary for a baseline sequence.

Figure 5:



Regulatory Activity A and B: paper submissions
Regulatory Activity C, D, E: eCTD submissions

Paper-based regulatory activity A must be completed in paper and should then be part of the baseline. Paper-based regulatory activity B must to be completed in paper as well, but should not be part of the eCTD baseline yet. As soon as regulatory activity B is completed, a consolidation sequence (submission type supplemental info and related sequence = baseline sequence) must be submitted, integrating the parts of regulatory activity B in the eCTD life cycle. Regulatory activity C and following must then be submitted as eCTD.

Table 1: Options for a baseline submission

| | Option to deal with the legacy | Legacy sequence(s) no. | Variation sequence no. |
|---|--|------------------------|------------------------|
| 1 | Rebuild of the complete previous CTD paper life cycle | 0000 - 0035 | 0036 |
| 2 | Baseline submission of legacy as "current active view" | 0000 | 0001 |
| 3 | Partial baseline of Quality legacy part at the beginning of transition | 0000 | 0001 |
| 4 | Partial baseline (Quality/CMC part) in the middle of eCTD life cycle | - 0035 | 0000 – 0034 0036 |

It is expected that option 1 will rarely occur with medicinal products that have a long regulatory history as this implies a relative high amount of additional work.

When submitting changes to Module 3 the full section Drug Substance and/or Drug Product (option 4) is expected. Exceptions (in case such submissions will not be of added value) should be justified in the cover letter.

In principle, all CTD subheadings should be addressed. Statements justifying absence of data for specific CTD sections should be provided in the relevant Quality overall summary. Placeholder documents highlighting *no relevant content* should be avoided.

To reflect the most recently approved status, all the documents of Module 1 relevant to the Marketing Authorisation need to be included into the baseline submission. Therefore Module 1 should contain as a minimum and where applicable:

- Cover Letter of the standalone baseline submission
- Form Application for Authorisation/Variation Human Medicines (of the last approved submission)

Annexes – Forms

- Form Full Declaration
- Form Manufacturer Information
- Form Status Marketing Authorisations Abroad
- Form Substances of Animal or Human Origin
- Form Pharmaceutical Information for Parenteral Preparations
- Form Co-Marketing Confirmation
- Form Import According to Paragraph 14 Section 2 TPA
- Form Change of Marketing Authorisation Holder
- Form PSUR/PBRER for Human Medicinal Products
- Form Declaration Radiopharmaceuticals
- Form Confirmation Substances from GMO
- Form DMF for First Authorisation and Variations
- Form Information on Product Quality (Article 13 TPA)
- Form Notification Sample Packages
- Form Notification of No Marketing or Interruption to Distribution
- Form Application for recognition of Orphan Drug Status
- Other Forms

Annexes - Documents on Drug Product Quality

- DMF Letter of Access
- Ph. Eur. Certificate of Suitability for Active Substance
- Ph. Eur. Certificate of Suitability for TSE
- EMA Certificate for Plasma Master File (PMF)

- EMA Certificate for Vaccine Antigen Master File (VAMF)

Annexes – Manufacturing

- GMP Certificate or Other GMP Documents
- Documentation Concerning Manufacturing Authorisation
- Complete Manufacturing Information with Flow Chart

Annexes – Others

- Information for Professionals
- Patient Information
- Packaging Information

Information Relating to Pharmacovigilance

- Pharmacovigilance System
- Risk Management System

Others

- Additional Information

7.7.2 Annual Updates of Influenza Vaccines

For the submission of the annual update in eCTD format a baseline is highly recommended and should be submitted in January at the latest.

Every submission requires a new sequence:

- Baseline (0000)
- Submission of the packaging material (e.g. 0001)
- Submission of the quality documentation (e.g. 0002)
- Submission of clinical documentation (e.g. 0003)

Module 3 must include the data of the latest approved annual update. Module 2.3 is not required.

8 Advice on specific application types

8.1 Submission of PSURs/PBRERs and E2E/RMP Updates in eCTD Format

Applicants who choose to file a PSUR/PBRER and or an E2E/RMP Update submission in eCTD format must comply with the following requirements.

8.1.1 PSUR/PBRER

For submissions that are part of the PSUR/PBRER program based on VAM and TPA (Art. 34 VAM, Art. 34 reference Art. 17 paragraph 2 VAM and Art. 16 paragraph 1 TPA) the following applies:

- the application type is *PSUR*
- if serving also as a supporting document for a Product Information Variation, two sequences are required, one for PSUR and one for VAR-PI.
- a statement that two associated sequences have been submitted must be included in the Cover Letter and in both the PSUR and the Application for Marketing Authorisation and Variation forms.

For submissions outside the PSUR/PBRER program (non-VAM and non-TPA based PSUR/PBRER and for other reasons such as: requested by Swissmedic, to inform about a safety signal, submission of a new version of the E2E/RMP) the application type is *supplemental info*.

8.1.2 E2E/RMP Update

For submissions that are part of the regular PSUR/PBRER program the application type is *PSUR*. For submissions outside the regular program the application type is *supplemental info*.

8.1.3 Structure for a PSUR/PBRER submission as part of the regular PSUR/PBRER program

Table 2

| Module / Requested Documents | Operator |
|---|---|
| 1.0 Cover Letter | operator -> <i>new</i> |
| 1.2.2.16 Form PSUR | operator -> <i>new</i> |
| 1.2.5.1 Comparison EU-SmPC vs. CH-FI | <ul style="list-style-type: none"> operator first version / eCTD submission -> <i>new</i> operator if changes from previous version -> <i>replace</i> |
| 1.2.5.2 CCDS | <ul style="list-style-type: none"> operator first version / eCTD submission -> <i>new</i> operator if changes from previous version -> <i>replace</i> <p>leave section empty if no changes and state in the PSUR-Form "Comment Field" that there are no changes</p> |
| 1.3.4 Information for Professionals other Countries (EU SmPC) | <ul style="list-style-type: none"> operator first version / eCTD submission -> <i>new</i> operator if changes from previous version -> <i>replace</i> <p>leave section empty if no changes and state in the PSUR form Comment Field that there are no changes</p> |
| 1.8.2 E2E/RMP Update | <ul style="list-style-type: none"> operator if changes from previous version -> <i>replace</i> operator also for attachments -> <i>new or replace</i> <p>main document should be listed first if possible leave section empty if no relevant changes</p> |
| 5.3.6 PSUR | operator -> <i>new</i> |

8.2 DMF/ASMF and PMF in eCTD format

8.2.1 DMF/ASMF

The following requirements have to be considered for electronic submission of DMFs/ASMFs to Swissmedic:

- The eCTD DMF dossier is a stand-alone dossier and is independent of the marketing authorisation eCTD dossier. Therefore, the DMF (DMF Holder, substance name) and the Drug Product (Authorisation Holder, tradename) consist of two individual eCTD life cycles.
- It is possible to submit the marketing authorisation application as eCTD and the DMF/ASMF dossier as a paper dossier and vice versa.
- The DMF/ASMF can be a hybrid submission, which means that the restricted part is submitted in paper whereas the open part is submitted in eCTD format as part of Module 3.

Regarding the envelope of a DMF submission the following information is needed (please see also appendix 2 of the Swiss Module 1 Specification):

- Swissmedic DMF number (if known)
- DMF Holder
- Galenic form name is *common*
- MAN is *n/a*
- Submission description: the corresponding version of the DMF should be described in the element, e.g.: AP & RP Version 3.00 / description.

For Module 1 the following has to be considered:

- In Module 1 the country code should be used as described in the Swiss Module 1 Specification
- The Letter of Access must be included in both the life cycle of the DMF/ASMF and the life cycle of the Drug Product (m 1.2.3.1). The signed Letter of Access must be provided electronically and in paper version by the DMF Holder.
- The Letter of Access should always clearly refer to the corresponding version of the DMF/ASMF.
- Swissmedic's form for DMFs/ASMFs has 2 parts: One filed by the applicant (Form Part A) and one filed by the DMF Holder (copy of Form Part A and the original Form Part B). This form must also be included in both life cycles (m 1.2.2 Annexes – Forms). The respective signed parts have to be filed in paper by both partners (see publication Swissmedic Journal from February 2010).

For Modules 2 and 3 the following has to be considered:

- The documents should have *ap* (corresponds to applicant part or open part) or *rp* (correspond to restricted part) as **suffix**.
- The open and the restricted part need to be submitted directly (and independently) by the DMF holder. The MAH may omit the submission of the DMF's open part. However this must be stated in the cover letter and a reference to the DMF must be given in module 3.2.S.1 of the product dossier. The MAH must provide sections 3.2.S.4.1, 3.2.S.4.4 and all parts of module 3.2.S which are different from the DMF's open part in eCTD format in the product dossier. Swissmedic prefers that the MAH submits the DMF open part integrated into the product dossier as scanned paper or PDF.

8.2.2 PMF

The scope of the documentation to be submitted for a PMF in eCTD format is the same as for a paper submission. A ToC is not required for an eCTD submission.

PMFs have to be submitted separately from the affected medicinal product as an independent life cycle beginning with sequence 0000. Swissmedic recommends beginning by submitting a baseline for Modules 2.3 and 3 (please refer to chapter 7.7).

The EU Module 1, however, should not be included.

The annual update can be submitted at the same time as the baseline, but as a separate sequence.

9 Test eCTDs

In order to prevent technical errors in eCTD applications, Swissmedic encourages the submission of test eCTDs for applicants with no or limited eCTD experience. The test submission process at Swissmedic is an informal process, intended to give pragmatic assistance to the applicant and to avoid a technical reject of live submissions.

In case of applications with prior notification and fast track applications, Swissmedic strongly recommends the submission of a test eCTD for applicants which have no or limited experience in eCTD publishing. This will help preventing technical errors and ensure compliance with deadlines.

A test eCTD can be provided at any time up to 3 weeks prior to the filing date. It is recommended to do so as early as possible. Swissmedic does not guarantee that a test submission is being processed if submitted later than 3 weeks prior the submission filing date.

The test eCTD should be as representative as possible, comparable with the final eCTD submission, particularly in terms of structure, envelope and metadata used. The individual files of the test submission will not be reviewed; therefore dummy files may be used.

The CD containing the test submission should be labelled appropriately in order to ensure easy identification of the test submission and its purpose. Here, the applicant name, invented name if known and *TEST eCTD* is sufficient.

The eCTD should be accompanied by a cover letter explaining the purpose of the test submission and indicate applicant contact details for feedback. The cover letter should also state the expected filing date for the actual submission.

The test eCTD will only be validated for technical issues and is not subject to a content validation.

A content validation (presentation in general, the accessibility of the documents, the correct use of structure and metadata and the functionality of hyperlinks) will be part of the tests. However, particular aspects of the eCTD, if highlighted by the applicant, may also be checked.

Swissmedic will reply to the applicant within 2 weeks of receipt of the test eCTD. The applicant will be provided with a copy of the technical validation report and any particular issues will be highlighted. The applicant will be advised to liaise with the responsible case manager if further business issues need to be clarified. The media containing the test submission will be discarded after testing.

Note that test eCTDs are not accepted as marketing authorisation applications or variations even if technical validation has been successful.

It is not possible to submitted test eCTDs via the Swissmedic eGov portal. For more information on the portal, please refer to the Information sheet *Swissmedic eGov Portal – Standard functions*.

10 Appendices

10.1 Appendix 1: eCTD Reference Documents

Swissmedic

Guidance for Industry on Providing Regulatory Information in eCTD Format (this document)

Swiss Module 1 Specification for eCTD

Swiss eCTD Validation Criteria

Questions and Answers to Swissmedic eCTD implementation

ICH

ICH: <https://www.ich.org>

ICH electronic Common Technical Document - eCTD v3.2.2: <https://ich.org/page/ich-electronic-common-technical-document-ectd-v322-specification-and-related-files>

European Medicines Agency, EMA

Standards for electronic submissions: <http://esubmission.ema.europa.eu>

10.2 Appendix 2: List of documents requested additionally in paper format

Please refer to the formal requirements on Swissmedic's website for more information:

https://www.swissmedic.ch/swissmedic/en/home/services/submissions/formale_anforderungen.html