Questions & Answers on Swissmedic eCTD Implementation

Authors:	Lead: Christiane Hofstetter, Swissmedic Madeleine Meusburger, Swissmedic Janine Weix, Swissmedic Ralph Maier, Swissmedic Céline Jurt Kuster, Swissmedic Urs Niggli, Swissmedic SGCI review team: Dorothée Alfonso, Sanofi-Aventis Eric Vinter, Sanofi-Aventis Jürg Häusler, BMS Anja Gödl, Pfizer Sergio Mantelli, Vifor Pharma Marcel Burger, Novartis
Responsible:	Submissions Team, Swissmedic
Version / Date:	1.8 / 01.11.2013

Document Control

Change Record

Version	Date	Comments	Author(s)
1.0	30.10.2009	1st valid version, published on Swissmedic website	SIMES Working Group
1.1	21.05.2010	Version published on Swissmedic website	SIMES Working Group
1.2	22.10.2010	Version published on Swissmedic website	Superuser eCTD
1.3	29.11.2010	Version published on Swissmedic website	SIMES Working Group
1.4	08.05.2012	Version published on Swissmedic website	Submissions Team
1.5	31.03.2013	Version published on Swissmedic website	Submissions Team
1.6	01.07.2013	Version published on Swissmedic website	Submissions Team
1.7	31.07.2013	Version published on Swissmedic website	Submissions Team
1.8	01.11.2013	Version published on Swissmedic website	Submissions Team

Reviewers

Version	Date	Organisation
1.0	30.10.2009	Review team SGCI, Review team Swissmedic
1.1	21.05.2010	Review team SGCI, Review team Swissmedic
1.2	22.10.2010	Review member SGCI, Superuser eCTD Swissmedic
1.3	29.11.2010	SIMES Step 3 Working Group
1.4	08.05.2012	Review member SGCI, eCTD Coreteam
1.5	31.03.2013	Review member SGCI, eCTD Coreteam
1.6	01.07.2013	Review member SGCI, eCTD Coreteam

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

1.7	31.07.2013	eCTD Coreteam
1.8	16.10.2013	Review member SGCI, eCTD Coreteam

Distribution

Version	Date	Name
1.0	30.10.2009	Official publication on Swissmedic website
1.1	21.05.2010	Official publication on Swissmedic website
1.2	22.10.2010	Official publication on Swissmedic website
1.3	29.11.2010	Official publication on Swissmedic website
1.4	08.05.2012	Official publication on Swissmedic website
1.5	31.03.2013	Official publication on Swissmedic website
1.6	01.06.2013	Official publication on Swissmedic website
1.7	31.07.2013	Official publication on Swissmedic website
1.8	01.11.2013	Official publication on Swissmedic website

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

Table of Contents

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

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 that is submitting information in support of an application.
Applicant's information	Regulatory information submitted by an applicant to seek or to maintain a marketing authorisation that falls within the scope of this guidance document
Application	A collection of documents compiled by a pharmaceutical company or its agent in compliance with Swiss legislation and guidelines in order to seek a marketing authorisation or any amendments thereof. An application may comprise a number of submissions.
Application number	The application number is assigned to the application by Swissmedic. It tracks the application at the agency level. A submission can consist of several application numbers.
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-Sequence	All files and folders in a submission in eCTD format are to be placed under the eCTD-Sequence number folder (equivalent to the term "sequence" used by the EMA)
eCTD-Submission	An eCTD-Submission is an electronic-only submission in the eCTD format that is not supported by paper documents (except some documents in module 1).
Marketing Authorisation Number	The Marketing Authorisation Number is the unique identifier for the medicinal product and the galenic form for the Swiss market. (Swissmedic Number)
Submission	A single set of information and/or documents supplied by the applicant as a part of, or as the complete application. In the context of eCTD, this is equivalent to 'eCTD Sequence'.
Test-eCTD-Submission	A Test-eCTD-Submission is an electronic-only submission by the applicant prior to the official submission. The objective is to test the technical attributes and suitability of the eCTD. A Test-eCTD-Submission may differ from the official submission and can be incomplete.

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

List of Abbreviations

CMC	Chemistry, Manufacturing, and Control Information
CTD	Common Technical Document
DMF	Drug Master File
eCTD	electronic Common Technical Document
EMA	European Medicines Agency
EU	European Union
GMO	Genetically Modified Organisms
ICH	International Conference on Harmonization
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MAN	Marketing Authorisation Number
NeeS	Non-eCTD electronic Submission
PDF	Portable Document Format
PI	Product Information
PMF	Plasma Master File
PSUR	Periodic Safety Update Report
Q&A	Questions and Answers document
SIMES	Project “Solution for the Implementation and Management of Electronic Submissions”
SmPC	Summary of Product Characteristics
STF	Study Tagging Files
Swissmedic	Swiss Agency for Therapeutic Products
ToC	Table of Contents
TPA	Therapeutic Product Act (Federal Law on Medicinal Products and Medical Devices) of December 15, 2000 / SR 812.21 Bundesgesetz vom 15. Dezember 2000 über Arzneimittel und Medizinprodukte (Heilmittelgesetz HMG) in the past known as LTP (Law on Therapeutic Products)
VAM	Ordinance on Medicinal Products of October 17, 2001 / SR 812.212.21(Verordnung über die Arzneimittel)
XML	Extensible Markup Language

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

1 Introduction

This questions and answers document aims to address the commonly-asked questions and to provide guidance on Swissmedic's plans to implement electronic-only submissions with eCTD. The document is a representation of Swissmedic's current view. It is intended to be a 'living' and dynamic document, on which feedback from applicants, other regulators, consultants and vendors impacted by the Swissmedic's plans for eCTD is actively encouraged.

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

2 General Questions

Question 2-1: *What do the expressions eCTD and eSubmission mean?*
(V1, 29.06.09)

Answer 2-1:
(V1, 29.06.09)

An electronic Submission (or eSubmission) is any submission of electronic information sent by an applicant to an agency in support of a marketing authorisation application procedure. It is a simple set of registration files submitted in electronic form. It could be a set of files (Portable Document Format (.pdf), Word files (.doc) or Rich Text Format (.rtf) and picture files like jpeg, or png, etc.) usually submitted in folders according to the current paper CTD guidance or files structured and organised according to the specifications for eCTD.
The *eCTD* as a specific format is an electronic version of the Common Technical Document (CTD). The structure, folder and file names correspond to those of the CTD. As a submission format, however, it contains additional technical components which enable the life cycle of individual files in the application, and the life cycle of the product itself, to be managed.
The CTD was developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as a standard format for regulatory submissions in the USA, Europe and Japan. The specification for the eCTD was developed in parallel with the guideline for the CTD (ICH Topic M4).
An eCTD has the following components:

- Folder structure
- Contents
- XML backbone

In Switzerland eCTD is the only format accepted for electronic submissions and may only be submitted on hard media as CDs or DVDs.

Question 2-2: *What is the difference between eCTD and other electronic submissions?*
(V1, 29.06.09)

Answer 2-2:
(V21, 17.07.09)

An eCTD is the electronic submission of registration files that are organised according to the current version of the ICH eCTD specification (see http://estri.ich.org/eCTD/index.htm) and the current version of the Swiss Module 1 Specification (see http://www.swissmedic.ch). The structure of a Non eCTD electronic Submission (NeeS) is based on the CTD-standard, but is not as strictly defined in terms of structure, metadata and document requirements. The only acceptable specification for full electronic submissions is eCTD. Documentation in NeeS format is possible (and also welcome) as supportive documentation to a paper submission according to Swissmedic's requirements

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

for paper submissions.

Question 2-3: *(V1, 29.06.09)*
Is it possible to submit completely paper-free dossiers after the implementation of eCTD?

Answer 2-3: (V1, 29.06.09)
As long as electronic signatures are not implemented, applicants are asked to provide Swissmedic with the administrative information of module 1 normally in one paper copy (originally signed), in addition to the electronic version. For exceptions please refer to Appendix 3 of the Guidance for Industry on Providing Regulatory Information in eCTD Format. A confirmation that both paper and electronic versions are identical, needs to be provided in the cover letter.

Question 2-4: *(V1, 21.12.2011)*
Is it possible to submit applications online via Gateway?

Answer 2-4: (V2, 21.12.2011)
Currently, online submissions are not possible. Swissmedic plans to implement a Gateway in the future.

3 Questions about the Submission

3.1 Paper Format versus eCTD Format

Question 3-1-1: *(Q3-2, V1, 29.06.09)*
Does Swissmedic still accept paper submissions after the implementation of eCTD?

Answer 3-1-1: (A3-2, V1, 29.06.09)
The filing of submissions in eCTD format is strongly encouraged but remains optional. It is up to the applicant to decide whether a paper or an electronic submission is chosen. Once the eCTD format is chosen for a given product, a switch back to paper submissions is not possible. However, applications that have been submitted in paper before the transition to eCTD must be completed in paper.

Question 3-1-2: *(Q3-6, V1, 29.06.09)*
Does the evaluation of an eCTD submission take less time than the evaluation of a paper submission?

Answer 3-1-2: (A3-6, V1, 29.06.09)
The same timelines apply for both paper and electronic submissions.

Question 3-1-3: *(Q3-12, V1, 29.06.09)*
Why are paper copies of some documents still required?

Answer 3-1-3: (A3-12, V5, new)
Please refer to question 2-3.

Question 3-1-4: *(Q3-22, V1, 29.06.09)*
Should all correspondence with Swissmedic be submitted as part of the eCTD?

Answer 3-1-4: (A3-22, V5, new)
Once an applicant has submitted an application in eCTD format, the format may not be changed back to paper. Exceptions which allow the submission of letters in paper form only, without a new eCTD sequence, are:

- Announcement of the deadline for submitting responses to the List of Questions
- Request to extend a due date (e. g. for responses to LoQs or to preliminary decisions)

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

- For applications which include the variation of the PI, the original or laser prints may also be submitted in paper only.

Regarding inclusion of correspondence documentation into the eCTD please refer to the Guidance for Industry on Providing Regulatory Information in eCTD format, chapter 3.4.

Question 3-1-5: *(Q3-46, V1, 21.09.10)*
How should a collective application be submitted which refers to a paper documented drug product and a drug product in eCTD format?

Answer 3-1-5: (A3-46, V5, new)
The application must be made in eCTD and paper formats according to their previous life cycle. However, Swissmedic recommends the conversion of the paper-based drug product via baseline into eCTD before the collective application is submitted in electronic form only For baseline submissions please refer to the Guidance for Industry on Providing Regulatory Information in eCTD format, chapter 6.

Question 3-1-6: *(Q3-20, V1, 29.06.09)*
When should a shift from paper to electronic submissions be made?

Answer 3-1-6: (A3-20, V2, 23.11.11)
A shift from the paper to the electronic format can be made at any time during the life cycle of the product. Please refer to the Guidance for Industry on Providing Regulatory Information in eCTD Format, chapter 6 and also question 3-1-1.

3.2 Baseline Submission

Question 3-2-1: *(Q3-25, V1, 29.06.09)*
What is a baseline submission?

Answer 3-2-1: (A3-25, V2, 17.07.09)
A baseline submission marks the change from a paper based submission to an eCTD submission. For detailed information about baseline submissions, please refer to Chapter 6 of the Guidance for Industry on Providing Regulatory Information in eCTD Format.

Question 3-2-2: *(Q3-39,* V1, 01.10.09)
In a baseline submission, is it acceptable to exclude information that does not apply anymore (e. g. for old products)?

Answer 3-2-2: (A3-39, V1, 01.10.09)
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).

3.3 Submission Procedure

Question 3-3-1: *(Q3-31,* V1, 01.10.09)
Should Swissmedic be informed in advance about the intention of filing a submission in eCTD format (letter of intent)?

Answer 3-3-1: (A3-31, V5, new)
No preliminary information is necessary.

Question 3-3-2: *(Q3-8, V2, 21.05.10)*
How can successful technical validation be supported?

Answer 3-3-2: (A3-8, V3, 21.05.10)
The use of validation tools ensures the detection of technical errors (please

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

refer to Q5-1 and 5-7). As some of the criteria can only be validated in the life cycle standalone validations are not recommended. For applicants with limited experience in producing eCTDs, Swissmedic recommends the submission of test eCTDs. Test submissions can be provided up to 3 weeks prior to the filing date (please refer to Chapter 9 of the Guidance for Industry on Providing Regulatory Information in eCTD Format).

Question 3-3-3:
(Q3-44, V1, 19.05.10, new)

What is the form Technical Validation and when should it be submitted?

Answer 3-3-3:
(A3-44, V1, 19.05.10)

The form Technical Validation lists the applicant's findings in the technical validation and the respective comments. Swissmedic comments on the findings, validates the submission and communicates the decision whether the submission is accepted or not.
The use of this form should contribute to the quality of the submitted eCTD and streamline the validation process at Swissmedic. The form has to be submitted in one paper copy only.
Please, ensure to use that the latest version of the form available on the Swissmedic's eSubmissions website. The form should be used in official language.

Question 3-3-4:
(Q3-50, V1, 08.11.10)

How should temporary marketing authorisations be handled?

Answer 3-3-4:
(A3-50, V1, 09.11.10)

There are two types of temporary marketing authorisations:

- Temporary marketing authorisations due to product shortage (stock-out situations)
  These refer to market surveillance, require specific documentation and are handled outside of the eCTD.
- Temporary marketing authorisations for new products
  These can be submitted as eCTD.

Question 3-3-5:
(Q3-54, V1, 23.11.11)

How should an application for Orphan Drug Status be submitted in eCTD format?

Answer 3-3-5:
(A3-54, V1, 23.11.11, new)

An Orphan Drug Status Application in eCTD format is accepted as stand-alone submission (sequence number 0000). The new application (ZL101) has to be submitted as a separate eCTD sequence (please refer to Appendix 2 of the Guidance for Industry).The form Application Recognition Orphan Drug Status should be attached to section 1.2.2.23 and the documentation should be attached to either section 1.11 "additional information" or to the corresponding part in module 5, e.g. to module 5.4 Literature References.

Question 3-3-6:
(new)

Is it possible to submit an application for Fast Track Status in eCTD format?

Answer 3-3-6:
(new)

Yes, a Fast Track Status Application in eCTD format is accepted as stand-alone submission. The application should be attached to section 1.2.2.24

Question 3-3-7:
(Q8-7, V1, 25.03.10)

What has to be done in cases of withdrawal or rejection of an application?

Answer 3-3-7:
(A8-7, V1, 25.03.10 and new)

If an application is withdrawn or rejected, a consolidation sequence has to be submitted.
For a consolidation sequence the application type in the envelope is

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

"supplemental info" and the related sequence should match the initial sequence number of the regulatory activity. In the cover letter the specifics of the submission should be explained clearly.
With regard to module 1, only documents with a life cycle should be consolidated. As a rule, rejected / withdrawn information concerning modules 2.3 and 3 should also be consolidated to preserve previously approved content in the current view.
However, if the rejected/ withdrawn application contains information considered as important and therefore should be preserved in the eCTD, please liaise with the responsible Case Manager.

Question 3-3-8:
(Q3-30, V1, 01.10.09)

How should multiple galenic forms be handled in cases where a drug product is available in more than one galenic form?

Answer 3-3-8:
(A3-30, V5, new)

Please refer to the Guidance for Industry, chapter 5.2.2life cycle

Question 3-3-9:
(Q3-45, V1, 21.09.10)

If a form has to be exchanged because of an error in the content, should the new form have the same date as the initial form, or should the date of the resubmission be chosen?

Answer 3-3-9:
(A3-45, V1, 21.09.10)

The dates of letters and forms should whenever possible, be in line with the submission date. Small deviations are however permitted. The form should therefore have the new date.

3.4 Content of the Submission

Question 3-4-1:
(Q3-24, V2, 30.03.10)

How should the form Pharmaceutical Information for Parenteral Preparations be referenced in the paper version and electronic version respectively?

Answer 3-4-1:
(A3-24, V2, 30.03.10)

The form Pharmaceutical Information for Parenteral Preparations should be referenced as follows:

3. Dauer der Haltbarkeit
[Fachinformation Rubrik 16. Sonstige Hinweise]

Referenz (Beilage oder Dokumentation Teil II bzw. Modul 3):

- Haltbarkeit des Arzneimittels:

• Die rekonstituierte XXXXXXXXX – Lösung ist nicht konserviert. Chemische und physikalische in-use Stabilität wurde für 24 Stunden bei Raumtemperatur (15-25°C) und für 48 Stunden im Kühlschrank (2-8°C) gezeigt. Aus mikrobiologischen Gründen sollte die gebrauchsfertige Zubereitung aber unmittelbar nach Rekonstitution verwendet werden. Nicht verwendete Lösungen sind zu verwerfen.

- 3.2.P.8.1
- 3.2.P.2: RPT-61254 S.25ff
- RPT-58381,
- RPT-59077,
- RPT-60684

The electronic version has to contain hyperlinks to the corresponding location of the information in module 3.

Question 3-4-2:
(Q3-27, V1, 01.10.09)

How should the form Swissmedic Bioequivalence Trial Information Form be referenced?

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

Answer 3-4-2: (A3-27, V1, 01.10.09) Wherever a cross-reference to modules 2-5 is requested, a hyperlink should direct to the corresponding place.

3.5 Structure of the Submission (Files and Folders)

Question 3-5-1: (Q3-15, V1, 29.06.09) *Should German or French titles for folders or file names of module 1 be used?*

Answer 3-5-1: (A3-15, V1, 29.06.09) English titles must be used for the folders and file names.
For the file names see Appendix 1 of Swiss Module 1 Specification for eCTD .
The language of the forms themselves is German or French (or English as an exception, for example the form Manufacturer Information is also available in English).
A translation of the majority of the terms into French and German is provided in Appendix 3 of the Guidance for Industry on Providing Regulatory Information in eCTD Format.

Question 3-5-2: (Q6-10, V1, 23.11.11) *How many characters are allowed for the submission description in the envelope?*

Answer 3-5-2: (A6-10, V1, 23.11.11) A maximum of 180 characters is allowed.

Question 3-5-3 (Q3-36, V1, 01.10.09) *Are ICH eCTD Appendix 4 filenames mandatory?*

Answer 3-5-3: (A3-36, V1, 01.10.09) No, but they are highly recommended.

Question 3-5-4 (Q3-47, V1, 21.09.10) *What are the rules for describing the "leaves"? Can the leaf name be chosen freely?*

Answer 3-5-4: (A3-47, V1, 21.09.10) The leaf name should be as self-explanatory as possible to facilitate the review. One possibility would be to select identical leaf names and file names.

Question 3-5-5 (Q3-18, V1, 29.06.09) *Where should documents be located in the folder structure and XML-backbones when different places are possible?*

Answer 3-5-5: (A3-18, V2, 18.05.10) If a document could be located in different places (e. g., a study report), it should be placed only once in the eCTD folder structure and can be referred to from all relevant locations in the XML-backbone.

Question 3-5-6: (Q3-14, V1, 29.06.09) *Which documents should be placed in the section 1.11 "additional information" addressed in Appendix 2 of the Swiss Module 1 Specification document?*

Answer 3-5-6: (A3-14, V5, new) This section should not be used if a document has a defined place within module 1. The section "additional information" can be used for documents which cannot be assigned to the other sections within module 1. New forms should be added to section 1.2.2.99.
In case of notifications, a copy of the form Variations Requiring Notification containing the preliminary decision of Swissmedic should be placed here (please refer to question 6-6).

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

Question 3-5-7: *(Q3-42, V1, 15.03.10)*

Does the cover letter have a life cycle?

Answer 3-5-7: (A3-42, V5, new)

No, the cover letter has no life cycle. Therefore in every submission the cover letter has the operator “new”. An attachment to the cover letter (e.g. tracking table), however, can have a life cycle with the operator “replace”.

Question 3-5-8: *(Q3-43, V1, 21.05.10)*

How should the information on GMO/non-GMO be structured?

Answer 3-5-8: (A3-43, V1, 21.05.10)

Information about GMO/non-GMO is documented under section 1.6 Environmental Risk Assessment. Only one of the sections, either 1.6.1 (Non-GMO) or 1.6.2 (GMO) should contain the information and no placeholder document should be present in the other section (the submission will be rejected if both sections contain information).
The form Confirmation Substances from GMO should be placed in section 1.2.2.18 (Form Confirmation Substances from GMO, Swiss Module 1 Specification for eCTD v1.2.

Question 3-5-9: *(Q3-16, V1, 29.06.09)*

How should information be provided when the applicant submits the Answers to Questions from EU countries?

Answer 3-5-9: (A3-16, V1, 29.06.09)

The document EU Responses to LoQ is placed under section 1.7.1 of the Swiss module 1. If further information is needed, such as reference documents of the EU Responses to LoQ document, these have to be provided under section 1.11 “additional information”.
It should be stated in the cover letter if modules 2 to 5 of the EU life cycle have been updated according to the answers to questions from EU countries. These data (modules 2-5) only have to be submitted on demand and need not be part of the eCTD.

Question 3-5-10: *(Q3-51, V1, 09.11.10, new)*

Are sections 1.7.1 – 1.7.2 reserved for EMA LoQ and Assessment Reports only or may these sections also be used for other European documents (e. g. national procedures) or non-European documents? What about section 1.7.3?

Answer 3-5-10: (A3-51, V1, 09.11.10, new)

Sections 1.7.1 -1.7.2 are intended for LoQ and Assessment Reports from all European procedures: CP, DCP and MRP. Also the corresponding documents from non-European procedures (e.g. FDA documents) can be placed there.
Section 1.7.3 is intended only for Decisions from all European procedures: CP, DCP and MRP (e.g. a decision from Germany can be placed there). The directory/file structure of the respective nodes will be adapted in the Swiss Module1 Specification for eCTD v 1.2 valid as of July 01st 2013.

Question 3-5-11: *(Q3-26, V1, 09.11.10 Q3-41, V1, 29.10.09)*

The structure of module 1 includes folders „galenic form“ and „common“. How are the documents structured and split between these folders?

Answer 3-5-11: (A3-26, V5, A3-41, V5, new)

Please refer to Guidance for Industry, chapter 5.2.1life cyclelife cyclelife cycle

Question 3-5-12: *(Q3-35,* V1, 01.10.09)

Is there a preference for the XML attribute entry of the galenic form? E. g., EU standard term or a shorter term? How are discrepancies in the EU, e. g. 'prolonged release' vs. 'extended release', handled?

Answer 3-5-12: (A3-35, V1, 01.10.09)

There is no preference.

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

Question 3-5-13: *(Q3-33,* V1, 01.10.09)
Does section 3.2.P.3 require one single file with multiple bookmarks relating to each manufacturing site, or one file per manufacturing site?

Answer 3-5-13: (A3-33, V1, 01.10.09)
There is no preference. The applicant should consider the following:
1) Site-specific differences of the manufacturing process
2) The ease of maintaining this information during the life cycle of the product (e. g. deletion or replacement of sites).

Question 3-5-14: *(Q3-34,* V1, 01.10.09)
EU eCTD CMC guidance offers a range of options for CMC XML attributes - are some preferred over others? Is it accepted that section 3.2 attributes are free-text fields that can be used as best decided by the applicant?

Answer 3-5-14: (A3-34, V1, 01.10.09)
There are no preferred approaches, there is no guidance from any region. Attributes are free-text fields that can be used as best decided by the applicant.

3.6 PI and Working Documents

Question 3-6-1: *(Q3-23, V2, 30.03.10)*
How should the paper version and the electronic version of the product information be referenced?

Answer 3-6-1: (A3-23, V4, 30.03.10)
The product information has to be referenced according to Swissmedic's current practice. For further information please refer to the actual publications in the Swissmedic Journal (e. g. Swissmedic Journal 03/2009; p. 234) as well as the ordinance on the requirements concerning the approval of medicinal products (SR 812.212.22).
The electronic version of the product information should contain hyperlinks to the corresponding location in modules 2 to 5.

Question 3-6-2: *(Q3-52, V1, 23.11.11)*
How should changes to the product information (PI) or packaging information be submitted?

Answer 3-6-2: (A3-52, V1, 23.11.11)
Please refer to Guidance for Industry, chapter 5.4 for further information.

Question 3-6-3: *(Q3-11, V1, 29.06.09)*
What requirements are applicable for mock-ups?

Answer 3-6-3: (A3-11, V5, 01.01.13)
The text for the packaging material can be provided as a manuscript or mock-up. The format of the files should be PDF 1.4, 1.5, 1.6 or PDF 1.7. If a higher resolution is necessary for the mock-ups, JPEG, GIF, PNG or SVG should be used on a case-by-case basis.

4 Questions about eCTD Specifications

Question 4-1: *(Q5-1, V1, 29.06.09)*
Which are the valid eCTD specifications?

Answer 4-1: (A5-1, V2, 09.11.10)
When a new version of the Swiss Module 1 Specification becomes effective, it will be made public on Swissmedic's eSubmission website and become the current version (see also question 4-2).
Modules 2 to 5 need to be organised according to the current version of the

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

ICH eCTD specification (estri.ich.org/eCTD).

Question 4-2: *(V1, 29.06.09)*
Are there differences between EMA and Swissmedic eCTD applications?

Answer 4-2: (V2, 17.07.09)
The Swiss Module 1 Specification follows closely the EU Module 1 Specification. However, due to the regional requirements, there are differences (For further information see the Swiss Module 1 Specification for eCTD).
Also the technical validation criteria of eCTD submissions in Switzerland follow closely the EU criteria (see Swiss eCTD Validation Criteria).

Question 4-3: *(new)*
How should applicants handle the inconsistency regarding module 1.2.2.19 "Form DMF for first authorisation and variations" in the DTD and the style sheet of version 1.2 of the Swiss Module 1 Specification?

Answer 4-3: (new)
The section name in the style sheet "m1-2-2-19-form-dmf-for-first-**application**-and-variations" is different from the section name in the DTD "m1-2-2-19-form-dmf-for-first-**authorisation**-and-variations". Due to this element name mismatch the section will not be displayed if the ch-regional.xml is opened in Internet Explorer. However, if the regional.xml is opened in XML pad/word pad the section is displayed correctly.
Swissmedic will correct the current style sheet with the next regular update of the Module 1 Specification.

5 Technical Conditions and Validation Issues

Question 5-1: *(Q6-1, V1, 29.06.09)*
Which hard- and software specifications are required to submit an eCTD application?

Answer 5-1: (A6-1, V1, 29.06.09)
The use of a publishing tool to create the eCTD is recommended. Furthermore the applicants should ensure that their tool vendor supports the Swiss Module 1 Specification for eCTD and the Swiss eCTD Validation Criteria.
Swissmedic allows applications in eCTD format provided on hard media (CD-ROM, CD-R, DVD-R).
Applicants are required to validate their application for compliance with the Swiss eCTD Validation Criteria before submission.

Question 5-2: *(Q6-2, V1, 29.06.09)*
Which file formats are accepted or are required to be submitted for an eCTD application?

Answer 5-2: (A6-2,V3, 21.02.12)
Generally PDF v1.4, v1.5, v1.6 or PDF v1.7 should be provided within the eCTD. (Please refer to chapter 5 of the Swiss Module 1 Specification for eCTD and chapter 4.3 of the Guidance for Industry on Providing Regulatory Information in eCTD Format.) Documents in PDF/A format are also accepted. Documents in PDF/X format are only accepted if they don't interfere with the review functionality since this format does not support hyperlinks or bookmarks. However, if hyperlinks or bookmarks are not functional to a critical extent the submission may be rejected in content validation.

Question 5-3: *(Q6-6, V1, 27.10.09)*
Are there any restrictions for the applicant in using a publishing tool?

Answer 5-3: (A6-6, V1, 27.10.09)
No, the applicant can use any eCTD publishing tool as long as the Swiss Module 1 Specification for eCTD and the Swiss eCTD Validation Criteria are

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

supported.

Question 5-4:
(Q6-9, V1, 15.03.10)

How should the 16BP2 and 16BP3 validation criteria of the Swiss Validation Criteria (broken links in a PDF document) be interpreted?

Answer 5-4:
(A6-9, V1, 15.03.10)

The 16BP2 and 16BP3 validation criteria of the Swiss validation criteria read: "hyperlinks and bookmarks within documents, or between documents within the same sequence, have a valid target." and "hyperlinks and bookmarks to destinations in a different sequence in the same eCTD have a valid target." Broken links are technically classified as best practice criteria (BP). Therefore they do not automatically lead to a refusal of a submission. Even though a submission is technically accepted, content validation may not be successful if hyperlinks or bookmarks are not functional to a critical extent, and the submission may be rejected due to formal reasons. As a general conclusion, broken links in a summary document (e. g. preclinical overview) is more critical than broken links in a study appendix which is due to different frequency these hyperlinks are used. Weblinks should not be used in a submission.

Question 5-5:
(Q3-48, V1, 05.11.10)

Are application types (according to the Swiss Module 1 Specification for eCTD, Appendix 2) multiple or unique?

Answer 5-5:
(A3-48, V1, 05.11.10)

The envelope element "application" of the Swiss Module 1 Specification for eCTD v1.2 is "repeatable" to allow for applications with more than one application type (e. g. na-nde with -ndo).

Question 5-6:
(Q6-11, V1, 21.12.11)

What should be done if the size of the entire submission is 10 GB or more?

Answer 5-6:
(A6-11, V5, new)

Please, verify whether file compression on the level of individual documents will lead to a submission of a size below 10 GB or use a blue-ray dvd.

Question 5-7:
(Q7-1, V1, 29.06.09)

How can the applicant verify if the submission in eCTD format complies with the valid specifications?

Answer 5-7:
(A7-1, V1, 29.06.09)

Please refer to the Swiss Validation Criteria on the Swissmedic eSubmission website. In addition, Swissmedic provides links to free-of-charge validation tools. Applicants are required to validate their submissions in advance.

Question 5-8:
(Q7-2, V1, 29.06.09)

How will validation errors be communicated by Swissmedic?

Answer 5-8:
(A7-2, V1, 29.06.09)

Swissmedic validates eCTD submissions according to the Swiss eCTD Validation Criteria. The form Technical Validation will be sent to the applicant, stating whether the submission has been accepted or needs to be corrected.

Question 5-9:
(Q7-4, V2, 20.03.10)

Who is the contact person in Swissmedic for technical problems?

Answer 5-9:
(A7-4, V2, 20.03.10)

Please contact Swissmedic via the eSubmissions email address eSubmission@swissmedic.ch.

Question 5-10:

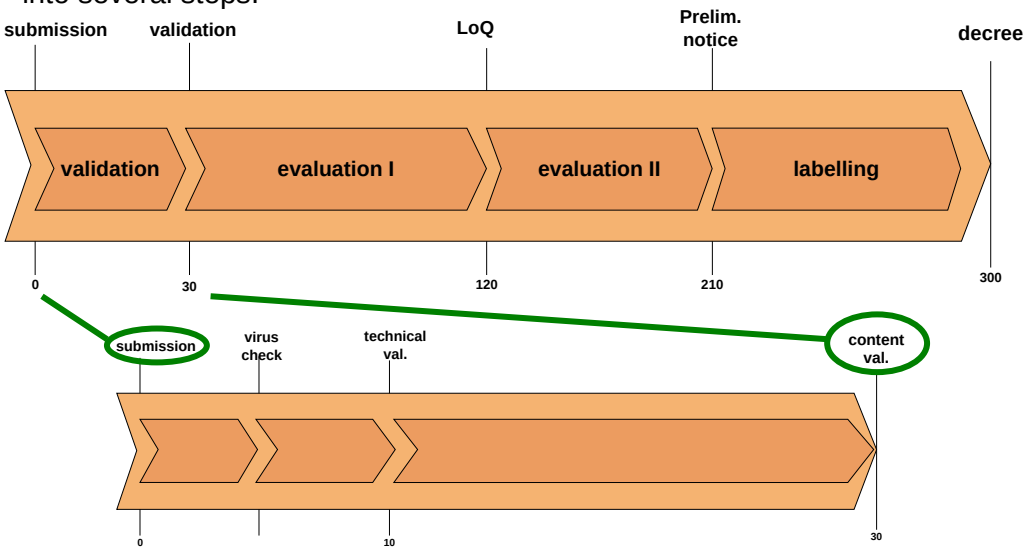
How is the validation process structured?

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

(Q7-5, V1, 20.03.10)

Answer 5-10:
(A7-5, V1, 20.03.10)

The validation process at Swissmedic is shown below. For eCTD it is divided into several steps.



The validation process of electronic submissions contains the three steps (1) virus check, (2) technical validation, and (3) content validation whereas the validation process of paper submissions consists of the content validation only. Despite this difference, both electronic and paper submissions meet the same timelines (please refer to ZL000_00_004d_RL_Fristen_Zulassungsgesuche, guideline „deadlines for applications“).
After Swissmedic has received an eCTD sequence it is first tested for viruses. In case a virus is detected, the applicant is granted 10 days to re-submit the eCTD sequence free of viruses. The second step is the technical validation. Maximum 10 days after the submission, the applicant receives the form Technical Validation with a statement whether the sequence has been accepted or not. If the submission is rejected, the applicant has to resubmit the eCTD sequence (same eCTD number) within 30 days. The next step is the content validation which is concluded at day 30 after submission the latest with either a formal approval of the submission or a request for resolving issues detected during the content validation.
According to paragraph 3 number 3 VAM the applicant is granted a 120 day deadline to fix formal issues of the application. If the applicant uses time to resolve virus or technical validation issues, this time is subtracted from this overall 120 day timeframe.

Question 5-11:
(Q7-6,V1, 23.11.11)

Will Swissmedic accept file references with destinations outside the current sequence i. e. file reuse (xlink:href)?

Answer 5-11:
(A7-6, V5, new)

Yes, Swissmedic will accept file references with destinations outside the current sequence. Please be aware of life cycle errors which may occur when using operations (or operators) on these files. These errors must be corrected and could lead to a reject of the sequence.

Question 5-12:
(new)

How should applicants handle the extension of the previously 4-6-digit application ID to a 9-digit number?

Answer 5-12:
(new)

With the changeover to SAP, the previously 6-digit application ID has been extended to become a 9-digit number. In the technical validation in accordance with version 1.1 of the "Swiss eCTD validation criteria", the length of the

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

application ID is checked, which – when using the longer number – leads to a B10 error. Since version 1.1 of the "Swiss eCTD validation criteria" will only be valid until December 2013, Swissmedic will no longer adjust the validators but will ignore the B10 errors and not issue objections to them.
Version 1.2 of the "Swiss eCTD validation criteria", valid as of 1 July 2013, does not check the length of the application ID, so the 9-digit application ID does not conflict with any validation criteria.

In the case of 9-digit application IDs, please proceed as follows:

- If your eCTD publishing software permits the entry of a number that is over 6 digits long, please enter the complete number in the envelope, and ignore the corresponding B10 error.
- If your eCTD publishing software does not permit the entry of a number that is over 6 digits long, please enter the last 6 digits of the 9-digit application ID in the envelope.

Please ensure that you always mention the full application ID in both the cover letter and in the corresponding forms.

This transitional rule will remain valid until end December 2013. As of 1 January 2014, Swissmedic will only accept the complete 9-digit application ID in the envelope.

6 Questions about the Submission of Variations, PMFs and VAMFs in eCTD Format

Question 6-1:
(Q8-1, V1, 03.03.10)

How do variations have to be submitted which need to be authorised or notified?

Answer 6-1:
(A8-1, V1, 12.11.10)

For both types of variations a cover letter should be submitted.
The form Variations Requiring Authorisation or the form Variations Requiring Notification should be submitted, in addition to the necessary documentation in the eCTD format (see Swiss Module 1 Specification for eCTD).
The MAN (if known) should be indicated in the envelope.
For details about the life cycle management please refer to the Guidance for Industry on Providing Regulatory Information in eCTD Format (Chapter 5).
For details about conditions and documentation please refer to case-related documents, such as

- ZL300_00_001d_MB Merkblatt Einreichung von Änderungen;
- ZL302_00_001d_FO Genehmigungspflichtige_Änderung_Qualität (Quality variation requiring approval);
- ZL301_00_001d_VV Verwaltungsverordnung Anleitung meldepflichtige Änderung

Question 6-2:
(Q8-9, V1, 21.09.10)

Where should the variations requiring notification or applications requiring authorisation be described?

Answer 6-2:
(A8-9, V1, 21.09.10)

The variations should be described in detail in the respective forms. However a cover letter must be part of the submission.

Question 6-3:
(Q8-2, V5, new)

How should a variation to several MANs be submitted (German:

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

Sammelgesuch; French: demande groupée)?

Answer 6-3:
(A8-2, V5, new)

The collective application concerns more than one life cycle:

- One sequence per eCTD life cycle has to be submitted including the updated documentation (module 2-5)
- Envelope: all MAN concerned within one life cycle should be indicated
- Cover letter: The same cover letter including all MAN concerned needs to be placed in each sequence. life cycleThe applicant should confirm in the cover letter that the wording of the changes within the documentation is identical for all life cycleMAN concerned
- The same form “Variations Requiring Notification” or “Variations Requiring Authorisation” including all MAN needs to be placed in each sequence
- In addition, a separate form “Application for Authorisation/Variation” for each MAN needs to be submitted for variations requiring authorisation

The collective application concerns several or all MAN within the same life cycle:

- One sequence has to be submitted including the updated documentation (module 2-5)
- In the envelope all MAN concerned should be indicated
- The same cover letter including all MAN concerned needs to be placed in the respective galenic form folder if the collective application concerns only several MAN within the same life cycle and in the common folder if all MAN of the life cycle are affected. The applicant should confirm in the cover letter that the wording of the changes within the documentation is identical for all MAN concerned
- The same form “Variations Requiring Notification” or “Variations Requiring Authorisation” including all MAN needs to be placed in the respective galenic form folder if the collective application concerns only several MAN within the same life cycle and in the common folder if all MAN of the life cycle are affected
- In addition, a separate form “Application for Authorisation/Variation” for each MAN needs to be submitted for variations requiring authorisation and placed in the respective galenic form folder

Question 6-4:
(Q8-4, V5, new)

How should several variations to one or more MANs be submitted (German: Mehrfachgesuch / French: demande multiple)?

Answer 6-4:
(A8-4, V5, new)

Variations requiring authorisation (ZL 302, ZL 303)

- One sequence per eCTD life cycle has to be submitted
- All variations to one or more MAN can be summarized on the same form (if several life cycles are affected, the same form needs to be placed in each sequence; in case more than one MAN within one life cycle is affected, the same form needs to be placed in the respective galenic form folder or in the common folder if all MAN of the life cycle are concerned)
- a separate form “Application for Authorisation/Variation” for each MAN has to be submitted

Variations requiring notification (ZL 301)

- One sequence per eCTD life cycle has to be submitted

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

- One form per notification is required, but within the same life cycle all notifications can be sent in one sequence (in case more than one MAN within one life cycle is affected, the respective form needs to be placed in the respective galenic form folder or in the common folder if all MAN of the life cycle are concerned)

Question 6-5:
(Q8-3, V5, new)

What about the submission of a sequential variation or a sequential variation requiring notification (German: Folgeänderung, Folgemeldung; French: modification consècutive, annonce consécutive)?

Answer 6-5:
(A8-3, V1, new)

The submission of a sequential notification or variation is not possible as it is not a valid application type. Sequential variations are always part of the variation / notification they depend on and have to be included in the same application form as the respective variation / notification.

Question 6-6:
(new)

What has to be done if a variation requiring notification is formally/ technically objected or is rejected?

Answer 6-6:
(new)

If a variation requiring notification is formally or technically objected, the form "variations requiring notification" with the preliminary decision must be included (under 1.11 "additional information") in the re-submission.
In case of a reject please refer to question 3-3-7 for information about the required consolidation sequence.

Question 6-7:
(Q8-8,V1, 21.09.10)

How should a PMF be submitted?

Answer 6-7:
(A8-8,V1, 12.11.10, new)

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. The following forms and documents are required:

- Form Application for Marketing Authorisation and Variation
- Form Variations Requiring Authorisation (Quality)
- EMA Certificate for Plasma Master File (PMF), if available (to be placed in 1.2.3.4)
- Evaluation Report from the EMA, if available (to be placed in 1.7.2)
- Documentation (modules 2.3 und 3)
- An expert statement evaluating safety and quality of drug product to be placed in the documentation for the drug product module 2.3.
- A signed declaration that the PMF and certificate can be applied to the drug product.

The start of the eCTD life cycle begins with sequence 0000. We strongly recommend to begin by submitting a baseline. The various options for a baseline are described in Guidance for Industry on Providing Regulatory Information in eCTD Format, chapter 6. For the PMF, we recommend a baseline for module 3 and module 2.3. The EU module 1 should not, however, be included. The annual update can be submitted at the same time as the baseline, but as a separate sequence.

Question 6-8:
(Q8-10,V1, 30.09.10)

How should an annual update of the influenza vaccine be submitted?

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12

Answer 6-8:
(A8-10,V1, 30.09.10, new)

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)

Additional / other variations (i.e. not relating to the annual update) have to be submitted separately but also in eCTD format ("once eCTD always eCTD").

For an efficient assessment of the application, the applicant is requested to inform the responsible Case Manager of the planned dates, by when the different parts of the documentation will be submitted. The title of each cover letter should refer to „annual update".

The baseline should contain the following documents:
module 1
please refer to Guidance for Industry on Providing Regulatory Information in eCTD format, chapter 6
module 3

- must include the data of the latest approved annual update
- module 2.3 is not required

Question 6-9:
(Q3-49, V1, 08.11.10)

How is the notification procedure for sample packaging handled?

Answer 6-9:
(A3-49, V2, 21.02.12)

The notification procedure is mandatory for every packaging size intended for marketing purposes which is not an approved packaging size. For the notification procedure, the form notification sample packages ("Formular Zulassung Musterpackungen im Meldeverfahren") should be used and placed under section 1.2.2.21. If sample packages have already been submitted as part of the first authorisation procedure, it is not necessary to submit any additional notification for sample packages.

[End of Document]

Swissmedic · Hallerstrasse 7 · CH-3000 Bern 9 · www.swissmedic.ch · Tel. +41 31 322 02 11 · Fax +41 31 322 02 12