Instructions for submitting changes and for reporting during the course of a clinical trial

Content

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1 In general

These instructions concern changes and reporting related exclusively to **clinical trials of Category B and C.**

Points to consider:

Incomplete dossiers will not be processed but returned. Please only submit **documents that are complete and ready for processing**.

All documents (including submission forms) have to be submitted where requested (as explained below) in **track change** mode or with visible changes, otherwise as clean version. Submitted documents should be non-editable (e.g. PDF format, preferred).

For **information on the submission process** please see the following web- page:
Home > Human medicines > Clinical trials > Submission of applications (Link)

If not specified otherwise, all documents must be submitted as long as they **cover the time period until study end in Switzerland** is reached. (LPLV in Switzerland)

An **updated CTA-form** needs to be submitted when additional IMPs are introduced with an Amendment.

2 Folder structure for submissions

Swissmedic provides you with a **pre-defined explorer folder structure** (**eDok_KLV)** to harmonize the incoming submissions. This folder structure can be downloaded from our web page. Please see:
Home > Human medicines > Clinical trials > Submission of applications (Link)

>Follow the link: **Applications for clinical trials for medicinal products** where you find

- **eDok_KLV folder structure** as a zip file for down load
- **Quick guide to submitting with the eDok_KLV folder structure** with instructions on the documents each folder can be filled with.
- Once downloaded the **folders you do not need** for your submission **have to be deleted.**

The Folder Structure is to be followed also for Changes and reporting to a running clinical trial and may lead to a formal deficiency letter if not applied.

3 Submission form

The following **original signed forms** must be used:

A. BW101_10_019e_FO Confirmation electronic submission

B. FO submission form (PDF)→ see instructions on submission topics below
Important:
Once a **form type** is selected and **the form type** is to be changed the **restart button** must be pressed to clear the form.

C. CIOMS form (international standard)

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The forms can be downloaded here:

Home > Human medicines > Clinical trials > Submission of applications (Link)

3.1 Changes to a running trial according to chapters 3.1 to 3.6 of this document

Form FO submission form (PDF)
open the form, fill in all fields and select the following:

- **Submission Type:** SUBMISSION to an AUTHORISED Clinical Trial
- **SELECT FORM TYPE:** CHANGE
- fill in all fields
- list all submitted documents in **section 8**

3.2 Reporting to a running trial according to chapters 4.8 - 4.11 of this

Form FO submission form (PDF)
open the form, fill in all fields and select the following:

- **Submission Type:** SUBMISSION to an AUTHORISED Clinical Trial
- **SELECT FORM TYPE:** REPORTING
- fill in all fields
- list all submitted documents in **section 8.**

3.3 Answers to conditions made by Swissmedic

Form FO submission form (PDF)
open the form, fill in all fields and select the following:

- **Submission Type:** ANSWER to CONDITION
- fill in all fields
- list all submitted ANSWER-DOCUMENTS* in **section 8**
  *ideally you submit the condition letter from Swissmedic as well.

3.4 Answers to formal deficiency made by Swissmedic

Form FO submission form (PDF)
open the form, fill in all fields and select the following:

- **Submission Type:** ANSWER to FORMAL DEFICIENCY
- fill in all fields
- list all submitted ANSWER-DOCUMENTS* in section 8
  *in case a wrong form was initially submitted the corrected form has to be listed and submitted.

3.5 Answers to further information request made by Swissmedic

Form FO submission form (PDF)
open the form, fill in all fields and select the following:

- **Submission Type:** ANSWER to FURTHER INFORMATION REQUEST
- fill in all fields
- list all submitted ANSWER-DOCUMENTS* in **section 8**
  *in case a wrong form was initially submitted the corrected form has to be listed and

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submitted.

3.6 Administrative Changes (including change of sponsorship and Swiss representative)

Form FO submission form(PDF)
open the form, fill in all fields and select the following:

- **Submission Type:** SUBMISSION to an AUTHORISED Clinical Trial
- **SELECT FORM TYPE:** CHANGE
- fill in all fields
- Select topics: **Change of Sponsorship** or **Other Administrative Change**
- list all submitted documents in **section 8**

3.7 SUSARs

Form CIOMS form (international standard)
Form FO submission form (PDF)
open the form, fill in all fields and select the following:

- **Submission Type:** SUBMISSION to an AUTHORISED Clinical Trial
- **SELECT FORM TYPE:** SUSAR
- fill in all fields
- list all submitted documents in section 8

IMPORTANT information on the above-listed topics 3.1 -3.7:

- A document related to several clinical trials can be submitted using a single submission form. **However, a separate form must be used for each sponsor representative**. The clinical trial(s) must be clearly identified with their Swissmedic reference numbers.
- Please **do not send any cover letter**.
  If this cannot be avoided due to the necessity of providing relevant information which cannot be included in the submission form, please list this letter as a document in the form under 01CL.
- Always give a **short and precise introduction** on the content of the submitted change of each document listed. This introduction has to be given in the field **Reason for Amendment / Submission** or further specific fields to give more information**.**
- **All documents** related to the notified changes or reporting have to be **listed in section 8** of the FO submission form (PDF). If several documents are submitted for the same **Topic Folder** (i.e. Folder 04) they have to be listed on the same folder. Add and remove documents by using the buttons below the folder heading.
- The sponsor is sole responsible for the **correct designation of the documents** on the form and thus for a clear identification of the documents that have been submitted to Swissmedic for acknowledgement or approval of changes. Incorrect identification of the documents may lead to findings during an inspection.

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4 Changes during the conduct of a clinical trial (amendments) (Art. 34 ClinO)

All changes in the documents as listed in ClinO Annex 4, 1.2 – 1.7 and 2.2. – 2.7 have to be submitted to Swissmedic.

Significant changes must be submitted to Swissmedic together with a rationale from the Sponsor (to be entered in the FO Submission form in the field **Reason for Amendment / Submission** or further specific fields to give more information. The amendments cannot be implemented before the approvals of both Swissmedic and the Ethics Committee have been obtained.

Exception: urgent safety measures may be implemented before Swissmedic approval.

The definition of significant changes that have to be submitted to Swissmedic is given in Art. 34 ClinO and below.

Other changes shall be sent to Swissmedic as soon as possible (Art. 34, para 5 ClinO).

4.1 Protocol Amendments related to the use and/or safety of the IMP (Section 4 of the CTA dossier)

All protocol amendments must be submitted to Swissmedic. The changes related to the use and/or safety of the IMP or any other significant modification according to art. 34 paragraph 3 ClinO must be approved by Swissmedic prior to implementation (exception: urgent safety measures). For all other changes (art. 34 paragraph 5 ClinO) Swissmedic will send an acknowledgement of receipt.

Protocol modifications must be documented in a summary of changes and the updated protocol version submitted in a **track change** (ideally a color print) mode or with visible changes. The updated clinical trial protocol must be dated and signed at least by the sponsor.

4.2 Changes to the pharmaceutical quality documentation (PQD) of the IMP (Section 7 of the CTA dossier)

Changes to the PQD or the IMPD shall only be submitted if related to the clinical trial.

All changes to the PQD or IMPD related to the clinical trial have to be submitted to Swissmedic.

A guidance on the substantial changes that need to be submitted to Swissmedic can be found in the European guideline “Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017 chapter 9).

Guidance for the submission of a change to the PQD:
Important: Submission of at least one document showing the modifications with the old text struck through and the new text bold or underlined and bold is mandatory. It can be either the PQD/IMPD or the tabular overview. For more details see below.

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1. Tabular overview of changes

A tabular overview **including all modifications**, with indication if substantial or not, has to be provided. This tabular overview of changes can be a separate document or it can be integrated in the amended document (PQD or IMPD). If this table is integrated in the amended document, it must be printed separately for each trial involved.

Example:

Amendment name, version, date			**Substantial?**	
Previous Document number	**New** Document number	**Reason** for change	**yes**	**no**
Chapter xy Previous information *Full text*	Chapter xy new information *Full text with changes in* ***- Bold*** *and* ~~*strike through*~~ *Or* *-track change mode*	Give rationale		X

2. CD-Rom:

- Form FO submission form (PDF)
- Amended documents in Track Change Version
- Amended documents Clean Version
- Tabular overview of changes as depicted above if not already contained in the amended document itself.

3. Paper Versions.

- Paper versions are not mandatory to be submitted.
  In case no paper versions are submitted the following form has to be added:
- BW101_10_019e_FO Confirmation electronic submission

4.3 Quality defects of IMPs

Quality defects of IMPs have to be submitted to Marketing Surveillance (MS) of Swissmedic (www.swissmedic/human medicines/market surveillance/quality defects and batch recalls) and not to the Division Clinical Trials. During the Quality defect assessment you will be informed if changes to the study documentation is requested. Changes to the IMPD due to a quality defect, have then to be submitted to Swissmedic Division Clinical Trials, as well as the "closing correspondence" between MS Swissmedic and the Sponsor. The submission has to be sent with a submission of change form.
Please be aware that OOSs (out of specifications) have to be submitted to MS as a quality defect.

4.4 Changes to Study Medication Labels (Section 8 of the CTA dossier)

Changes of the **IMP-name** have to be submitted to Swissmedic for approval. All other changes to the study label shall be submitted for information only.

4.5 Updated Investigator's Brochure (IB) (Section 5 of the CTA dossier)

The updated IB needs to be submitted **until the final clinical study report is available**. The reference safety information (RSI) in the IB should fulfil the requirements according to the “Q&A

document – Reference Safety Information" dated November 2017 and the RSI cover note dated March 2018 of the Clinical Trial Facilitation Group CTFG (published on the HMA – CTFG website (www.hma.eu)). The changes to the IB as compared to the previously approved version must be documented in a summary of changes **as shown in the model below** and the updated version shall be submitted **in track change** mode or with visible changes.

Moreover, it must be indicated if, and to what extent, the **risk/benefit analysis** of the trial substance has changed. Should any measures have been taken on the basis of the new analysis, these should also be described.

Model: summary of changes

section	Old text	New text	Rational for change
1.0 Change	Original text to be changed in this section.	~~Original~~ New text ~~to be changed~~ in this section with visible changes.	Reason for changes
1.1 New information	Original text	Original text Added text	New information
1.2 Deleted text	Original text to be deleted	~~Deleted text~~	Reason for deletion

4.6 Change of Sponsor / Sponsor Name or Address / other administrative changes (Form Type CHANGE)

Swissmedic's authorisation to perform a clinical trial **cannot** be transferred from a sponsor to another one. **If a new sponsor takes over a clinical trial** that has already been authorised for another sponsor, he must ask Swissmedic for a new authorisation. For this purpose, use the Form Type "**Change**", tick "**change of sponsorship**" and fill in the information requested.

The completed form must be sent to Swissmedic **at least 30 days prior to the date of take-over** of the sponsorship. The submission must include a statement (signed and dated) of the previous sponsor that he gives up the sponsorship of the clinical trial.

Examples for Change of Sponsorship:

- **New Sponsor**: Company 'ABC-Pharma' is the current Sponsor and Company 'DEFMedical' will be the Sponsor in the future.
- **New Country same Sponsor**: Company 'ABC-Pharma' in Germany moves to Italy and will have a new country address.
- **New Sponsor name, same address**: Company 'ABC-Pharma' changes the name to 'ABCD-Pharma-CHEM'.

For other administrative changes, use the Form Type "**Change**", tick "**other administrative change**" and fill in the information requested.

Examples for Other Administrative Change:

- **Change of contact person** of a Company (Sponsor, Swiss representative)
- **Change of email or phone number** of contact person
- **Change of address** of Swiss representative or Sponsor **(**except sponsor changes country)

For a change of sponsor or sponsor name or a change of sponsor address involving a **change of country**, a "Change of Sponsorship" has to be submitted and Swissmedic will issue an authorisation for the new sponsor or sponsor with new name or address, respectively and withdraw the previous authorisation.

Trial documents that have to be modified due to the change of sponsorship / change of sponsor name or address (protocol, labels, etc.) must be sent to Swissmedic according to ClinO annex 4.

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4.7 Change Swiss Representative/ Representative Name or Address / other administrative changes (Form Type CHANGE of Swiss Representative)

If a **new Swiss representative** takes over responsibilities for a sponsor, Swissmedic must be informed.

For this purpose, the Form Type "**Change of Swiss representative**" has to be selected in the FO Submission form under submission to an authorized clinical trial (including date and signature).

The completed form must be sent to Swissmedic **at least 30 days prior to the date of change of the Swiss representative**.

Change **of Swiss representative name or address** has to be submitted under other administrative changes (see above)

4.8 Safety reporting in clinical trials of the categories B and C (Form Type REPORTING)

Urgent safety and protective measures in clinical trials of the categories B and C must be taken immediately, without waiting approval by Swissmedic. They must be **reported within 7 days** to Swissmedic by the Sponsor.

In case an urgent safety measure is triggered by a **Quality Defect** please see the process for Quality Defects in section 4.3 of this document.

Detailed information on safety measures including urgent safety measures, SUSARs or Annual Safety Report can be found on the Swissmedic website under "Safety measures in clinical trials".

4.9 Premature discontinuation / Trial interruption (Form Type REPORTING)

The sponsor must report a premature discontinuation or interruption of a clinical trial to Swissmedic, stating the reasons for the discontinuation or interruption.

The reporting timeline is **15 days** (Art. 38 para. 2 ClinO). If a trial is stopped prematurely for safety-relevant reasons, Swissmedic must be informed within **7 days** (Art. 37 para. 1 ClinO).

A final clinical study report (further details below) must be submitted.

4.10 Beginning and end of the trial (Form Type REPORTING)

The **beginning** of the trial is considered as the "first subject first visit" for study purposes in Switzerland. The sponsor must report the beginning of the clinical trial to Swissmedic within 30 days. No acknowledgement of receipt will be sent.

The **end** of the trial is considered to be the 'last subject last visit' of the last open centre in Switzerland, unless differently defined in the trial protocol. The sponsor must report the end of a clinical trial to Swissmedic.

The timeline for reporting the end of the study is **90 days** (Art. 38 para. 1 ClinO).

A final clinical study report (further details below) must be submitted.

For international trials, Swissmedic accepts the international end date of the trial as the reference date for submitting the final report. Therefore, in order to determine the time limit that will be applied, Swissmedic must also be informed (in addition to the date, on which the trial ends in Switzerland) on the date of international trial end.

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4.11 Final clinical study report (Form Type REPORTING)

A final clinical study report on the whole study must be submitted in line with Art 38 para. 5 of the ClinO within **1 year** of trial end or premature discontinuation.

Swissmedic has not published any guidelines on the formal requirements for the final report; however, the ICH E3 guidelines (Structure and content of clinical study reports) should be followed. The final report should adequately summarize the data collected in the clinical trial.
The complete report without annexes (corresponding to chapters 1-15 of ICH E3) and a synopsis shall be submitted.

For international clinical trials which did not include subjects in Switzerland, no submission of the report or a synopsis is needed.

In the case of international trials that last longer than the participation of the Swiss centres, the final report should be submitted within **1 year of the end of the international trial** (Art. 38 para. 5 ClinO).

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Change history

Version	Valid and binding as of:	Description, comments	Author's initials
11.1	12.05.2023	Alignment to portal submission requirements, Typos and errors cleared, Clarification on format of submitted documents Clarification on submission of 'other administrative changes'	plp
11.0	23.11.2022	Adaptation of eDok_KLV structure, typos and errors cleared	gav
10.0	19.06.2022	Alignment to paper free process, typos and errors cleared	gav
9.0	10.09.2021	Corrections on formal aspects with respect to "New VO form and new format for authorisation applications plus changes/ notifications/ reports regarding clinical trials with medicinal products as of 13 September 2021"	gav
8.0	17.01.2020	Inclusion of information on quality defect reporting (formerly included in the FAQ document), change of FPFV acknowledgement procedures, clarifications, correction of links	hch
7.0	20.12.2018	Updates to submission of PQD changes, clarifications, corrections	hch
6.0	10.09.2018	Replacement of the forms change of sponsorship and change of Swiss representative by the form administrative changes Clarification concerning notification of study start	hch, jaf
5.0	01.06.2018	Inclusion of additional information on requirements for reference safety information and for reporting of study start; clarifications	hch
04	05.05.2017	Clarifications for submission requirements	hch, jaf
03	15.01.2017	New submission requirements with introduction of two new submission forms, clarifications	hch, gav, jaf
02	25.01.2016	New order of chapters for changes and reporting clarifications and corrections	hch
01	26.06.2015	Document belongs to new process (new QM-Ident) Old: BW101_20_001e_AL New: BW101_10_003_AA Clarification concerning submission of some changes / Introduction of the new form Change of Swiss Representative	hch
12	30.04.2015	Inclusion of guidance for the submission of a change to the pharmaceutical quality documentation and to the Investigator's Brochure / inclusion of information on change of sponsor and change of sponsor representative / clarifications for Clinical Study Report	hch
11	27.11.2014	Clarifications of submission requirements	hch
	30.07.2014	New change history inserted in the document, dropdown field inserted in the header	wis

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