Guideline

Guideline Amendments Clinical Trials

Identification number:	BW101_10_003
Version:	12.0
Valid from:	01.11.2024

Inhaltsverzeichnis

1 In general

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

Points to consider:

Incomplete dossiers cannot be processed. Please only submit documents that are complete and ready for processing in order to avoid queries and delays.

All documents have to be submitted in a clean version and in a version with **track change** mode (~~old text~~ vs. **new text**) or with visible changes. Submitted documents should be non-editable (e.g., PDF format). Documents and information can be submitted in English or a Swiss national language.

For information on the submission process please see the Swissmedic website > Services & lists > Submissions > Applications for clinical trials for medicinal products.

If not specified otherwise, all documents must be submitted until study completion is reached in Switzerland.

2 Folder structure for submissions

Swissmedic provides you with a pre-defined explorer folder structure (eDok_KLV) to harmonize all incoming submissions. This folder structure can be downloaded from Swissmedic website > Services & lists > Submissions > Applications for clinical trials for medicinal products.

You will find:

- the eDok_KLV folder structure as a zip file for download
- a Quick guide on how to submit using the eDok_KLV folder structure with instructions on documents each folder could be filled with.

Once you have downloaded the folders, the ones you do not need for your submission have to be deleted. Please follow the predefined folder structure also for changes and reportings in the context of a running clinical trial. Not following this structure will lead to a formal deficiency letter.

3 Submission form

The following original signed forms must be used (not applicable in case of KLV portal submissions):

A. BW101_10_019e_FO Confirmation electronic submission

B. FO submission form
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 initial form (international standard, see cioms.ch)

The forms can be downloaded here: Swissmedic website > Services & lists > Submissions > Applications for clinical trials for medicinal products

3.1 Changes to a running trial according to chapters 4.1 to 4.8 of this document

Form FO submission form
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 - 4.12 of this document

Form FO submission form
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 Change of Swiss representative according to chapter 4.13 of this document

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

- **Submission type:** SUBMISSION to an AUTHORISED Clinical Trial
- **Select form type:** CHANGE OF SWISS REPRESENTATIVE
- fill in all fields
- list all submitted documents in section 8

3.4 SUSARs

Form CIOMS initial form

Form FO submission form
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

3.5 Answers to conditions made by Swissmedic

Form FO submission form
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.

3.6 Answers to formal deficiency made by Swissmedic

Form FO submission form
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.

3.7 Answers to further information request made by Swissmedic

Form FO submission form
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 submitted.

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

- Documents 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 in 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.

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

All changes within documents as listed in Annex 4, numbers 1.1 – 1.7 ClinO 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). Important to note, 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.

When submitting changes to complex trials, please also submit an updated flow chart where the status of each existing sub-study/cohort is updated and new cohorts are depicted, if applicable.

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 or AxMP (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/AxMP 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. The updated protocol should be submitted in a clean version and in a version with **track change** mode (~~old text~~ vs. **new text**) or with visible changes. The updated clinical trial protocol (clean version) must be dated and signed at least by the Sponsor.

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

All quality changes to the PQD related to the respective clinical trial have to be submitted to Swissmedic.

A guidance on the kind of 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:

Submission of at least one document showing the modifications in **track change** mode (~~old text~~ vs. **new text**) or with visible changes is mandatory. It can be either directly in the PQD or the summary of changes, preferably the PQD in track change mode.

A summary of changes has to be provided and should include all modifications, with indication whether they are substantial or not. This summary of changes can be a separate document or it can be integrated in the amended PQD.

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 ~~crossed out~~* *Or* *-track change mode*	Give rationale	Yes/no

In case of modular PQD, where each section is tracked with its own version number/identifier, and the individual updated sections (clean and track change format) are submitted independently as modifications to the whole PQD, then there must also be a table clearly identifying the previous and current version number/identifier for all sections of the modified PQD. This can be included in the summary of changes table or in a separate table of content/document directory.

4.3 Quality defects and OOS of IMPs and AxMPs

Quality defects of IMPs and AxMPs have to be submitted to Marketing Surveillance of Swissmedic (Swissmedic website > 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 whether changes to the study documentation is requested or not. Changes to the PQD due to a quality defect, have then to be submitted to Swissmedic Division Clinical Trials, as well as the "closing correspondence" between Marketing Surveillance of Swissmedic and the Sponsor.

Please be aware that out of specifications (OOS) have to be submitted to Marketing Surveillance of Swissmedic as a quality defect.

4.4 Changes to labels (Section 8 of the CTA dossier)

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

4.5 Updated safety documentation (Section 5 of the CTA dossier)

Updated safety documentation (e.g., IBs and SmPCs) needs to be submitted until trial completion in Switzerland. In case there is an impact on the safety or wellbeing of subjects, who have completed the trial, safety documentation updates have to be submitted also after LPLV. Generally, a yearly update of the IB is expected. In case the IB does not need to be updated, an IB memo or similar explaining the reason is expected.

The reference safety information (RSI) in the Investigator's Brochure (IB) should fulfil the requirements according to the "Q&A document – Reference Safety Information" dated November 2017 and the "CTFG RSI Q&A cover note" dated March 2018 (see hma.eu) of the Clinical Trial Facilitation Group CTFG (see hma.eu).

The changes to the safety documentation as compared to the previously approved version must be documented in a summary of changes document as shown below. The updated document shall be submitted in a clean version and in a version with **track change** mode (~~old text~~ vs. **new text**) or with visible changes.

Moreover, it must be indicated if, and to what extent, the risk/benefit analysis of the trial has changed. Any safety measures taken on the basis of new analyses or new data should also be described.

Summary of changes:

Section	Old text	New text	Rational for change	Substantial?
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	Yes/no
1.1 New information	Original text	Original text Added text	New information	Yes/no
1.2 Deleted text	Original text to be deleted	~~Deleted text~~	Reason for deletion	Yes/no

4.6 Change of sponsorship / other administrative change (Form Type CHANGE)

Swissmedic's authorisation to perform a clinical trial cannot be transferred from one Sponsor to another one. If a new Sponsor takes over an already authorized clinical trial, the new Sponsor needs to ask Swissmedic for a new authorisation. For this purpose, please use the Form Type "CHANGE", tick "**Change of Sponsorship**" and fill in the requested information.

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 hands over 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.

4.7 Extend the deadline of 2 years for the application to the second authority and for enrolment of the first participant (Form Type CHANGE)

In case Swissmedic is the first authority who granted authorisation of the clinical trial in Switzerland, the request for extension of the deadline for the authorisation by the second authority (Art. 23 para. 1bis ClinO) has to be submitted to Swissmedic.

The request for extension of the deadline for enrolment of the first participant (Art. 23a para. 3 ClinO) has to be sent to both authorities.

For both cases the form type “CHANGE” has to be selected and the topic “**Substantial Amendment to an authorised Clinical Trial**” has to be ticked. The reason for the amendment has to be filled in the specific field.

4.8 Dear Investigator Letter (Form Type CHANGE or REPORTING)

Dear investigator letters (DIL) that do not represent safety and protective measures notifications according to ClinO, art 37 para. 3 can be submitted either as a change or as a reporting depending on the content of the DIL. Please use either the form type “CHANGE” and select “**DIL (Dear Investigator Letter)**” or select the form type “REPORTING” and select “**other Reporting or not safety relevant DIL (Dear Investigator Letter)**”.

4.9 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 have to be implemented immediately, without waiting for an approval by Swissmedic. However, they must be reported within 7 days to Swissmedic by the Sponsor. This includes DIL that represent safety and protective measure notifications according to ClinO, art 37 para. 3.

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 DSUR/Annual List of Events and Deficiencies can be found on Swissmedic website > Human medicines > Clinical trials > Clinical trials on medicinal products > Safety measures in clinical trials).

4.10 Early termination / trial interruption and resumption (Form Type REPORTING)

The Sponsor must report a premature early termination/discontinuation, interruption and resumption of a clinical trial to Swissmedic, stating the reasons for the discontinuation or interruption/resumption.

The reporting timeline is 15 days (Art. 38 para. 2 ClinO) for non-safety related premature discontinuations or interruptions. However, Swissmedic must be informed within 7 days (Art. 37 para. 1 ClinO) if a trial is discontinued or interrupted prematurely for safety-relevant reasons.

4.11 Beginning and completion of the trial (Form Type REPORTING)

The **beginning** of the trial is considered as the **enrolment of the first participant** in Switzerland. The Sponsor must report the beginning of the clinical trial in Switzerland to Swissmedic within 30 days.

The **completion** of the trial is considered to be the LPVL, unless differently defined in the trial protocol. The Sponsor must report the end of a clinical trial in Switzerland to Swissmedic. For international trials, the Sponsor must also report the end of the clinical trial internationally.

The timeline for reporting the end of the study in Switzerland is 30 days and globally it is 90 days (Art. 38 para. 1 and para. 1 bis ClinO).

4.12 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. 3 and 5 ClinO within 1 year of trial completion or early termination. For international trials, Swissmedic accepts the international end date of the trial as the reference date for submitting the final report.

Swissmedic has not published any guidelines on the formal requirements for the final report; however, Annex IV of EU Regulation No 536/2014 (EU CTR) (see ema.europa.eu) should be followed. The final report should adequately summarize the data collected in the clinical trial. The complete report and a synopsis shall be submitted.

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

4.13 Change of Swiss representative (Form Type CHANGE OF SWISS REPRESENTATIVE)

If a new Swiss representative takes over responsibilities for a Sponsor, Swissmedic must be informed. For this purpose, form type “**Change of Swiss representative**” has to be selected. 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 form type “CHANGE”, tick “Other Administrative Changes” (see above).

Änderungshistorie

Version	Beschreibung	sig
12.0	Editorial changes, clarifications and adaptions to new submission form. Updates associated with the revision of ordinances relating to the Human Research Act Documents and information can be submitted in English or a Swiss national language. When submitting changes to complex trials, please also submit an updated flow chart. Guidance for the submission of a change to the PQD is updated. A yearly update of the IB is expected. Summary of changes of IB should include whether a change is substantial or not. Annex IV of EU Regulation No 536/2014 (EU CTR) can be followed for the final clinical study report.	sis
11.2	IB updates are no longer required to be submitted after the end of trial in Switzerland, unless there is an impact on the safety or wellbeing of the subjects who have completed the trial.	plp
11.1	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	Adaptation of eDok_KLV structure, typos and errors cleared	plp
10.0	Alignment to paper free process, typos and errors cleared	gav
9.0	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	Inclusion of information on quality defect reporting (formerly included in the FAQ document), change of FPFV acknowledgement procedures, clarifications, correction of links	gav
7.0	Updates to submission of PQD changes, clarifications, corrections	hch
6.0	Replacement of the forms change of sponsorship and change of Swiss representative by the form administrative changes Clarification concerning notification of study start	hch
5.0	Inclusion of additional information on requirements for reference safety information and for reporting of study start; clarifications	hch, jaf
04	Clarifications for submission requirements	hch
03	New submission requirements with introduction of two new submission forms, clarifications	hch, jaf
02	New order of chapters for changes and reporting clarifications and corrections	hch, gav, jaf
01	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	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	Clarifications of submission requirements	hch
	New change history inserted in the document, dropdown field inserted in the header	hch
		wis