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 as **paper copy** (where requested as explained below in track change mode or with visible changes, otherwise as clean version) **AND** as an **electronic copy e.g. on CD-ROM or via the Filetransfer Service tool** (clean version for all documents and where requested as explained below additionally in track change mode or with visible changes).

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

2 Submission form

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

1. All instructions and templates for all **submission to an approved clinical trial** can be found on our wep page: Home > Human medicines > Clinical trials > Clinical trials on medicinal products.

2. Use the **FO Submission Form** for the Submission for all applications. This form contains all 5 possibilities of submissions on clinical trials 1) New CTA, 2) submission to an authorised clinical trial, 3) answer to condition, 4) answer to formal deficiency and 5) answer to further information request. The form can be downloaded from our webpage. For instructions on this form see <*Quick instruction for use of new submission form*>.
   For amendments you can chose the following **Form Types** within the FO Submission Form:
   - submission to an authorised clinical trial
     - Changes
     - Change of Swiss representative
     - Reporting
     - SUSAR
     - Temporary authorisation for use project
   - answer to condition
   - answer to formal deficiency
   - answer to further information request

3. Use the **eDoc folder structure** we provide you with on our web page as Zip File for down load <*eDoc-file structure (ZIP file)*>.
   For instructions on the filing of the submission package into the E-Doc see <*Instructions for filling the eDoc folder structure*>

   Important:
   - Please note that **the FO Submission Form** has to be filed in the **01FM** folder as a PDF, a scan is not allowed here.
   - The scan of this **signed form** or the **scanned Signature** page of this form has to be filed in the **02FO** folder.

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- Empty folders have to be deleted.
  Documents with the content "this folder is empty", or "this folder is NA" must not be placed in the folders.

Safety measures in clinical trials

➢ **Please consult our information sheet *Safety Relating to Clinical Trials – Compulsory notification*** under www.swissmedic.ch > Human medicines> Clinical trials on medicinal products > Safety measures in clinical trials > Instructions and forms.

IMPORTANT information

- 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 file this letter in the correct folder 01CL.
- Always give a **short and precise overview** on the content of the submitted change in the Form under Submission details, "Reason for Amendment / Submission".
- All documents related to the notified changes or reporting have to be listed in the Folder sections at the Endo of the FO-Submission Form.
- 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.
- For submissions concerning a approved clinical trial a letter will be issued by Swissmedic. The content of the letter will inform about decision od acknowledgememtn of the changes and reportings.

3 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 under point 2 on the form *Submission of Changes to a Clinical Trial and Answer to Conditions*). 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).

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4 Protocol Amendments related to the use and/or safety of the IMP (Section 04P of the eDoc structure)

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.

5 Changes to the pharmaceutical quality documentation (PQD) of the IMP (Section 07Q of the eDoc structure)

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-type submission to an authorised clinical trial
- 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.

- Form-type submission to an authorised clinical trial
- , signed by applicant
- **Full track change version** (color print)
  In case only a clean version can be submitted all changes have to be clearly visible in the tabular overview of changes.
  If the amendment concerns **more than one trial**, only one printout has to be provided.
- **Tabular overview of changes with modifications clearly visible**
  Please provide a copy of the overview for each trial concerned by the submission.

4. 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.

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6 Changes to Study Medication Labels (Section 08LA of the eDoc structure)

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.

7 Updated Investigator's Brochure (IB) (Section 05S of the eDoc structure)

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

8 Change of Sponsorship / other administrative changes (no documents submitted, only the FO-Submission Form)

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'.

Examples for Other Administrative Change:

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

For a change of sponsor or sponsor name or a change of sponsor address involving a **change of country**, 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.

9 Change Swiss Representative/ Representative (no documents submitted, only the FO-Submission Form)

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)

10 Safety reporting in clinical trials of the categories B and C (Art. 37 ClinO; section 11USM of the eDoc structure)

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.

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”.

11 Premature discontinuation / Trial interruption

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.

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12 Beginning and end of the trial

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.

13 Final clinical study report (section 14FSR of the eDoc structure)

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 on CD and the synopsis shall additionally be submitted as a hard copy.

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
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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