swissmedic

Guideline
Clinical Trial Application Dossier

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List of contents

1 Introduction

The content of a clinical trial application (CTA) submission dossier to Swissmedic can be found in Annex 4 number 1 of the Clinical Trials Ordinance (ClinO, SR 810.305).

The present guideline clarifies the requirements for clinical trial applications concerning **clinical trials with medicinal products**.

Application format:

1. All instructions and guidelines concerning the submission of a new Clinical Trial Application (CTA) can be found on our Swissmedic website > Human medicines > Clinical trials > Clinical trials on medicinal products

2. All information concerning the technical requirements and templates for the submission of new CTA can be found on our Swissmedic website > Services & lists > Submissions > Applications for clinical trials for medicinal products

3. Use the **FO Submission Form** for the submission of a new Clinical Trial Application. This form contains all five Submission Types:
   1) APPLICATION for a NEW Clinical Trial
   2) SUBMISSION to an AUTHORISED Clinical Trial
   3) ANSWER to CONDITION
   4) ANSWER to FORMAL DEFICIENCY
   5) ANSWER to FURTHER INFORMATION REQUEST

4. The **FO Submission Form** can be downloaded from our Swissmedic website. For further instructions refer to the information sheet "*Quick instruction for use of submission form"*.

5. It is mandatory to use the **eDok_KLV folder structure** provided on our web page as Zip File for download.
   For instructions on the filing of the submission package into the eDok_KLV folders please see the information sheet *"Instructions for filling the eDok_KLV folder structure"*

Important:

6. Please note that the FO Submission Form has to be filed in the 00FM folder in the following way:
   a) as an active PDF (no scan, no electronic signature)
   b) The signature page of the form as a scan (not applicable in case of KLV portal submissions)

Please consider the following points:

7. **Incomplete submission** dossiers cannot be processed. We therefore ask you to ensure that all necessary documentation is provided in order to avoid queries and delays.

8. If any of the documents submitted – such as Investigator's Brochure (IB) or Pharmaceutical Quality Dossier (PQD) – were previously approved by Swissmedic for another clinical trial, please **cross reference** via the **Case ID** (i.e. 700123) and **Service order number** (i.e. 102987123) to the other clinical trial. Nevertheless, all documents must be included for a complete dossier for the new clinical trial.
   Any **documents modified** since last approval (i.e., Investigator Brochure, Investigational Medical Product Dossiers) should be submitted in **a) track change** and **b) clean** format. In case the track change version was not submitted initially, it may be requested by the assessor.

9. **Updated documents becoming available** during the review period cannot be submitted to an ongoing application and will not be considered as part of the first application. The updated documents have to be submitted as a new submission (in the form of an amendment) after approval of the originally submitted documents.

10. **Parallel submission:**
    For confidentiality reasons documents may be submitted by different providers. For example, in Investigator-Initiated trials, the PQD is submitted by the Drug master File (DMF) holder and the rest of the dossier is submitted by the Sponsor.
    For parallel submission of the confidential documents, the following procedure has to be followed:

    a) The Sponsor submits **Part 1 of the Submission** except of the PQD and GMP documentation. For this, the Sponsor chooses the Submission type <APPLICATION for a NEW Clinical Trial>.
    "CTA Parallel Submission Part 1" shall be indicated in the reference line of the Cover Letter, and it shall be mentioned that folders 06 and 07 are empty. The name of the company who will submit the missing PQD has to be indicated in the letter as well.

    b) Swissmedic will answer to the receipt of Part 1 of the dossier with a letter and **will request Part 2 of the Submission** of the Dossier to be submitted. The Case ID (i.e., 700123) and the Service number (i.e., 102987123) will be communicated in this letter.

    c) The DMF holder shall **submit Part 2 of the dossier (confidential documents)** with the Submission Form with the Submission type <ANSWER to FORMAL DEFICIENCY>.
    The DMF holder shall indicate "**CTA Parallel Submission Part 2**" in the reference line of the Cover letter and mention that the GMP documents and PQD to be submitted are located in folders 06 and 07. The name of the Sponsor and the Study Code has to be mentioned to make the reference to the Sponsor Cover Letter.

d) Thereafter, the submission is complete and the dossier enters the first step of the CTA Process with the formal control of the submission followed by confirmation of receipt.

11. Investigational medicinal products capable of **emitting ionising radiation:** The dossier must additionally include the documents according to Annex 4 number 5 ClinO. For respective category C studies, a complete dossier including hardcopy and electronic copy must also be submitted to the Radiological Protection Division of the Federal Office of Public Health (FOPH). Both dossiers must be submitted within a time window of 7 days in parallel to both authorities.

Deadlines

12. In accordance with Art. 33, para. 1, 2 and 4 ClinO, Swissmedic shall
    a) acknowledge receipt of application within **7 days** and notify the sponsor of any formal deficiencies in the application documents;
    b) reach a decision **within 30 days** of acknowledgement of receipt of the formally correct application documents.

13. In accordance with Art. 33, para. 3 and 4 ClinO, the abovementioned evaluation time may be extended by a maximum of 30 days (i.e., **60 days in total**).
    a) for **First in Human trials** (medicinal product is to be used in persons for the first time)
    b) if a medicinal product is being produced with a **new manufacturing process** defined by:
        i. a new pharmaceutical form or any other substantial change in the manufacturing process. This also applies to a new manufacturing process used for a medicinal product known to Swissmedic.
        ii. In case a medicinal product is not yet known to Swissmedic.

14. In accordance with Art. 36, para. 4 and Art. 33, para. 4 ClinO Swissmedic shall
    a) reach a decision on category C clinical trials of medicinal products capable of **emitting ionising radiation within 60 days** of acknowledgement of receipt of the formally correct application documents

Contact

Should you have any questions, please contact the secretary's office of the Clinical Trials division, tel. +41 (0)58 462 03 87 or ct.medicinalproducts@swissmedic.ch.
If you have any questions with regards to the formal submission process and to the technical requirements, please contact esubmission@swissmedic.ch.

Content

The dossier must be compiled in the following order:

2 Section 00F FO Submission Form

1. The **FO Submission form** with the Submission Type <APPLICATION for a NEW Clinical Trial> has to be submitted for each CTA.
   Please be aware that JavaScript must be activated in order to complete the form. If JavaScript is not active, important functions of the form will not work and the form will be filled out incorrectly. This can trigger formal deficiencies or requests for further information delaying the evaluation of the CTA.
2. The **FO Submission Form** must be fully and accurately completed.
3. Only **one Sponsor** may be named.
4. The Sponsor must be headquartered or represented in Switzerland (Art. 2 ClinO).
   If the **Sponsor is abroad**, the Sponsor`s representative in Switzerland must be named. Swissmedic will address future correspondence (incl. invoices) to the Sponsor`s representative in Switzerland. For further information regarding Sponsor representation in Switzerland, please refer to the Interpretation Guide *"Obligations of representatives of foreign sponsors"*, available on our website Human medicines > Clinical trials on medicinal products > Clinical Trial Application.
   For **sponsors headquartered in Switzerland**, Swissmedic will address future correspondence and invoices to a single address, i.e., to the named contact address in Switzerland (sponsor or representative).
5. The **FO Submission Form** must be dated and signed by the Sponsor or by the Sponsor`s representative, or by the CRO as per contractual authorisation. Contractual agreements or delegations between Sponsor and CRO do not have to be submitted to Swissmedic. Swiss Affiliates of a foreign Sponsor may sign the notification form without contractual authorisation.
6. The complete information has to be entered for each **Investigational Medicinal Product (IMP)** investigated in the clinical trial. This also applies to the **comparator**, the **placebo** and the **Auxiliary Medicinal Products** (AxMPs**) as applicable.
7. Different quantities of active substance per pharmaceutical unit of the same formulation (different strengths, e.g. 20 mg and 30 mg tablets) have to be listed as separate IMPs.
8. When an investigational medicinal products product is constituted of several active substances, the information on all active substances must be provided.
9. For investigational medicinal products capable of **emitting ionising radiation,** the following form needs to be additionally completed:
   a) For category C studies: form for clinical trials of radiopharmaceuticals or radiolabelled compounds (form on FOPH website: www.bag.admin.ch).
      The completed form must be submitted to both Swissmedic and FOPH.
   b) For category B studies: form for clinical trials category B with medicinal products capable of emitting ionising radiation swissmedic.ch > human medicines > Clinical trials on medicinal products > Clinical Trial Application > Forms and Checklists

      The completed form must be submitted to Swissmedic.

10. **Import and distribution of investigational medicinal products** (IMPs) (see also Swissmedic Journal issue dated 07/2010):

    a) In case the IMP(s) is/are imported from a foreign country and intended to be sent **directly to the Swiss study sites**, Swissmedic issues an import licence based on the information provided in the CTA Form. This import licence concerns exclusively the IMP(s) used in the clinical trial and is valid only for the duration of the clinical trial. This import licence will be issued in the authorisation letter for the clinical trial.
    The same applies for import of auxiliary medicinal products (AxMPs**) used in the clinical trial, based on the information provided in the FO Submission Form.

    b) In case of import of the IMP(s) by a **distributor located in Switzerland** (e.g. hospital pharmacy or packaging company), the distributor must have the appropriate licences from Swissmedic to import, store and distribute the IMP(s). In case the company is not in possession of the licences required, the licence(s) need to be applied for. The instructions and forms for the application are available on the website swissmedic.ch Human medicines > Licensing > Authorisations > Forms > *"Gesuch Betriebsbewilligung ")*.
    Meanwhile, this company can pursue its activities until the decision with regard to licences has been taken.
    The same applies for import of auxiliary medicinal products (AxMPs**) used in the clinical trial, based on the information provided in the FO Submission Form.

    c) If substances which are under the control of the **narcotics** law (narcotics like opioids or psychotropics like benzodiazepines) must be imported, a import authorisation according to the narcotics law is required for each import. This authorisation can only be issued by the Narcotics Division of Swissmedic. For more information, please refer to swissmedic.ch > Human medicines > special categories > Authorised narcotics.

    d) If substances capable of **emitting ionising radiation** must be imported, the import for this substance must be covered by the handling licence of the Federal Office of Public Health (FOPH).

**In order to decide whether a product is an Investigational Medicinal Product (IMP) or an auxiliary medicinal product (AxMP), please refer to EU Regulation N°536/2014, the "Recommendations on the use of Auxiliary Medicinal Products in Clinical Trials written and endorsed by the Clinical Trials Coordination and Advisory Group (CTAG - 01 Mar 2024), and Eudralex 10 - 1 March 2024.

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3 Section 01CL Cover Letter

1. This section must contain the cover letter to the Clinical Trial Application (CTA) as well as a copy of any other correspondence with Swissmedic (incl. e-mails) related to this CTA.
2. If for confidentiality reasons, documents are submitted by different providers (e.g. in Investigator-Initiated trials, the Pharmaceutical Quality Dossier (PQD) is submitted by the Marketing Authorisation Holder (MAH) and the rest of the dossier is submitted by the Sponsor), reference to the other provider / company has to be made in the cover letter.
3. For category C studies with investigational medicinal products capable of emitting ionising radiation it must be confirmed that the identical dossier was submitted in parallel to the Federal Office of Public Health (FOPH) within 7 days.
4. In case auxiliary medicinal products (AxMPs) are used in the study, information on product(s), marketing approval(s), and import must be provided.
5. Any answer requested **before study approval** must be submitted with the FO Submission form by choosing the correct Submission Type, as explained in "*Quick instruction for use of submission form"* (i.e. answer to formal deficiency, answer to further information request and answer to preliminary decision) The electronic version of all documents (including cover letter) must be included and filed in the eDok_KLV folder 01CL.
   For information on submission requirements **after study approval** including answers to conditions, please consult our Guideline Amendments and Guideline Safety Reporting.

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4 Section 02EC EC Correspondence

1. Information on any applications currently being reviewed by a Research Ethics Committee in Switzerland (**lead EC only**) and any decisions of a Swiss REC must be provided (Annex 4 number 1 ClinO).

   The information includes:

   a) A copy of the “Research Project Application Form” of the REC

   b) The cover letter sent to the REC

   c) Relevant correspondence between the applicant and the REC providing details on conditions or issues raised.
   Attachments such as protocol, IB, etc. should **not** be submitted.

   d) Approvals with or without conditions received **before** the submission to Swissmedic

2. The authorisation delivered by the REC **after** submission to Swissmedic will be provided to Swissmedic by the REC (Art. 26, para. 4 ClinO).

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5 Section 03RA Foreign Regulatory Authorities

1. This section applies only to **multinational trials**.
2. A list of foreign drug Regulatory Authorities (RA) to which the clinical trial was submitted including details on the approval status (submitted, pending/in review, authorised/authorised with conditions/refused) must be provided.
3. Any decisions of foreign drug RA concerning the clinical trial, including any conditions imposed and the reasons given must be provided (Annex 4 number 1 ClinO), as well as relevant information on ongoing applications.
4. It is sufficient to provide information regarding the first three European countries to which the trial has been submitted and the USA, as applicable at the timepoint of submission to Swissmedic.
5. This includes the relevant documents available at the time of submission to Swissmedic. e.g., entire correspondence (**without** submitted attachments such as protocol, IB, etc.) between the applicant and the responsible RA, with details on grounds for non-acceptance (GNAs), conditions or issues, any approvals with or without condition or refusals, and a list of submitted/approved versions of the crucial documents such as protocol, IB, IMPD. Any decision becoming available during the review period should be submitted.
6. If a RA has given its approval, further updates or other correspondence with this RA do not have to be submitted to Swissmedic.

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6 Section 04P Trial Protocol

1. The final and most recent version of the clinical trial protocol must be submitted. This must be the version that has also been submitted to or already approved by the Research Ethics Committee.
2. The protocol must be dated and signed by the Sponsor
3. The trial protocol must be signed by the sponsor and the investigator prior to the start of the clinical trial (ICH E6 8.2.2). The protocol with the sponsor signature only must be submitted to Swissmedic.
4. If the protocol is signed electronically, the person signing the CTA form takes the responsibility for the validity of the submitted protocol.
5. If the protocol refers to additional documents such as **working instructions** for the personnel designated to perform reconstitution / preparation, these additional documents need to be submitted in the respective section (Pharmacy Manual).

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7 Section 05S Safety Documentation

1. For Investigational Medicinal Products (IMPs) **without a marketing authorisation** in Switzerland or a country whose GMP control system is recognised as equivalent to the Swiss system* (“GMP-equivalent country”), the current version of the **Investigator’s Brochure (IB)** must be provided.
    a) The version submitted should not be older than 18 months and contain a paragraph clearly identified as **reference-safety information (RSI)**.
2. For IMPs **with a current marketing authorisation**, the Summary of Product Characteristics (SmPC) or Product Information have to be submitted.
   The latest version has to be submitted.
    a) For IMPs with a marketing authorisation in several countries having different Product Information / SmPCs, the sponsor should select the most appropriate Product Information / SmPC as RSI. Justification of the choice of RSI must be provided in the cover letter and / or the protocol.
    b) If the IMP is identified in the protocol only by its active substance (e.g. INN name) and different products with marketing authorisation containing this substance may be used in the trial, only one Product Information/ SmPC must be elected as RSI. Justification of that choice should be provided in the cover letter and / or the protocol. A list of the products (name and authorisation number) used at Swiss clinical trial sites must be provided.
3. The **Reference Safety Information** 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 Heads of Medicines Agency HMA – CTFG website (www.hma.eu).
4. For **First-in-human (FIH) studies**, toxicity reports as well as PK(PD) modelling report (if applicable) must be submitted in folder 19 (please refer to chapter 12 of this Guideline).
5. If an **IMP** with a current marketing authorisation is **not being used in accordance with the terms of** that **authorisation** (e.g., a new route of administration, a new dosage or frequency, a new indication, etc.), an IB specific to that new use should be prepared or a new paragraph should be added to the general IB. The IB should contain separate RSI paragraphs for each indication.
6. For **Investigator Initiated Trials (IITs)**, a scientific summary according to the Guideline ICH-E6 chapter 7 (Investigator's Brochure) may be accepted. In cases where preparation of a formal IB is impractical, the Sponsor-Investigator should provide, as a substitute, an expanded background information paragraph in the trial protocol containing the minimum current information described in guideline ICH E6.
   Regarding the RSI, if the IMP is used outside the terms of marketing authorisation within the trial and/or if the sponsor does not have access to an IB for the marketed IMP, the Product Information or paragraph 4.8 of the SmPC could be used as RSI, if justified by the sponsor in the clinical trial application cover letter (refer also to point 2.a) for selection of the most appropriate PI/SmPC as RSI). Otherwise, the RSI should always be a clearly separated specific paragraph within the IB as detailed in point 1. See also Point 3 of this chapter.

7. For an **auxiliary medicinal product** (AxMP**) with marketing authorisation in Switzerland or in a country whose GMP control system is recognised as equivalent to the Swiss system*, the Product Information / SmPC must be submitted. For an AxMP without marketing authorisation as defined above, the Investigator's Brochure (IB) must be submitted.

*For the actual list please go to swissmedic.ch > Legal matters, standards > Current law > Legislation governing therapeutic products in Switzerland > *"List countries with comparable control of human medicinal products"*

**In order to decide whether a product is an Investigational Medicinal Product (IMP) or an auxiliary medicinal product (AxMP), please refer to EU Regulation N°536/2014, the "Recommendations on the use of Auxiliary Medicinal Products in Clinical Trials written and endorsed by the Clinical Trials Coordination and Advisory Group (CTAG - 01 Mar 2024), and Eudralex 10 - 1 March 2024.

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8 Section 06G GMP Documentation

1. Investigational Medicinal Product

Valid proof of GMP compliance has to be submitted for the manufacturers of an Investigational Medicinal Product (IMP) as listed in the Pharmaceutical Quality Documentation (see chapter 9) or for a subset of these manufacturers as documented by the applicant in the FO submission form.

a) For manufacturers located in Switzerland or in a country whose GMP control systems is recognised as equivalent to the Swiss system*:

a valid proof of GMP compliance documenting the relevant manufacturing operation(s) is one of the following:

- Copy of the current valid manufacturing license (not older than 3 years)
- GMP Certificate (not older than 3 years)
- Qualified Person (QP) declaration listing the concerned manufacturing site(s) (with name(s) and address(es)) and indicating the date of the last independent audit performed for the site(s) (not older than 3 years); the QP declaration needs to be dated and signed and the supporting Manufacturing and Import Authorization needs to be provided (with annexes).
- Document of the respective authority confirming that the manufacturer complies with PIC/S GMP (i.e., inspection report including Inspection report with a final assessment of GMP status, not older than 3 years).

For US manufacturing sites:

If only a registry number/registration document of the United States Food and Drug Administration (FDA) is submitted as GMP documentation for a manufacturing site located in the USA, it should be complemented with information about the scope of the last GMP inspection performed by the FDA, which should not be older than 3 years. This FDA GMP inspection should cover the manufacturing operations as described in the quality documentation for that site. Alternatively, the US manufacturing site can be included in the QP declaration and the supporting audit documented therein.

b) For all other manufacturers:

a valid proof of GMP compliance documenting the relevant manufacturing operation(s) is one of the following:

- A GMP Certificate (not older than 3 years) of the authority of the not recognised* country of origin

and at least one of the following documents:

- GMP Certificate (not older than 3 years) from a country whose GMP control systems is recognised as equivalent to the Swiss system
- Qualified Person (QP) declaration listing the concerned manufacturing site(s) (with name(s) and address(es)) and indicating the date of the last independent audit performed for the site(s) (not older than 3 years); the QP declaration needs to be dated

and signed and the supporting Manufacturing and Import Authorization needs to be provided (with annexes).

- Document confirming that the manufacturer complies with PIC/S GMP (e.g. Inspection report with a final assessment of GMP status, not older than 3 years)
- Audit report on GMP compliance for the manufacturing of the IMP (not older than 3 years)

2. Certificates of Analysis

Certificates of analysis must be submitted only in exceptional cases, where impurities are not justified or unexpected impurities are detected, or as requested by Swissmedic.

3. Auxiliary Medicinal Products (AxMPs)

The AxMPs** should be listed in the FO submission form and mentioned in the cover letter (see chapter 2, Section 00F and chapter 3, Section 01CL).

No proof of GMP documentation has to be submitted for AxMPs **with marketing authorisation in Switzerland or in a country whose GMP control systems is recognised as equivalent to the Swiss system***.

If the AxMP does not have a marketing authorisation as defined above, documents shall be submitted as for IMPs according to pargraph 1 in this chapter 8, Section 06G.

4. Investigational Medicinal Products (IMP) to be reconstituted before use

No copy of the manufacturing license is to be submitted, if

a) after shipment to study site the IMP **only** has to be reconstituted, **or only** has to be reconstituted and subsequently blinded, for administration

   AND

b) no further manufacturing step according to the Therapeutic Product Act (HMG/LPTh/LATer, SR 812.21) and the Medicinal Products Authorisation Ordinance (AMBV/OAMéd/OAMed, SR 812.212.1) is performed at the study site

   AND

c) the procedure is patient specific and not for a group of individuals (no batch blinding)

Instead, the following has to be submitted:

Working instructions for the personnel designated to perform this reconstitution / preparation, or the reference to this instruction if provided in another document of the CTA-Dossier.

These working instructions can be provided either in the study protocol or in an independent document bearing a document name, version and version date (e.g. Pharmacy Manual).

Important:

It is the responsibility of the sponsor to ensure that the designated personnel have been properly trained for reconstitution/preparation tasks, that the training is documented, and that IMP accountability and traceability are guaranteed.

*For the actual list please go to swissmedic.ch > Legal matters, standards > Current law > Legislation governing therapeutic products in Switzerland > *"List countries with comparable control of human medicinal products"*

**In order to decide whether a product is an Investigational Medicinal Product (IMP) or an auxiliary medicinal product (AxMP), please refer to EU Regulation N°536/2014, the "Recommendations on the use of Auxiliary Medicinal Products in Clinical Trials written and endorsed by the Clinical Trials Coordination and Advisory Group (CTAG - 01 Mar 2024), and Eudralex 10 - 1 March 2024.

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9 Section 07Q Quality Documentation

The manufacturing, handling and storage conditions of the Investigational Medicinal Products must comply with Good Manufacturing Practice (GMP) according to PIC/S (Pharmaceutical Inspection Conventions / Cooperation Scheme) and Eudralex Volume 4 including Annex 13.

Investigational Medicinal Products (IMPs) are test product(s), comparator(s) or placebo(s).

1. <u>Formal aspects of the document:</u>

a) The document has to be structured as described in the **Guidance on Pharmaceutical Quality Dossier** (BW101_10_006e_AA Guidance Pharmaceutical Quality Dossier) provided on the Swissmedic homepage, using the suggested chapter numbers and titles.
Swissmedic accepts the EMA-EU format for a QIMPD.

b) The following formats of the **PQD** or IMPD are accepted:

i. Simplified IMPDs
ii. One-Document IMPDs
iii. m3-Structure IMPDs (in accordance with the eCTD structure)

Depending on the Structure of the IMPD the corresponding eDok_KLV–Folder has to be chosen.

71_sIMPD	Simplified IMPDs
72_one_doc	One-Document IMPDs
73_m3	**m3**-Structure IMPDs (in accordance with the eCTD structure)

Place the documents into the eDok_KLV Structure and delete unused folders. Do not submit empty folders. A Table of Content (TOC) has to be submitted, where it is requested.

c) **Data presented** in the PQD should be structured as described in the Guidance on Pharmaceutical Quality Dossier (BW101_10_006e_AA Guidance Pharmaceutical Quality Dossier). This document structure is to be followed regardless whether the compiler of the document is the **Sponsor-Investigator, the hospital pharmacy, the contract manufacturer or the pharmaceutical company**. In case independent or separate documents or working instructions are the basis of the quality documentation, all these documents have to be compiled into one PQD under the respective headings and according to the given structure. Not applicable chapters must be included and clearly identified as not applicable (e.g. with the mention “NA”).
A different form of documentation cannot be accepted.

d) If an IMP is used in a previously approved Clinical Trial Application (CTA) in Switzerland, a **cross reference** to this reference study should be made in the FO submission form. For this you have to provide the corresponding **IMP-ID** (IMP Identifier 4 digits number, as given in the approval letter of the reference study), and/or the Swissmedic Case ID of the reference study (i.e. 700123).

i. If **no new data** are provided as compared to the previously approved CTA, a clean version of the (same) quality documentation has to be submitted

ii. If **new data** are provided as compared to the previously approved CTA, at least one document showing the modification(s) in **track change mode** between the submitted version of the quality documentation and the latest approved version of the quality documentation in the reference study has to be submitted.
A summary of changes (SOC) shall also be submitted, listing all sections changed with the reason for each change, thus providing transparency on the development of the quality data of the IMP. In case of modular PQD where e.g. each section as listed in point 1. a) is tracked with its own version number/identifier, then the SOC must also clearly identify the previous version (i.e. in the PQD of the reference study) and current version number/identifier for all sections of the PQD.

2. Submission requirements for IMPs

a) IMPs with Marketing authorization

The following submission requirements are applicable for IMPs with current Marketing Authorization (MA) in **Switzerland or a country whose GMP control systems is recognised as equivalent to the Swiss system***.

i. The IMP **is authorised in Switzerland, an unchanged** (including final packaging) **market batch** with only **a reduced study label** on final packaging:

- The Product Information for Switzerland has to be submitted. No further quality documentation has to be submitted in this section.

ii. For an unchanged IMP with marketing authorisation in a country whose **GMP control system is recognised as equivalent** to the Swiss system*, with only a **full study label added** to the final packaging the following has to be submitted:

- A simplified IMPD providing:
- An **Introduction Part**, confirming the use of a marketed product, listing all countries where the authorised product is sourced form, and providing corresponding SmPC(s) / Product information(s) or referring to this document if submitted as appendix to the simplified IMPD.
- A **Drug Product Part** listing the manufacturer(s) responsible for labelling and release of the final IMP.

iii. The IMP is **blinded or modified post-market release** the following has to be submitted:

- A simplified IMPD providing:
- An **Introduction Part**, confirming the use of a marketed product, naming the country where the authorised Product is sourced form and providing corresponding SmPC / Product information or referring to this document if submitted as appendix to the simplified-IMPD.

- A **Drug Product Part** listing all activities or changes performed with the marketed product (e.g. reformulation, repackaging, over-encapsulation, blinding etc.) and the responsible manufacturer(s) for each of these activities.

iv. The IMP is **another pharmaceutical form or strength** of a medicinal product with marketing authorisation and the Marketing Authorisation Holder (MAH) provides the IMP, the following has to be submitted:

- A simplified IMPD providing:
- An **Introduction Part** providing the differences with the PQD or IMPD of the product authorised in the country of reference
- A **Drug Product Part** including appendices
- A **summary table** accompanying the simplified IMPD summarising the modifications made in each sub-section (Drug Product part) and Appendices as compared to the PQD or IMPD of the product authorised in the country of reference.
  In addition, it must be clear from the summary that there is no difference in the Drug Substance part when compared to the marketed product.

b) IMPs <u>without</u> Marketing authorization

i. The **IMP has no MA**, but the **Drug substance** of this IMP **is part of a product with MA in Switzerland or a country whose GMP control systems is recognised as equivalent to the Swiss system*;**
the following has to be submitted:

<u>If the IMP is supplied by the MAH of the marketed product:</u>

- Country of reference of the authorised product
- A simplified IMPD providing:
- An **Introduction Part** providing the differences with the PQD or IMPD of the product authorised in the country of reference.
- A **Drug Product part** including appendices
- A **summary table** accompanying the simplified IMPD, summarising the modifications made in each sub-section (Drug Product part) and Appendices as compared to the PQD or IMPD of the product authorised in the country of reference.
  In addition, it must be clear from the summary that there is no difference in the Drug Substance part when compared to the marketed product
- If the differences to the marketed product concern only secondary packaging and labelling, the confirmation from the MAH that the product, including primary packaging, is produced according to MA may be provided instead of a simplified IMPD together with a list of the manufacturers involved in secondary packaging and labelling. This confirmation has to be signed by the “Fachtechnisch verantwortliche Person”/”Responsable technique” in Switzerland or a Qualified Person (QP, or Responsible Person = RP).

If the IMP is not supplied by the MAH of the marketed product:

- A PQD or IMPD with Drug Substance part, Drug Product part, and Appendices.

ii. **If the IMP is NOT authorised in Switzerland or a country whose GMP control systems is recognised as equivalent to the Swiss system*, the following documents have to be** submitted**:**

- A PQD or IMPD with Drug Substance part, Drug Product part, and Appendices.

Appendices to the IMPD – according to Guidance on Pharmaceutical Quality Dossier (BW101_10_006e_AA Guidance Pharmaceutical Quality Dossier) - have to be submitted as applicable

Additional information on the quality of the IMP maybe requested by Swissmedic on a case by case basis.

3. Placebo

For placebo the Drug Product part of the Pharmaceutical Quality Dossier including appendices has to be submitted: These data and information can be provided in a separate document or included in the PQD or IMPD of the active IMP.

4. Auxiliary Medicinal Products (AxMPs)

The AxMPs** should be listed in the FO submission form and mentioned in the cover letter (see chapter 2, Section 00F and chapter 3, Section 01CL).

No pharmaceutical quality documentation has to be submitted for AxMPs with marketing authorisation in Switzerland or in a country whose GMP control systems is recognised as equivalent to the Swiss system.

If the AxMP does not have a marketing authorisation as defined above, pharmaceutical quality documentation shall be submitted as for unauthorised IMPs according to paragraph 2 in this chapter 8, Section 07Q.

*For the actual list please go to swissmedic.ch > Legal matters, standards > Current law > Legislation governing therapeutic products in Switzerland > *"List countries with comparable control of human medicinal products"*

**In order to decide whether a product is an Investigational Medicinal Product (IMP) or an auxiliary medicinal product (AxMP), please refer to EU Regulation N°536/2014, the "Recommendations on the use of Auxiliary Medicinal Products in Clinical Trials written and endorsed by the Clinical Trials Coordination and Advisory Group (CTAG - 01 Mar 2024), and Eudralex 10 - 1 March 2024.

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10 Section 08LA Labels

For clinical trials of **Category B and C,** examples of the IMP labels must be provided.

1. For **IMPs <u>without</u> Marketing authorization**, the labels must comply with the requirements of Annex VI of the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use ". The following elements are essential on the immediate and the outer packaging:

    a) IMP name (incl. placebo, if applicable) and strength of the product
    b) Pharmaceutical form, route of administration and quantity of dosage units
    c) "For clinical trial use only" or similar wording
    d) Number or name of the clinical trial
    e) Batch number
    f) Expiry date or retest date
    g) Patient number or randomisation number
    h) "Keep out of reach of children" (if IMP administered by the patient himself)
    i) Name, address and telephone number of the main contact: main contact can be Sponsor, principal investigator or CRO
    j) Storage conditions

    These parameters have to be clearly identifiable. Parameters which are not self-explaining or which are not depicted on the label, but are compiled in a unique identifier, because Interactive Randomisation Technology is involved, have to be explained by listing them. The following has to be obvious for the assessor:

        i. Which number or sign is the unique identifier
        ii. Which of the mandatory parameters are connected with the unique identifier
        iii. Which is the Sponsor Study code

2. For **IMPs <u>with</u> Marketing authorization in Switzerland and purchased directly from the Swiss market**, the reduced labels must comply with the requirements of Annex VI of the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use. The following elements are essential:

    a) Number or name of the clinical trial
    b) Name of Sponsor, Principal Investigator or CRO
    c) "For clinical trial use only" or similar wording

3. For **IMPs <u>with</u> Marketing authorization in a country whose GMP control systems is recognised as equivalent to the Swiss system*,** a full label must be submitted in order to guarantee the language requirements and compliance.

4. In case of immediate and outer packaging provided together or in case of small immediate packaging, please refer to Annex VI of the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use.
5. The labels must be available in the appropriate **Swiss national language**. The labels may be provided in English if the trial product is administered directly by the investigator to the trial subject at the trial centre.
6. For IMPs capable of **emitting ionising radiation**, labels must also comply with art. 46 of the Radiological Protection Ordinance (SR 814.501).
7. A copy of the labels must be submitted for both primary and secondary packaging (outer and inner packaging).
8. For **auxiliary medicinal products** (AxMPs*) with marketing authorisation in Switzerland, no study-specific labels have to be submitted. Otherwise, labels must be submitted according to points 1 and 3-6 in this chapter 10, Section 09LA.
9. If an IMP is **reconstituted at site or reconstituted and subsequently blinded for administration** at site – i.e. no further manufacturing step according to the Therapeutic Product Act (HMG/LPTh/LATer, SR 812.21) and the Medicinal Products Authorisation Ordinance (AMBV/OAMéd/OAMed, SR 812.212.1) is performed at the study site – and the IMP is thereafter transferred to a final container which is different from the primary packaging of the delivered IMP, then the following applies concerning the labeling:

   It is in the responsibility of the sponsor to instruct the personnel designated to perform this reconstitution / preparation to label the final container in order to provide the following information:

   a) Number or name of the clinical trial
   b) IMP name/identifier and strength/potency and or placebo
   c) Patient number or randomisation number
   d) If needed: Date/time of reconstitution
   e) Use-up date/time
   f) Storage requirements

*For the actual list please go to swissmedic.ch > Legal matters, standards > Current law > Legislation governing therapeutic products in Switzerland > *"List countries with comparable control of human medicinal products"*

**In order to decide whether a product is an Investigational Medicinal Product (IMP) or an auxiliary medicinal product (AxMP), please refer to EU Regulation N°536/2014, the "Recommendations on the use of Auxiliary Medicinal Products in Clinical Trials written and endorsed by the Clinical Trials Coordination and Advisory Group (CTAG - 01 Mar 2024), and Eudralex 10 - 1 March 2024"

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11 Section 09PM Pharmacy Manual

Pharmacy Manuals containing instructions for the pharmacist on dilution, preparation or storage of the IMP shall be submitted. This Document is important to underline the compliance with the storage and handling conditions written in the IMPD. If not already submitted with the initial Submission Package the Pharmacy Manual may be requested by the assessor during the clinical study assessment.

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12 Section 19 Toxicology Reports

For **First-in-human (FIH) studies**, toxicity reports as well as PK(PD) modelling report (if applicable) must be submitted.

Change history

Version	Change	sig
13.0	Updates related to the revision of ordinances relating to the Human Research Act Restructuring of Safety, GMP and Quality section for better understanding Updated reference or AxMPs, Updated requirements and reference for IMP labels General updates, revisions and clarifications	plp
12.2	New layout, no content adjustments to the previous version	tsj
12.1	Alignment to portal submission requirements, Typos and errors cleared	plp
12.0	Adaptation of eDok_KLV Structure, typos and errors cleared	gav
11.0	Revised requirements for FIH studies: toxicology and PK(PD) modelling reports	plp
10.0	Parallel submission Part included	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	Revised section 8, clarifications, correction of links	hch
7.0	Deletion of requirement for special import licence for immunological products, blood and blood products due to revised AMBV/OAMéd/OAMed Clarifications regarding RSI, AxMP, PQD submission for market batches Corrections and administrative changes	hch
6.0	Inclusion of additional information in requirements for reference safety information and for auxiliary medicinal products AxMPs, clarifications	hch
5.0	Change of terminology from “non-investigational medicinal product NIMP” to “auxiliary medicinal product AxMP” in accordance with Eudralex Vol. 10 Chapter III - Auxiliary Medicinal Products in Clinical Trials and clarifications concerning protocol signature and manufacturing licenses.	hch
4.0	Clarifications for submission requirement	hch, jaf
3.1	Information on certificates of analysis in section 8 moved to point 2	hch
3.0	EU-harmonised submission requirements for quality and GMP documentation, added information on import of NIMPs and on requirements for reconstitution of IMPs, included clarifications	hch, gav, jaf
2.0	Addition of information on requirement for submission of pre-clinical reports and of documentation for non-authorised NIMPs emitting ionising radiation Minor corrections	hch
1.9	Language corrected	sel
1.8	QM ident. changed old: BW101_10_001e_AL_Guideline_Clinical_Trial_Application_Dossier new: BW101_10_004e_AA_Guideline_Clinical_Trial_Application_Dossier Minor modifications in submission requirements, clarifications and corrections	hch
1.7	Inclusion of information concerning radiopharmaceuticals / deadlines / clarifications concerning reference safety information / clarifications concerning contact details on labels / correction in 8.1	hch
1.6	Clarifications for submission requirements	hch
1.0	New change history inserted in the document; dropdown field inserted in the header	wis