

# Requirements for documents to be submitted for a clinical trial with transplant products (TpP), gene therapy (GT) or with GMOs

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## 1. Scope

This Information Sheet is intended for sponsors and investigators<sup>1</sup> who are either requesting approval from Swissmedic for a clinical trial with transplant products, gene therapy products or GMOs, or who wish to notify an amendment to an application that has already been approved.

In view of the special aspects of these products, adaptations have to be made to certain requirements. These are described in the following sections and should be taken into account in the submission of the documentation.

## 2. Legal basis/instructions

### Legally binding basis:

- Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA), Art. 53 to 57
- Federal Act concerning the Transplantation of Organs, Tissues and Cells (Transplantation Act of 8 October 2004, in force since 1 July 2007)
- Federal Act on Research involving Human Beings (Human Research Act, HRA) of 30 September 2011 (version: 1 January 2014)
- Ordinance on Clinical Trials in Human Research (Ordinance on Clinical Trials, ClinO) of 20 September 2013 (version: 1 January 2014)
- ICH Good Clinical Practice Guideline E6 (CPMP/ICH/135/95)
- Annex 2 of the EU-GMP-Guidelines
- General requirements for medicinal products for the conduct of clinical trials as listed in the Internet at [www.swissmedic.ch](http://www.swissmedic.ch) / Licences / Clinical trials and [www.swissmedic.ch](http://www.swissmedic.ch) / Licences / Documents and Forms

Other instructions that are not legally binding in Switzerland / EU Guidelines (as an aid to the preparation of the documentation):

### European Guidelines / Reflection papers

- European Commission 03/12/2009 ENTR/F/SF/dn D (209 35810); Detailed guidelines on good clinical practice specific to advanced therapy medicinal
- 21 May 2008, Doc. Ref. EMA/CHMP/410869/2006; Guideline on human cell based medicinal products
- 16 March 2010, EMA/CAT/571134/2009, Committee For Advanced Therapies (CAT); Reflection paper on stem cell-based medicinal products
- 11 March 2011, EMA/CAT/571134/2009, Committee For Advanced Therapies (CAT); Reflection paper on stem cell-based medicinal products
- EMA/149995/2008; CHMP Guideline on safety and efficacy follow-up – Risk management of advanced therapy medicinal products
- 22 March 2007 Doc. Ref. EMA/CHMP/SWP/28367/2007 Corr.; Committee for medicinal products for human use (CHMP) DRAFT Guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products
- 17 December 2009, EMA/CHMP/CPWP/288934/2009; DRAFT Concept paper on the development of a guideline on the risk-based approach according to annex I, Part IV of DIR. 2001/83/EC applied to advanced therapy medicinal products

### FDA-Guidances / Regulations

- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy

<sup>1</sup> For investigator-driven trials, the investigator is responsible for both the sponsor's and investigator's tasks.

### 3. Definitions

#### **Transplant product TpP (Finished product)**

Under Article 2, paragraph 1, letter c of the Transplantation Ordinance (SR 810.211), the following have been deemed to be transplant products since 1 May 2016:

1. Products that consist of or contain human organs, tissue or cells, where the organs, tissue or cells:
  - have been substantially processed or
  - are not intended to exercise the same function in the recipient as in the donor.
2. Products comprising or containing animal organs, tissue or cells.

According to Article 2 paragraph 1 letter d of the Transplantation Ordinance, the following are deemed to be substantial processing:

1. Cell propagation by cell culturing
2. Genetic modification of cells
3. Differentiation or activation of cells

This may concern somatic cell therapy medicinal products or ex-vivo gene therapy (as defined in Annex 1 part IV of EU Directive 2003/63/EC) and tissue engineered medicinal product as defined in the EU Regulation 1394/2007 of 13 November 2007 on advanced therapy medicinal products. TpP are used, for example, to restore, correct or modify human physiological functions by exerting a pharmacological, immunological or metabolic action in human beings, or else can be used to replace human tissue or to cure or prevent diseases, injuries or disabilities.

#### **Sponsor**

According to ClinO Art. 2c, the sponsor is a person or institution headquartered or represented in Switzerland that takes responsibility for organising, i.e. initiating, managing and financing, a clinical trial in Switzerland.

#### **Investigator**

According to ClinO Art. 2d, the investigator is a person responsible in Switzerland for the practical conduct of the clinical trial and for the protection of the participants at the trial site; an investigator who takes responsibility for organising a clinical trial in Switzerland is also a sponsor.

#### **Sponsor-initiated trials (or investigator-initiated trials)**

Trial initiated by doctors without a commercial sponsor, where the principal investigator assumes the role of sponsor.

#### **Source data (original data)**

All information obtained from original records in the course of a clinical trial, e.g. ECG printouts, medical records, laboratory printouts, etc., that are required for seamless reconstruction and evaluation.

#### **Case Report Form (CRF)**

Paper or electronic document in which the trial data required by the study protocol are entered for reporting to the sponsor.

#### **Study protocol**

Document describing the objective(s), design, methodology, statistical considerations and organisation of a clinical trial.

**Investigational medicinal product**

Pharmaceutical form of an active substance or placebo tested in a clinical trial or used as the reference substance.

**Investigator's Brochure (IB)**

A compilation of the clinical and nonclinical data on the investigational product that is relevant to the study of the investigational products in human subjects.

**Gene therapy medicinal product**

As defined in EU Regulation 1394/2007.

**GMOs**

Medicinal products containing genetically modified organisms as defined in the Release Ordinance of 10 September 2008, particularly viruses capable of replication.

**Somatic cell therapy medicinal product**

As defined in EU Regulation 1394/2007.

**Tissue-engineered product**

As defined in EU Regulation 1394/2007.

**Finished product (finished medicinal product)**

"Consists of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products" (see Directive 2009/120/EC and 2003/63/EC Part IV).

**Active substance**

Composed of engineered cells and/or tissues or genetically modified cells (see Directive 2009/120/EC).

**Additional substances for manufacture (raw material)**

"Materials used during the manufacture of the active substance (e.g. culture media, growth factors), and that are not intended to form part of the active substance" (see Directive 2009/120/EC and Instructions for authorisation documents for TpP).

**Starting materials**

See Directive 2009/120/EC and Instructions for authorisation documents for TpP.

**4. Abbreviations**

CRF	Case Report Form
GT	Gene therapy product
GMOs	Genetically modified organisms
IB	Investigator's Brochure
ICH E6	ICH guideline for Good Clinical Practice
IMPD	Investigational Medicinal Product Dossier
ClinO	Ordinance on Clinical Trials in Human Research (Ordinance on Clinical Trials)
SAMS	Swiss Academy of Medical Sciences
TpP	Transplant product

## **5. General and formal requirements for an authorisation dossier for clinical trials with TpP, GT and GMOs**

The documents for the first authorisation and for the reporting of amendments to a clinical trial must be submitted as follows: 1 Original in hardcopy form and, in addition, all submitted documents on CD-ROM or DVD. If the application involves gene therapy or GMOs, 3 additional CD-ROMs or DVDs should be submitted in addition to the original.

All correspondence should be sent to the following address:

Swissmedic  
Swiss Agency for Therapeutic Products  
Division Inspectorates and Licences / Section Transplants  
Case Manager  
Hallerstrasse 7  
3012 Bern

The documents for the authorisation should be submitted in a particular order in a 20-part register. The requirements stated in the checklist "Documents for TpP/GT/GMOs clinical trials" (I-315.AA.01-A12) and, correspondingly, the requirements for the documents that need to be submitted for the authorisation of a clinical trial with medicinal products apply to the order and the labelling of the individual registers.

The accompanying letter should clearly show the following numbers:

- "Trial number/Protocol number"
- EudraCT number (if available)
- Swissmedic reference number (if an amendment to an existing approved trial is involved)
- List of submitted documents with version number and date

Any specific substantive requirements for the individual registers in respect of transplant products, GT or GMOs are described in the following sections.

## **6. Processing of applications at Swissmedic**

### **6.1 Authorisation procedure for somatic cell therapy and tissue engineering transplant products**

Anyone wishing to conduct clinical trials with transplant products based on somatic cell therapy and tissue engineering must, according to Art. 54 of the Therapeutic Products Act, obtain authorisation before the trial starts. The sponsor is notified of any formal deficiencies in the application documents within 7 days of receipt of the application (ClinO Art. 33, para. 1). A decision concerning the application will be made within 30 days after acknowledgement of receipt of the formally correct application documents (ClinO Art. 33 para. 2).

If a medicinal product is to be used in humans for the first time or manufactured in a new process, this deadline may be extended by a maximum of 30 days according to ClinO Art. 33 para. 3. The sponsor shall be informed of the extended deadline. If additional information is demanded in accordance with Art. 31 para. 2 of ClinO, the clock shall be stopped until this information is received.

If Swissmedic has no objections or queries, the application is authorised by the deadline, and a reference number and confirmation of authorisation are issued. The relevant cantons (Cantonal Pharmacist, Cantonal Medical Officer) and ethics committees are informed.

If the legal requirements are not observed, the agency can submit queries or make the authorisation dependent on the fulfilment of conditions (must be fulfilled before the first patient is enrolled) and/or requirements (can be fulfilled after the first patient has been enrolled, but within the specified deadline).

## 6.2 Authorisation procedure for gene therapy (GT) or GMOs

Anyone wishing to conduct clinical trials with gene therapy products or GMOs must, according to Art. 54 of the Therapeutic Products Act and ClinO Art. 35, obtain authorisation before the trial starts. The sponsor is notified of any formal deficiencies in the application documents within 7 days of the receipt of the application (ClinO Art. 33, para. 1). In accordance with Art. 35 para. 5 ClinO, the agency shall reach a decision within 60 days after acknowledgement of receipt of the formally correct application documents.

If a therapeutic product is to be used in humans for the first time or manufactured in a new process, this deadline may be extended by a maximum of 30 days according to ClinO Art. 33 para. 3. The sponsor shall be informed of the extended deadline.

Before granting authorisation, the agency shall seek opinions from the Swiss Expert Committee for Biosafety (SECB), the Federal Office for the Environment (FOEN) and the FOPH (ClinO Art. 35 para. 2).

In the event of a positive decision, Swissmedic shall authorise the trial within the deadline and issue a reference number and confirmation of authorisation, and inform the relevant cantons (Cantonal Pharmacist or Cantonal Medical Officer), the relevant ethics committees, the FOPH, the FOEN and the SECB. According to Art. 35 para. 6 ClinO, the authorisation shall remain valid for the duration of the clinical trial, subject to a maximum of 5 years after granting.

## 6.3 Authorisation procedure for an amendment

A distinction is made between significant and minor amendments (changes).

According to Art. 34 para. 1 ClinO, significant amendments to the authorised clinical trial must be approved by the agency before they can be implemented. Exempt from this requirement are measures which have to be taken immediately in order to protect the participants. An acknowledgement is sent to the sponsor within 7 days of receipt of the application, and the sponsor is informed of any formal deficiencies in the application documents.

Apart from the amendment types specified under Art. 34 ClinO, major changes can include the following types:

- Amendments to the protocol
- New centre
- Change in principal investigator (per centre)
- Change of sponsor
- Change of co-investigator or additional co-investigator
- Amended Patient Information
- Amended Informed Consent
- New/amended documents for patients
- New/amended advertisements
- New/amended contracts
- Amended insurance
- New batch number/new certificate of analysis (this type can be classed as "minor"; "case by case" decision)
- New/amended Investigator's Brochure
- Changes in the manufacture/quality of the IP

All significant amendments are approved within 30 days after receipt of the complete application documents affected by the change.

Other changes which affect the documents submitted to the Agency must be notified to the Agency as quickly as possible. These are acknowledged with a "For your information" letter. The relevant ethics committees are informed of the authorisation of a major amendment to the protocol. In clinical trials with gene therapy products or GMOs, the FOPH, FOEN and SECB are involved if necessary. If the legal requirements are not observed, the agency can submit queries or make the approval of the amendment dependent on the fulfilment of requirements and/or conditions.

## 7. Specific requirements to be satisfied by the trial protocol

Basically, the content and structure of a protocol must be in accordance with the requirements of ICH E 6. During the drafting of a protocol for the implementation of a clinical trial with transplant products, GT or GMOs, the following points require particular attention and should be adequately addressed in the protocol:

- Clear definition of the start and end of the study (e.g. "first patient in" (first patient: first visit) and "last patient: out" (last patient: last visit))
- Detailed information on donor suitability and the donation procedure
- Detailed information on the [traceability](#) of the products (from donor to recipient and from recipient to donor, even if the donor and recipient are the same person)
- Explanation of how traceability is also ensured after the end of the study
- If medical devices are involved: Detailed description of the function and details of the conformity assessment
- Details of surgical procedures required in connection with removal and application and any concomitant treatments. Are these standardised procedures/treatments? Are they part of the study?
- Information concerning follow-up (including long-term follow-up), based on a risk assessment. How is contact with the subject/patient ensured and maintained, including after the study has ended? Precise details about what is covered by the scheduled study. Brief reference to any further studies that are scheduled. State whether follow-up also applies to subjects/patients who have not completed the study (voluntarily or involuntarily)
- Clear explanation as to what counts as "source data"

## 8. Specific requirements to be satisfied by the information and declaration of consent for trial subjects

The templates for the patient/subject information can be downloaded from the website of the Association of Swiss Ethics Committees on research involving humans (swissethics) ([http://swissethics.ch/templates\\_e.html](http://swissethics.ch/templates_e.html)).

The following points should be addressed specifically for transplant products and for GT and GMOs:

- State which parts of the trial are experimental. If the trial involves clinical products that have never previously been tested in humans, this must be clearly communicated;
- Information about all established treatment options. Whenever the patient's/subject's own health insurance fund has to pay for something, this must be mentioned;
- Understandable explanation concerning any potential, and as yet little known, risks arising from the transplanted cells (e.g. concerning tumorigenicity, cell expansion);
- If tissue or cell samples are collected during a clinical trial for future analyses connected with the investigated disease or investigated study product, the patient must be informed about these samples, the corresponding analyses and storage periods in the Patient Information. The patient's consent must be clarified with a yes/no checkbox. Furthermore, the patient must be informed of his/her right to have these samples destroyed at any time;
- If samples are collected for an as yet unclear or indeterminate purpose, the patient's general consent may be obtained for this purpose. Templates for such general consents can be downloaded from the website of the Association of Swiss Ethics Committees on research involving humans (swissethics) ([http://swissethics.ch/templates\\_e.html](http://swissethics.ch/templates_e.html));
- State whether data will be published. If so, in what form (anonymised?)

## 9. Specific requirements for the Investigator's Brochure (IB)

An Investigator's Brochure must be submitted for the approval of a clinical trial (this also applies to investigator-initiated trials).

The sections concerning quality should contain detailed information on the manufacture and quality of the investigational product (IP). The sections concerning non-clinical studies (preclinical evidence) and clinical evidence should describe the non-clinical and clinical studies that have been conducted with the investigational product (including the occurrence of adverse events). If no preclinical or clinical data has yet been acquired for the investigational product, studies with other investigational products can be described. The extent to which the data are applicable to the investigational product must be explained.

#### **10. Specific requirements for the documentation of the trial preparations (Investigational Medicinal Product Dossier, IMPD)**

The guidelines on the pharmaceutical quality of investigational medicinal products are based on the Federal Act on Medicinal Products and Medical Devices of 15 December 2000 (Therapeutic Products Act, TPA, SR 812.21) and its implementation in the Federal Act on Research involving Human Beings (Human Research Act, HRA, SR 810.30) of 30 September 2011 and in the Ordinance on Clinical Trials in Human Research (Ordinance on Clinical Trials, ClinO, SR 810.305) of 20 September 2013 (version: 1 January 2014).

Although the ICH does not define any formal requirements for the documentation of clinical trial preparations, the formal requirements specified in ICH guideline M4Q (R1) "The Common Technical Document" are applicable to the quality section.

The following requirements apply to the quality part (CMC, Chemistry, Manufacturing and Controls) of the documentation to be submitted for authorisation. These sections describe the structure and formal aspects for quality documentation. The requirements were drawn up on the basis of the EMA "Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials" (CHMP/QWP/-185401/2004). The structure of this EMA Guideline largely corresponds to that of ICH Guideline M4Q (R1), thereby allowing for continuous development of the "Quality" part, from the time of authorisation of a clinical trial up to the submission of the authorisation documents. Annex 1 of this document contains a description of the contents according to the matching headings/sections. These are not conclusive and are designed to illustrate the possible contents. If possible, the content of a section should be based on the corresponding ICH guidelines.



**Annex 1:**

Documentation of the investigational medicinal products: Further details on the individual sections

**2.2.1.S. Active substance (drug substance)****2.2.1.S.1. General information**

- The exact constituents of the drug substance(s), including the manufacturer, should be stated.
- A summary of the physical, physiological and biological properties of the drug substance (origin, phenotype, cell marker etc.), including a description of other materials, e.g. bioactive molecules (growth factors etc.) and/or structural components (matrices, medical devices etc.) if these are an integral component of the active substance.

**2.2.1.S.2. Manufacture****2.2.1.S.2.1. Manufacturer**

- The name, address and responsibility of each manufacturer, including contractors (incl. analytics), and each proposed production site/plant involved in manufacture and testing should be stated.

**2.2.1.S.2.2. Description of manufacturing process and process controls**

- Detailed overview of the manufacturing process in a flow chart, from donor testing through to the completion and testing of the drug substance. The flow chart should show the following:
  - the critical work steps involved;
  - the starting materials and raw materials required for each step;
  - the controls implemented for each step;
  - the equipment used for each step;
  - the facilities in which the respective steps are implemented;
  - the relevant manufacturing specifications;
  - the flow chart should show any produced intermediates.
- Each manufacturing step should be described in detail, starting with donor testing through to the completion and testing of the drug substance. Information should also be provided on:
  - the devices used to collect for cell and tissue samples, sampling procedures, requirement criteria/exclusion criteria for donors;
  - a summary description of the manufacturing processes;
  - process parameters (e.g. volumes, temperatures, population doubling levels, incubation conditions, critical time requirements, cell concentrations, confluence);
  - process controls and their acceptance criteria (details in the "Control of critical steps and intermediates" section);
  - starting materials used (details in "Control of materials" section);
  - containers used (details in the "Container closure system" section);
  - equipment and facilities used (details in the "Facilities and equipment" section).
- Sampling plan.
- Description and characterisation of intermediates (e.g. cell bank systems, gene vectors, primary cultures).
- If required, information on the storage of the drug substance and possible intermediates.
- If required, description of the transfer procedures for starting materials, intermediates and drug substance between equipment, clean room zones and buildings and, if applicable, description of the shipment.
- Description of the batch numbering system and batch size.
- If required, the description of possible microbe-reducing methods performed on the cellular starting material.
- Methods and measures for ensuring aseptic production.

**2.2.1.S.2.3. Control of materials**

- All raw materials used in the manufacture of the drug substance or intermediates (e.g. cellular starting material, cell banks, excipients, medical devices, biomaterials, viral vectors, plasmids,

- medicinal products, solutions, media, containers, biologically active substances - e.g. growth factors and enzymes, single-use materials and reusable materials, including their sterilisation methods - which are in direct contact with the product) should be listed and described in detail.
- Information in summary form on the donation, procurement and testing of starting materials of the human tissues and cells used. If cells or tissues used as starting materials are critical (e.g. cancer tissue, stem cells), a corresponding explanation should be provided.
  - Certificates (e.g. Certificate of Analysis, Certificate of Conformity, CE markings) for all raw materials.
  - Specifications for raw materials.
  - Information on the suitability of the raw materials (for in vitro use or human use).
  - Requirements for viral safety/viral harmlessness of the raw materials, including evidence.
  - Description of the source, manufacturer and characterisation (incl. biological activity) of materials of biological origin.
  - If required, specific requirements for materials of human origin and animal origin in respect of transmissible spongiform encephalopathy (TSE) in animals.
  - For xenogeneic cell-based products, information should be provided on the source of the animals (e.g. geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious pathogens, including vertically transmitted microorganisms and viruses and evidence of the suitability of the animal facilities.
  - The test system for all additional substances (scaffolds or matrices, medical devices, biomaterials, biomolecules and/or other components) which are combined with tissue engineered cells of which they form an integral part should be described and justified.
  - Controls performed on raw materials, including a brief description of the analytical methods used.
  - Sampling plan for all raw materials.
  - Description of the storage of the raw materials.

#### *2.2.1.S.2.4. Control of critical steps and intermediates*

- Risk analysis for the whole manufacturing process in order to identify critical manufacturing steps.
- Listing of critical steps.
- Listing of all analytical methods for monitoring the critical steps and intermediates, incl. the acceptance criteria.
- Validation of analytical methods.

#### *2.2.1.S.2.5. Process validation and/or evaluation*

- Information provided here only in connection with pivotal studies.

#### *2.2.1.S.3. Characterisation*

- Origin (autologous, allogeneic or xenogeneic) of the cells (including the country of origin for animal-based starting material).
- The identity of the active substance and the type of cells.
- If available, the determination of the biological activity (Potency assay).
- The purity (requirements for possible cellular contaminants, microbiological impurities, other adventitious agents).

#### *2.2.1.S.4. Control of the active substance (drug substance)*

##### *2.2.1.S.4.1. Specifications for the active substance*

- Description of the release specifications for the active substance (including a brief description of the active substance, tested parameters, acceptance criteria, methods used).

*2.2.1.S.4.2. Analytical procedures*

- Description of all critical analytical methods used for quality control (e.g. identity, purity, contamination, functionality).

*2.2.1.S.4.3. Validation of analytical procedures*

- If available, the validation of the analytical methods (validation plan and report).

*2.2.1.S.4.4. Batch analyses*

- Implementation and documentation of the batch review.
- Release of the active substance.

*2.2.1.S.4.5. Justification of specifications*

*2.2.1.S.5. Reference standards or materials*

- Information on reference standards and reference materials (certificates of analysis).

*2.2.1.S.6. Container closure system*

- Description of the primary container (including components) and if applicable of the secondary container.
- Labelling of containers.
- Quality requirements for the primary container.
- Discussion of the suitability of the primary container/secondary container (incl. safety, adsorption behaviour, extractables & leachables, protection against contamination, compatibility of active substance and the starting materials of the container etc.).

*2.2.1.S.7. Stability*

- If available, description of studies conducted with the active substance.
- Description of the study plan (incl. storage conditions, environmental conditions, sampling plan).
- Definition of checked parameters, including acceptance criteria.
- Summary of stability studies.
- Conclusions from the stability studies (e.g. storage temperature to be used, definition of expiry dates).

*2.2.1.P. Drug product*

*2.2.1.P.1. Description and composition*

- Description of the qualitative and quantitative composition (e.g. active ingredients, excipients, preservatives, non-cellular components such as matrices, scaffolds or medical devices).
- Function of the components.
- Description of the dosage form.
- Description of the containers.

*2.2.1.P.2. Pharmaceutical development*

- Brief description of the development of the investigational medicinal product.

*2.2.1.P.3. Manufacture*

*2.2.1.P.3.1. Manufacturer*

- The names, addresses and responsibilities of all manufacturers involved in manufacture and testing (incl. external analysis).

*2.2.1.P.3.2. Batch formula*

- If required, the batch size should be provided.

#### 2.2.1.P.3.3. Description of manufacturing process and process controls

- A flow chart and summary description of the manufacturing process should be provided. If required, a description and justification should be provided if starting materials such as medical devices, scaffolds or matrices, biomaterials, biomolecules and/or other components are added.
- Detailed measures for ensuring microbiological quality should be presented.

#### 2.2.1.P.3.4. Control of critical steps and intermediates

- The identification of critical manufacturing steps and their controls should be presented in a brief summary.

#### 2.2.1.P.3.5. Process validation and/or evaluation

- Not required.

#### 2.2.1.P.4. Control of excipients

##### 2.2.1.P.4.1. Specifications

- Refer to pharmacopoeias or, if not described there, attach a certificate of analysis.
- If possible, refer to the corresponding pharmacopoeia or, if not described there, present the corresponding certificates of analysis.

##### 2.2.1.P.4.2. Analytical procedures

- If a pharmacopoeia method cannot be referenced, the method used should be described.

##### 2.2.1.P.4.3. Validation of analytical procedures

- If available, initial evaluation studies.
- A comprehensive validation of the analytical procedures is absolutely essential in connection with pivotal studies.

##### 2.2.1.P.4.4. Justification of specifications

- If available. Absolutely essential for pivotal studies.

##### 2.2.1.P.4.5. Excipients of human and animal origin

- All excipients, whether of human or animal origin, that come into contact with the manufactured product during the manufacturing process should be identified and their use in production described.

##### 2.2.1.P.4.6. Novel excipients (e.g. component of the transport medium)

- Information should be provided on each excipient and, where required, the interactions between the excipient and cells/tissues should be described.
- All relevant information on a medical device that is used in a combined investigational product should be presented. In cases where the assessing authority (notified body) has carried out an assessment of the equipment part, the results of this assessment should be stated.

#### 2.2.1.P.5. Control of the investigational medicinal product

##### 2.2.1.P.5.1. Specification(s)

- Provisional specifications should exist for Phase I/II clinical trials (including the checked parameters, acceptance criteria and analytical method used).
- Corresponding final specifications should be provided for pivotal studies.

##### 2.2.1.P.5.2. Analytical procedures

- Every analytical method stated in the specification should be described.

*2.2.1.P.5.3. Validation of analytical procedures*

- The applicability or qualification of the analytical methods in connection with Phase I/II clinical trials should be stated. If a pivotal study is involved, the validity of the analytical methods used should be stated (validation plan and report).

*2.2.1.P.5.4. Batch analyses*

- Should be provided in tabular form or as a certificate of analysis. The batch number, batch size, manufacturing site, analytical methods, acceptance criteria and test results should be listed.

*2.2.1.P.5.5. Characterisation of impurities*

- Additional impurities in the investigational medicinal product that are not already mentioned under section 3.1.S.3.2 should be stated.

*2.2.1.P.5.6. Justification of specifications*

- The justification for provisional/final specifications, including the methods used for checking and the acceptance criteria, if available, should be stated.
- Upper limits are to be set for impurities. They can be preliminary and have to be justified taking the results of the preclinical studies into account.

*2.2.1.P.6. Reference standards or materials*

- Where applicable, the parameters for characterisation of the references or standards should be stated. Section 3.2.S.5 may be referred to if necessary.

*2.2.1.P.7. Containers*

- Brief description of the packaging (primary and secondary containers). The labelling of the investigational medicinal product and, if necessary, the means required for reconstitution.

*2.2.1.P.8. Stability*

- Results of the stability studies in tabular form, including a summary of the stability tests implemented to date. A shelf-life for the investigational medicinal product should be derived on the basis of these results.

*2.2.1.A. Appendices*

*2.2.1.A.1. Adventitious agents safety evaluation*

- Any forms of a TSE risk potential should be presented in a table and discussed in a risk analysis. Detailed information should be provided on the minimisation/avoidance of a TSE risk.
- Regarding viral safety, information should be provided on the risk assessment with respect to potential viral contamination. The introduction of viruses into the product and the capacity of the manufacturing process to eliminate viruses should be evaluated.
- A risk analysis should have been carried out beforehand. The selection and control of starting materials, excipients and reagents should be subjected to critical review. The analysis should be accompanied by a discussion of the strategies for detecting additional substances or performing viral reduction steps during manufacture.