INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER

<PRODUCT>, VERSION <XX.YY>

<DATE>

QUALITY

AUTHORS

Explanatory text: Depending on the nature of the IMP one of the following EU guidelines on quality documentation for clinical trial applications is applicable as expressed in the scope-section of each guideline:

- *Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials - Revision 1 (EMA/CHMP/QWP/545525/2017) https://www.ema.europa.eu/en/requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational-medicinal*
- *Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials – Revision 1 (EMA/CHMP/BWP/534898/2008 rev. 1 corrigendum) https://www.ema.europa.eu/en/requirements-quality-documentation-concerning-biological-investigational-medicinal-products-clinical*
- *(Draft) guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (EMA/CAT/852602/2018) https://www.ema.europa.eu/en/guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy-medicinal#current-version--section*

Please note that for placebo products (as well as modified authorised test and comparator products) guidance is also laid down in the Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials - Revision 1 (EMA/CHMP/QWP/545525/2017) https://www.ema.europa.eu/en/requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational-medicinal

In general, the guidance as presented in the above guidelines should be followed for each section. Where additional information is requested, this is indicated below in that particular section. Please do not leave out any headings; in case there is no information indicate that the section is not applicable.

Depending on the development stage of the product the amount of information required is more or less extensive. For early phase trials less information is expected than for later phase trials. For some sections of the IMPD this is also indicated in the relevant guidance.

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1 INTRODUCTION

Explanatory text: This paragraph should give a short introduction to the compound and its level of pharmaceutical and clinical development.

2.1 CHEMICAL PHARMACEUTICAL DATA

2.1.S DRUG SUBSTANCE

2.1.S.1 General Information

2.1.S.1.1 Nomenclature

Please refer to the relevant guideline depending on the nature of the IMP (provide information concerning the nomenclature of the active substance, e.g. INN, etc)

2.1.S.1.2 Structure

Please refer to the relevant guideline depending on the nature of the IMP.

2.1.S.1.3 General Properties

Please refer to the relevant guideline depending on the nature of the IMP. Additional information can be provided in tabulated form

2.1.S.2 Manufacture

2.1.S.2.1 Manufacturer(s)

Please refer to the relevant guideline depending on the nature of the IMP. In general, the name(s) and address(es) and responsibilities of each manufacturer, including contractors, and each proposed production site or facility involved in manufacture, testing, packaging and batch release should be provided.

2.1.S.2.2 Description of Manufacturing Process and Process Controls

Please refer to the relevant guideline depending on the nature of the IMP. Please also include (safety-relevant) IPCs.

2.1.S.2.3 Control of Materials

Please refer to the relevant guideline depending on the nature of the IMP. For raw and starting materials of biological origin CoAs should be provided.

2.1.S.2.4 Control of Critical Steps and Intermediates

Please refer to the relevant guideline depending on the nature of the IMP. In general, tests and acceptance criteria for the control of critical steps (if any) in the manufacturing process should be provided.

2.1.S.2.5 Process Validation and/or Evaluation

Please refer to the relevant guideline depending on the nature of the IMP. Additionally, provide information on the status of validation.

Typically more information is required in case of sterile drug substance (e.g. validation of aseptic process).

2.1.S.2.6 Manufacturing Process Development

Please refer to the relevant guideline depending on the nature of the IMP.

2.1.S.3 Characterisation

2.1.S.3.1 Elucidation of Structure and Other Characteristics

Please refer to the relevant guideline depending on the nature of the IMP.

2.1.S.3.2 Impurities

Please refer to the relevant guideline depending on the nature of the IMP. For non-pharmacopeial drug substances process and product related impurities should be addressed.

2.1.S.4 Control of Active Substance

2.1.S.4.1 Specification

Please refer to the relevant guideline depending on the nature of the IMP. This paragraph should provide the specification for the batch(es) of the active substance to be used in the clinical trial. The specification should preferably be tabulated and

include which methods are used for each test (including referral to international quality standards, where applicable) and the acceptance criteria. Example (chemical DS):

Table 1: Specifications for <PRODUCT> drug substance

Attribute	*Method*	*Acceptance criteria*
Appearance	*Visual observation*	*Record results*
Identification *(1)* *(2)* *(3)*	 *UV Absorption* *IR Absorption* *X-ray powder diffraction method*	 *Conforms to the reference spectrum* *Conforms to the reference spectrum* *Conforms to the reference X-ray diffraction pattern*
Melting point	*PhEur*	*141 to 145°C*
Purity *(1) Heavy metals* *(2) Related substances* *(3) Methanol* *Ethanol*	 *Ph.Eur., Method IV* *HPLC* *GC*	 *≤ 20 ppm* *Each: ≤ 0.5 %* *Total: ≤ 2.0 %* *Methanol: ≤ 0.3 %* *Ethanol: ≤ 0.5 %*
Water	*Ph.Eur., KF method (coulometric titration)*	*≤ 1.0 %*
Residue on ignition	*PhEur*	*≤ 0.10 %*
Assay	*Titration*	*97.5 to 102.5 %*

N.B.: Contents of the table are for illustrative purposes only. Specifications used in routine testing are acceptable as well.

2.1.S.4.2 Analytical Procedures

Please refer to the relevant guideline depending on the nature of the IMP. A brief description of all non-compendial analytical procedures should be provided.

2.1.S.4.3 Validation of Analytical Procedures.

Please refer to the relevant guideline depending on the nature of the IMP. The suitability of the analytical methods used should be addressed.

Depending on the stage of development of the product a tabulated summary of the results of the validation carried out should be provided. It is not necessary to provide full validation reports.

2.1.S.4.4 Batch Analyses

Please refer to the relevant guideline depending on the nature of the IMP. Batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed together with the use of the

DS batches. Please also indicate the GMP status and manufacturing process used for each DS batch.

2.1.S.4.5 Justification of specification

Please refer to the relevant guideline depending on the nature of the IMP. Provide justification of the acceptance criteria as laid down in the specification provided in section 2.1.S.4.1.

Where possible refer to pharmacopeial monographs.

In case acceptance criteria are based upon a calculation (e.g. endotoxin limit), please also provide the calculation itself.

2.1.S.5 Reference Standards or Materials

Please refer to the relevant guideline depending on the nature of the IMP.

Stability of the reference standard should be monitored, however no data are necessary.

2.1.S.6 Container Closure System

Please refer to the relevant guideline depending on the nature of the IMP. The immediate packaging material should be described and interaction between the active substance and the immediate packaging should be considered.

2.1.S.7 Stability

Please refer to the relevant guideline depending on the nature of the IMP. This paragraph may be divided in a section indicating the stability summary and conclusions, a section on the post-approval stability protocol and commitment, and a section with the actual stability data/ results in tabulated form depending on the amount of information. Please indicate the retest period/ shelf-life of the drug substance.

2.1.P DRUG PRODUCT

2.1.P.1 Description and Composition of the investigational medicinal Product

Please refer to the relevant guideline depending on the nature of the IMP. The qualitative and quantitative composition of the IMP should be provided. Please also provide a physical description of the drug product.

The qualitative composition of the drug product should be provided in a table. Pharmaceutical Standards (e.g. Ph. Eur.) should be provided where applicable. Example (chemical DS)

> *The qualitative compositions of <PRODUCT> 50- and 100-mg tablets is listed in Table 3. The tablets are round (diameters 7.1 mm (50-mg) and 8.1 mm (100-mg)).*
>
> *Table 3: Qualitative composition of <PRODUCT> 50- and 100-mg and placebo tablets*

Component	*Reference to standards*	*Function*
<PRODUCT>	*In house*	*Active ingredient*
D-Mannitol	*Ph.Eur.*	*Filler*
Low Substituted Hydroxypropylcellulose	*Ph.Eur.*	*Disintegrant*
Hypromellose	*Ph.Eur.*	*Binder*
Purified water	*Ph.Eur.*	*Solvent*
Magnesium Stearate	*Ph.Eur.*	*Lubricant*
Purified water	*Ph.Eur.*	*Solvent*

2.1.P.2 Pharmaceutical Development

Please refer to the relevant guideline depending on the nature of the IMP. For early development there may be only limited information to include in this section. A short description of formulation development, including justification of any new pharmaceutical form or excipient, should be provided.

Provide a qualitative description of the formulation used in the study. Mention if different formulations were used for earlier studies.

2.1.P.2.1 Components of the Medicinal Product

Additional relevant information with respect to drug substance and excipients should be provided here.

2.1.P.2.2 Medicinal product

Additional relevant information with respect to the formulation development can be provided here.

2.1.P.2.3 Manufacturing Process Development

Please refer to the relevant guideline depending on the nature of the IMP. Changes in the manufacturing process (if any) including changes in formulation and dosage form compared to previous clinical trials should be described. Comparability should be addressed.

2.1.P.2.4 Container Closure System

No development information needs to be provided.

2.1.P.2.5 Microbiological Attributes

Provide only relevant information.

2.1.P.2.6 Compatibility

Provide only relevant information.

2.1.P.3 Manufacture

2.1.P.3.1 Manufacturer(s)

Please refer to the relevant guideline depending on the nature of the IMP. In general, the name(s) and address(es) and responsibilities of all manufacturers for each proposed production site in manufacture, testing and batch release should be provided. In case that multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities need to be clearly stated.

2.1.P.3.2 Batch Formula

Please refer to the relevant guideline depending on the nature of the IMP. In general, the batch formula for the batch(es) to be used for the clinical trial should be presented. This should include a list of all components. The batch sizes or range of batch sizes should be given.

2.1.P.3.3 Description of Manufacturing Process and Process Controls

Please refer to the relevant guideline depending on the nature of the IMP. This paragraph should include a flow-chart including relevant in-process controls (IPCs) as well as a brief process description. This should not be a detailed instruction for production, but details/precautions taken, relevant for the safety of the drug product for testing in human subjects should be provided. (Example: actions taken to ensure viral safety in a biotech product).

2.1.P.3.4 Control of Critical Steps and Intermediates

Please refer to the relevant guideline depending on the nature of the IMP. In general, tests and acceptance criteria for the control of critical steps (if any) in the manufacturing process should be provided.

2.1.P.3.5 Process Validation and/or Evaluation

Please refer to the relevant guideline depending on the nature of the IMP. Additionally, provide information on the status of process validation.

2.1.P.4 Control of Excipients

2.1.P.4.1 Specifications

Please refer to the relevant guideline depending on the nature of the IMP. Refer to the Pharmacopoeias for the excipients used, where possible. For excipients not covered by the aforementioned standards, an in-house specification should be provided.

2.1.P.4.2 Analytical Procedures

Please refer to the relevant guideline depending on the nature of the IMP. In general, in cases where reference to a pharmacopoeial monograph cannot be made, the analytical methods used should be indicated.

2.1.P.4.3 Validation of Analytical procedures

Please refer to the relevant guideline depending on the nature of the IMP.

2.1.P.4.4 Justification of Specifications

Please refer to the relevant guideline depending on the nature of the IMP. Only when different from internationally accepted pharmaceutical standards.

2.1.P.4.5 Excipients of Human or Animal Origin

Please refer to the relevant guideline depending on the nature of the IMP.

2.1.P.4.6 Novel Excipients

Please refer to the relevant guideline depending on the nature of the IMP.

2.1.P.5 Control of the investigational medicinal Product

2.1.P.5.1 Specifications

Please refer to the relevant guideline depending on the nature of the IMP. The same principles as described for setting the active substance specification should be applied for the medicinal product. This paragraph should provide the specification for the batch(es) of the IMP to be used in the clinical trial. The specification should preferably be tabulated and include which methods are used for each test (including referral to international quality standards, where applicable) and the acceptance criteria.

Please note that drug product specific tests and acceptance criteria should be included in the specifications in line with the pharmaceutical form used. The omission of drug product specific tests should be justified.

Provide release and shelf life specifications in tabulated form.

Example (chemical DS):

Clinical trial batches of the <PRODUCT> 50-mg and 100-mg will meet the following specifications.

Table 4: Release and shelf-life specifications for <PRODUCT> 50-mg and 100-mg tablets

Test Item	***Method***	***Acceptance Criteria***
Description	*Visual observation*	*Light yellow film-coated tablet*
Identification	*HPLC/UV spectrum*	*The <PRODUCT> retention time and UV spectrum are the same as those of reference standard.*
Related Substances	*HPLC*	*Each: NMT 0.5%* *Total: NMT 2.0%*
Content Uniformity[*]	*HPLC*	*Conforms to Ph. Eur.*
Assay	*HPLC*	*Release:* *NLT 95.0% and NMT 105.0%* *Shelf-life* *NLT 93.0% and NMT 107.0%*

Dissolution Test	*USP apparatus 2, 50 rpm, 900 mL of simulated gastric fluid without pepsin (USP), UV spectrophotometry*	*Q = 75% at 30 minutes Conforms to USP*

**: Only applied at release; NMT: Not more than; NLT: Not less than*

2.1.P.5.2 Analytical Procedures

Please refer to the relevant guideline depending on the nature of the IMP. A brief description of all analytical procedures should be provided.

2.1.P.5.3 Validation of Analytical Procedures

Please refer to the relevant guideline depending on the nature of the IMP. The suitability of the analytical methods used should be addressed.

Depending on the stage of development of the product a tabulated summary of the results of the validation carried out should be provided. It is not necessary to provide full validation reports.

2.1.P.5.4 Batch Analyses

Please refer to the relevant guideline depending on the nature of the IMP. Batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed together with the use of the DP batches. It should be indicated which batches will be used in the clinical trial and whether additional batches not yet manufactured might be used.

2.1.P.5.5 Characterization of Impurities

Please refer to the relevant guideline depending on the nature of the IMP. In general, additional impurities and degradation products observed in the IMP, but not covered by section 2.1.S.3.2 should be identified and quantified as necessary.

2.1.P.5.6 Justification of Specification(s)

Please refer to the relevant guideline depending on the nature of the IMP. In general, the proposed acceptance criteria should be justified.

Where possible refer to pharmacopeial monographs.

In case acceptance criteria are based upon a calculation (e.g. endotoxin limit), please also provide the calculation itself.

2.1.P.6 Reference standards

Please refer to the relevant guideline depending on the nature of the IMP. The parameters for characterisation of the reference standard should be submitted, where applicable. Section 2.1.S.5 may be referred to, where applicable.

2.1.P.7 Container Closure System

Please refer to the relevant guideline depending on the nature of the IMP. In general, the intended primary packaging of the IMP in the clinical trial should be described and compatibility with the drug product addressed.. Where appropriate, reference should be made to the relevant pharmacopoeial monograph.

2.1.P.8 Stability

Please refer to the relevant guideline depending on the nature of the IMP. In general, the same requirements as for the active substance are applied to the medicinal product.

This paragraph may be divided in a section indicating the stability summary and conclusions, a section on the post-approval stability protocol and commitment, and a section with the actual stability data/ results in tabulated form depending on the amount of information.

Please indicate the shelf-life of the drug product.

2.1.Q PLACEBO PRODUCT

The quality documentation to be submitted for placebos is limited to the following sections of the product part.

2.1.Q.1 Description and composition

Please refer to the guidance on placebo. In general, the complete qualitative and quantitative composition of the placebo should be stated.

2.1.Q.2 Pharmaceutical development

Please refer to the guidance on placebo. It should be described how possible differences of the placebo preparation in relation to the IMP regarding taste, appearance and smell are masked, where applicable.

2.1.Q.3 Manufacture

2.1.Q.3.1 Manufacturer(s)

Please refer to the guidance on placebo. In general, the name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed site involved in manufacture, packaging/assembly and testing should be provided.

2.1.Q.3.2 Batch Formula

Please refer to the guidance on placebo. In general, the batch formula for the batch to be used for the clinical trial should be presented.

2.1.Q.3.3 Description of Manufacturing Process and Process Controls

Please refer to the guidance on placebo. In general, a flow chart and brief narrative description of the manufacturing process should be included.

2.1.Q.3.4 Control of Critical Steps and Intermediates

Please refer to the guidance on placebo.

2.1.Q.3.5 Process Validation and/or Evaluation

Please refer to guidance on placebo.

2.1.Q.4 Control of Excipients

2.1.Q.4.1 Specifications

Please refer to the guidance on placebo. Refer to the Pharmacopoeias for the excipients used, where possible. For excipients not covered by the aforementioned standards, an in-house specification should be provided.

2.1.Q.4.2 Analytical Procedures

Please refer to the guidance on placebo. In cases where reference to a pharmacopoeial monograph cannot be made, the analytical methods used should be indicated.

2.1.Q.4.3 Validation of Analytical procedures

Please refer to the guidance on placebo. In general, not applicable.

2.1.Q.4.4 Justification of Specifications

Please refer to the guidance on placebo. In general, not applicable.

2.1.Q.4.5 Excipients of Human or Animal Origin

Please refer to the guidance on placebo.

2.1.Q.4.6 Novel Excipients

Please refer to the guidance on placebo.

2.1.Q.5 Control of the Placebo Product

2.1.Q.5.1 Specifications

Please refer to the guidance on placebo. Of note, the specifications should at minimum include a test which enables to clearly differentiate between the respective investigational medicinal product and the placebo.

2.1.Q.5.2 Analytical Procedures

Please refer to the guidance on placebo. A brief description of all analytical procedures should be provided.

2.1.Q.7 Container Closure System

Please refer to the guidance on placebo.

2.1.Q.8 Stability

Please refer to the guidance on placebo. In general, the shelf-life and storage conditions of the placebo should be defined.

2.1.A APPENDICES

2.1.A.1 Facilities and Equipment

Not applicable.

2.1.A.2 Adventitious Agents Safety Evaluation

See the relevant guideline depending on the nature of the IMP. In general, all materials of human or animal origin used in the manufacturing process of both the active substance and the medicinal product, or such materials coming into contact with active substance or medicinal product during the manufacturing process, should be identified. Information assessing the risk with respect to potential contamination with adventitious agents of human or animal origin should be provided in this section.

Reference to the relevant guidance for avoidance of TSE agents and potential viral contamination is indicated in the relevant guideline.

2.1.A.3 Novel Excipients

For novel excipients, information as indicated in section 2.1.S should be provided in line with the respective clinical phase.

2.1.A.4 Solvents for Reconstitution and Diluents

For solvents for reconstitution and diluents, the relevant information as indicated in section 2.1. P should be provided.