Guide: Investigational medicinal product dossier for ATMP

Introduction:

Purpose and scope

In the absence of detailed guidance or a template for the content of the Investigational medicinal product dossier (IMPD) for Advanced therapy medicinal product (ATMP) quality, this document has been created as an authoring guide for first in human (FiH) and early clinical studies where the focus is on safety. Efficacy aspects are more predominant in later development and have not been considered to the same extent.
This document may be used as a guide. However, the content should be adjusted to the nature of the product/process. The guide should preferably be used together with the Regulatory guide, with useful links to different documents important to consider in the creation of the IMPD. Please, remember that each ATMP is unique.
For the Intellectual property, the information in the IMPD may be considered more confidential compared to the Investigator Brochure (IB). Therefore, in some cases some of the information especially the non-clinical data can be placed in the IMPD instead of the IB. However, in our guide this part only can be found in the IB.

Format, structure and content

Where possible and applicable the Common Technical Document (CTD) structure (ICH Module 4) https://www.ich.org/page/ctd and guidance in the EMA Quality Guideline for Biologics IMPDs have been used as a basis, IMPD guideline and template.
This guide assumes that CTD sections 3.2.S (drug substance) and 3.2.P (drug product) will
be authored. To enable efficient authoring, it is helpful if a decision has been made where drug substance manufacture ends and drug product manufacture starts as this will dictate how the IMPD will be structured. In some cases, it may not be possible or meaningful to have a P-section, e.g. when the drug product is a simple dilution of the drug substance with a commercially available diluent and takes place close to administration to the patient.

For some ATMPs, the starting material, the active substance and the finished product can be closely related or nearly identical. In some cases, an artificial (based on regulatory reasons) distinction between drug substance (DS) and drug product (DP) might be included in the IMPD, but this is not always possible. In general, these distinctions are done based on the individual characteristics of each product. When feasible, the applicant should clearly define in the IMPD what it is considered intermediate products, what is considered drug substance and drug product. Starting from these definitions and based on characterization studies, appropriate in-process and release controls need to be established for each step. It is acknowledged that, depending on the product and on the manufacturing process, and when appropriately justified, release testing of the final product might be performed at earlier stages in the manufacturing process.

The DS is defined as an active ingredient that is intended to furnish biological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure or any function of the human body. For instance, it could be the purified starting material or complete efficacious material that will furnish pharmacological activity e.g. autologous or allogenic cells with or without genetic modification.

DP in this guide is defined as the final product in the final presentation e.g. pre-filled syringe with cells or cells in a transfer bag. In this case, the DP shall be described as the finished dosage form that contains the DS, generally, but not necessarily in association with one or more other ingredients (e.g. excipients). The DP may require reconstruction or dilution prior to administration.

Risk based approach

In development of an ATMP a risk-based approach may be applied. It may be used to priorities experimental work or to justify the development approach taken.

A **risk** is a potential unfavourable effect that can be attributed to the clinical use of the investigational ATMP (iATMP). Typical risks may be tumour formation due to off-target activity, disease transmission due to microbiological

contamination or presence of viral or non-viral adventitious agents, immunogenicity, toxicity, or simply lack of efficacy. A **risk factor** is a characteristic that contributes to the risk, eg origin of the cells, the method used for genetic modification, the manufacturing process, the non-cellular components and the specific therapeutic use as applicable.

In early clinical development a **risk analysis** could be a simple list of identified risks and how these have been evaluated by experiments, and minimised by appropriate controls of materials, the process and the product. The latter may be called control strategy. After putting the control strategy in place, the residual risk should be acceptable. This risk analysis is important if there is significant residual risk left and could be the place to explain extra measures taken.

Although risks typical for an iATMP will often be evaluated by the nonclinical studies the quality aspects should be presented in the quality part of the IMPD. The risk analysis in the CTD will be presented n module 2.2. For an IMPD/IB the preferred place would be in the IB where safety is assessed. eg Section 2 summaries. A summary may be presented in P.2 'Pharmaceutical development', or if drug product manufacture is minimal it may be more appropriate in S.2.6 'Manufacturing process development' or on the characterisation section, eg S.3.1 'Elicidation of structure and other characteristics'. It may also be presented outside of the CTD structure, in a quality introduction or in an appendix. For this guide, an example is provided in S.2.6.

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Final version of this guide was reviewed by the Swedish Medical Products Agency (MPA).

Disclaimer:
The following guide are produced and designed as a support for users within the ATMP-field.
The project group aims to ensure that the guide available on the website are up to date but cannot provide any guarantees. Users themselves are therefore responsible for checking that the content is correct and current with applicable regulations.

Document History:

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1.0	2019-05-09	First version
2.0	2020-05-08	Second version includes control and correction of the text

Proprietary & confidential
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INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER:

TITLE

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Edition	Date	Changes
1	YYYY-MM-DD	New
2	YYYY-MM-DD	Complementary changes

TABLES OF CONTENTS

Tables

List tables in the IMPD

Abbrevation and acronyms

List the abbreviations that will be used during the document.

ATMP	*Advanced therapy medicinal product*
CAR-T	*Chimeric antigen receptors-T-cells*
CD	*Cluster of differentiation*
CPMP	*Committee for Proprietary Medicinal Products*
CTD	*Common Technical Document*
DP	*Drug product*
DS	*Drug substance*
EDQM	*European Directorate for the Quality of Medicines*
FiH	*First in human*
HSA	*Human serum albumin*
iATMP	*Investigational ATMP*
ICH	*International Conference on Harmonisation*
IMPD	*Investigational medicinal product dossier*
IMP	*Investigational medicinal product*
INN	*International non-proprietary name*
MA	*Market authorisation*
MSC	*Mesenchymal stroma cells*
PCR	*Polymerase chain reaction*
Ph.Eur.	*European Pharmacopoeia*
PV	*Process validation*
TSE	*Transmissible spongiform encephalopathy*
WCB	*Working cell bank*
QA	*Quality attributes*
QP	*Qualified person*

1. Introduction

Give a short study specific introduction that may be helpful for the reviewer. The introduction should cover but not be limited to:

- What is included in the quality Investigational medicinal product dossier (IMPD)? (documentation on drug substance (DS), drug product (DP), device etc)
- What is the drug substance? (name, type of modality (eg recombinant adeno-associated virus, allogenic mesenkymal stem cell etc, a few words about the mode of action)
- What is the drug product, e.g. route of administration. Is it ready to use or requires processing such as reconstitution or dilution, is it sterile, information about strength if possible. How is it supplied (container closure), etc. Address the drug product by using EDQM standard terms.
- If a diluent or placebo is included this should be stated
- Any special arrangements for the supply chain may be mentioned, however no details

Clinical development phase and patient population. However, details on the treatment and rationale for the study are presented in the Investigator's Brochure (including pre-clinical and clinical data) as well in the clinical study protocol.

2. Information on the biological, chemical and pharmaceutical quality concerning biological investigational medicinal products in clinical trials

S. DRUG SUBSTANCE

Prior to start of authoring of the S-section of the IMPD, it is helpful to have a good understanding of the different materials used in the DS manufacture.

Raw material is defined as unmodified material and it could be substances used in the production or extraction of the active ingredient, i.e. reagents, culture media, additives and buffers.
Starting material is the material procured or generated that will ultimately provide one of the key functional components within the drug substance. For example, blood, biopsy or- bone marrow aspirate. Both vector and the bone marrow aspirate for CAR-T gene therapy act as starting materials (see also 2001/83/EC, Part IV, Advanced therapy medicinal products). For combined products where a medical device is an integrated part of the active substance (e.g. implantable devices), the medical device shall be included as starting material for the ATMP.

DS is defined as the processed starting material used in manufacturing. An intermediate could be a processed starting material which is stored during the manufacturing of the drug substance or drug product.
For certain investigational ATMPs (iATMPs), the starting material, the active substance and the finished product can be closely related or nearly identical. The active substance, any intermediate and the final product should be identified, if possible. In those cases where the iATMPs production is a continuous process and active substance cannot be separated from the final product, it is sufficient to provide information only once (eg in the DS part).

S.1 General information

S.1.1 Nomenclature

Describe the DS and explain the type of material i.e cells, nucleic acid sequence, genetically modified microorganism or virus. Introduce lab codes, acronyms or abbreviations which may be used if the descriptive name is too long.

Distinguishing between DS and DP may be difficult for the products, due to the complex nature of the manufacturing processes. Some gene therapy products may not have defined DS. Others may consist of two or more different DSs that are combined to make the DP. The nucleotide comprises the starting material, the DNA-sequence and enzymes act as the raw material.
This guidance does not recommend how sponsors should distinguish between the DS and DP or define materials.
Typical there is no International non-proprietary name (INN) yet available for early phase, according to Definition (2001/83/EC Annex Part IV: Engineered cells/tissues). An ATMP does not need to have a non-proprietary name, just describe the source. For those products having an INN, this should be stated. In all other cases the in house name should be stated.

S.1.2 Structure

Describe where the materials are harvested/sourced from. There is no formal structure for cells. However, a short description of the active substance including the cell composition should be provided. For certain gene therapy products there may be, however you should submit information on the molecular structure (including genetic sequence) and/or cellular components of the DS. The substance for the gene therapy products based on gene transfer methods *in vivo* or *ex vivo*.

For gene therapy: The genetic sequence can be represented in a schematic diagram that includes a map of relevant regulatory elements (e.g. promoter/enhancer, introns, poly(A) signal), restriction enzyme sites and functional components (e.g. transgene, selection markers). For viral vectors, you should include a description of the composition of the viral capsid and envelope structures, as appropriate, and any modifications to these structures (e.g. modifications to antibody binding sites or tropism-changing elements). You should also describe the nature of the genome of viral vectors, whether single-stranded, double-stranded or self-complementary, DNA or RNA, and copy number of genomes per particle. For bacterial vectors, you should include defining physical and biochemical properties, growth characteristics, genetic markers (e.g. auxotrophic or attenuating mutations, antibiotic resistance) and the location (e.g. on plasmid, episome, or chromosome) and description of any inserted foreign genes and regulatory elements.

S.1.3 General properties

Describe the important feature for the ATMP, such as: function, mechanism, physiological, chemical and biological properties, such as ability to achieve a defined biological effect. If possible, refer to articles and avoid speculations.

S.2 Manufacturer

S.2.1 Manufacturer

Describe the name, address and responsibilities for the sites involved in manufacturing and testing the drug substance, beginning with the starting materials. State the following: “The activities for the drug substance XXXX are performed in accordance with GMP at the sites listed in Table X.”. Indicate in the table the manufacture certified GMP status of the site (QP-declaration or market authorisation (MA)). If this is the same site as for DP manufacture state that and refer to P.3.1. Include tissue establishment permit when applicable, Directive 2004/23/EC.

S.2.2 Description of manufacturing process and process controls

The description should include the following steps (if applicable):

- A flow chart – overview of processes starting with the inclusion of starting materials as defined in S.2.3. Indicate intermediates and in-process controls in line with S.2.4.
- A detailed narrative description of all manufacturing steps: including times, volumes, cell numbers, temperatures, yields, batch scale, pooling, equipment. The process needs to be defined with ranges and decision points.
- Reprocessing during manufacture should be described and justified (if applicable). For biological products, these situations are usually restricted to certain re-filtration and re-concentration steps upon technical failure of equipment or mechanical breakdown of a chromatography column.

Materials and their control will be described in sections 2.S.3 and S.2.4 respectively and should not be included in this section.

S.2.3 Controls of materials

S.2.3.1 Raw and starting materials

Raw materials

Materials used in manufacturing of the active substance (e.g. raw materials, starting materials, cell culture media, growth factors, column resins, solvents, reagents) should be listed (preferably in a table) identifying where each material is used in the process as well as their quality standard (e.g. Ph Eur. or In house). Avoid describing the materials in terms of product names.

Raw materials are reagents that are used during the process but are not intended to be part of the final product, eg culture media or enzymes.

Starting materials are all materials that are incorporated in or part of the active substance, such as cells, tissues or viral vectors.

When applicable, the process of tissue/cell procurement, donation, compliance with 2004/23/EC, should be described. For blood components used as raw materials compliance with the Guideline on plasma-derived medicinal products, and GMP annex 14 should be confirmed.

For gene therapy, DNA vectors (e.g. plasmids, transposon vectors) as well as viral vectors and bacteria act as starting materials and should be described accordingly.

Reference to quality standards (e.g. compendial monographs) should be made. For non-compendial materials, information demonstrating that materials (including biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) meet standards applicable for their intended use should be provided, as appropriate.

The information shall include (if applicable):

- Identification of critical materials
- Biological materials e.g. serum, trypsin, growth factors–where used in process, cross-ref Appendix A.2
- Specifications including substrate stability and QC testing for materials
- Evidence of biological functionality, where appropriate
- Serum growth promotion data
- Enzyme activity
- Growth factors

S.2.3.2 Source, history and generation of the cell substrate/Viral seed

For all materials of biological origin (including those used in the cell bank generation), the source and respective stage of the manufacturing process where the material is used should be indicated.

The description may include following steps (if applicable):

- Summary of source and generation (flow chart) for the material.

A summarised description of the source and generation (flow chart of the successive steps) of the material; e.g. cell substrate, analysis of the expression vector used to genetically modify the cells and incorporated in the parental / host cell used to develop the Master Cell Bank (MCB), and the strategy by which the expression of the relevant gene is promoted and controlled in production should be provided, following the principles of Committee for Proprietary Medicinal Products/International Conference on Harmonisation (CPMP/ICH) guideline Q5D.

- Donor selection criteria (allogeneic) – inclusion and exclusion criteria
- Approvals/licenses for the use of donated human material
- Procedure for harvest of donated material
- Storage and testing prior to use of starting material
- Summaries of adventitious agents safety information for biologically-sourced materials should be in Appendix A.2.

S.2.3.3 Cell bank system, characterization and testing

The description should include the following steps (if applicable):

- Cell bank characterization per principles of ICH Q5D, if applicable
  A MCB should be established, under GMP, prior to the initiation of phase I trials. It is acknowledged that a working cell bank (WCB) may not always be established. Information on the generation, qualification and storage of the cell banks is required. The MCB and/or WCB should be characterised and results of tests performed should be provided. Generation and characterisation of the cell banks should be performed in accordance with the principles of CPMP/ICH Guideline Q5D. Cell banks should be characterised for relevant phenotypic and genotypic markers so that the identity, viability, stability and purity of cells used for production are ensured. The nucleic acid sequence of the expression cassette including the sequence of the coding region should be confirmed prior to the initiation of clinical trials.
- Data on material safety:
  - Virus testing strategy – choice of viruses and any relevant omissions based on risk analysis
  - Potency, specificity test (no contaminating cell types) and viability test
  - Identity test: demonstrated to be human, normal diploid cells/tissue, confirmed cell identity
  - Genomic stability: i.e. relation to tumorigenic transformation

S.2.4 Control of critical steps and intermediates

Tests and acceptance criteria for control of critical steps should be provided.

Due to limited data at an early stage of development (Phase I/II) complete information may not be available. When critical steps and intermediates have been identified, tests and acceptance criteria for the controls (in-process controls or intermediate specifications) should be provided and supported by data, as appropriate.

These may include but are not limited to:

- hold times and storage conditions for process intermediates as well as thawing protocol
- yields consistent with expected values
- identity and purity maintained
- microbiology acceptable
- intermediates which require limitation of hold times and/or storage conditions

Reference to an integrated control strategy may be helpful.

S.2.5 Process validation and- /or evaluation

Describe the process validation (PV) performed. The level of evaluation should be based on the risk analysis. Risk analysis document should be updated by the applicant throughout the product life cycle as new data become available. Key points relevant to the understanding of the product development approach chosen, should be summarized in the IMPD. Depending on how the DS and DP are defined, the PV can also be described in P.3.5.

Different aspects need to be addressed when applicable such as, absence of adventitious viruses, absence of modifying enzymes and nucleic acids, removal of infectious particles, transduction efficiency, vector copy number, structure and function of expressed molecules, removal or reduction of impurities associated with the manufacturing process.
During the clinical trial phases, where PV data are incomplete, the quality attributes to control the active substance are important to demonstrate pharmaceutical quality, product consistency and comparability after process changes.
Due to often limited availability of cells/tissues, the approach to PV should take in consideration the particular aspects of each product and should focus on gaining maximum experience with each batch processed. For further guidance consult Volume 4 GMP for ATMPs.

For early phase the manufacturing process for investigational ATMPs is not expected to be validated but appropriate monitoring and control measures should be implemented to ensure compliance with the requirements in the clinical trial authorisation. Additionally, it is expected that the aseptic processes have been validated.

Aseptic PV: Process simulation test = the performance of the manufacturing process using a sterile microbiological growth medium and/or placebo (e.g. culture media of cells which is demonstrated to support the growth of bacteria). The aseptic PV needs to be repeated at least three times.

S.2.6 Manufacturing process development

The manufacturing process development should be described in this section, with an emphasis on the link between batches used in non-clinical safety studies and batches to be used in the clinical study. Comparability between batches should be presented, where applicable.

A Risk Analysis focusing on quality aspects and/or an integrated control strategy may be presented in this section or elsewhere.

Manufacturing process development including comparability

There is no need to describe the process development from scratch, rather from the point where batches have been made to conduct non-clinical studies that will be presented in the submission, and where such batches are included in S.4.4. For first in human (FiH) studies, it is recommended to use material representative (as similar as possible) of the material used in non-clinical studies, and in that case the development part could be very brief. If the process used for non-clinical and clinical batches is identical, simply state that.

If changes to the manufacturing process and controls have been made these should be summarized and the rationale for the changes should be presented. Most important in early development are changes between batches used for non-clinical safety and clinical batches.

Describe the process changes, e.g. by listing them in a tabulated format or in narrative text, illustrated by comparative flow charts, where appropriate, e.g. genetic engineering, medium formulation, feeding schedule, trypsination processes and product iterations. Discuss the impact of such changes, the need for comparability studies and the evaluation of comparability.

Comparability to establish a link between batches pre-change and post-change may be limited in early development, e.g. comparison by the routine release testing only. However, to establish comparability additional characterisation tests (including orthogonal methods) should be considered. Present the results, e.g. by cross-referencing S.4.4 for routine test data and listing any additional characterisation data.

Control strategy
A control strategy is a summary of the controls put into place to ensure that the final product will meet the critical quality attributes. In early development it may not be clear which attributes are critical, and it may be more appropriate to address these as quality attributes (QA) only. It is particularly important to present a control strategy in cases where end-product testing is limited, when the release relies on PV and tests carried out after use of the product, e.g. due to a short shelf life.

A control strategy is an integrated strategy and combines:
- Control of materials (starting materials, raw materials, intermediates)
- Manufacturing process (process parameters, in-process controls)
- End-product testing (drug substance specification, also link to DP specification)

A control strategy in early development can be a relatively simple list of QA and how they are controlled (control of input materials, process, end-product testing or a combination). QA are often similar to the items in the specification but may include additional attributes which are not ensured by end-product testing. In many cases the QA attributes are ensured by more than one measure where end-product testing only verifies the quality built into the process.

Below, a list of controls with link to the Common Technical Document (CTD) module for references. To clarify, this is an example to present the control strategy rather than a list of attributes. The references do not need to be included in the table.

Identity

	CTD module
Source and control of the starting material(s)	*2.3.S.2.3*
Acceptance criteria in specification for identity and appropriate test method	*2.3.S.4.1* *2.3.S.4.2*

Table S.2.6.a. List of control identity and link to relevant CTD modules

Viability

	CTD module
…	*2.3.S.2.3*
Process parameters such as hold times, temperatures, concentration, IPCs	*2.3.S.2.2* *2.3.S.2.4*
Storage media and storage conditions	*2.3.S.2.2* *2.3.S.7*
Acceptance criteria in specification for viability and appropriate test method	*2.3.S.4.1*

Table S.2.6.b. List of control viability and link to relevant CTD module

Microbiological quality and adventitious agents
Sterility, mycoplasma and endotoxins are controlled by the process and by end-product testing.
TSE and viral safety evaluation is presented in A.2.

	CTD module
Sterility and absence of mycoplasma are controlled by… *Endotoxins are controlled by…*	*2.3.S.2.2*
Acceptance criteria in specification for sterility and mycoplasma	*2.3.S.4.1*
TSE safety – see adventitious agents safety evaluation	*2.3.A.2*
Viral safety – see adventitious agents safety evaluation	*2.3.A.2*

Table S.2.6.c. List of control of microbiological quality and adventitious agents and link to relevant CTD modules

Risk analysis

Due to the specific nature of ATMPs, a risk-based approach may be used to determine the extent of quality, non-clinical and clinical data to be generated. The risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to ATMP is described in separate guideline and applies for marketing authorization. Quality related aspects of the risk analysis may be summarised in the quality part of the IMPD, whereas cross-functional aspects should be presented elsewhere.

A risk analysis is particularly useful in cases where due to the specific characteristics of an iATMP there are gaps in the IMPD compared with expectations according to relevant regulatory guidance or compared with more conventional IMPs. The content of the IMPD may be adapted with regard to the identified risks, based on existing knowledge on the type of product and its intended use. Key points relevant to the understanding of the product development approach chosen, should be summarised in the IMPD. In deciding on the appropriate measures to address the identified risks, the priority should be the safety of subjects enrolled in the trial.

Example of a risk analysis

There is no given format for the risk analysis. An example is presented for a product where full release testing prior to administration is not possible due to the limited stability of the product.

Risk analysis

The gene edited xxx cells are viable for a limited time. Therefore, it will not be possible to carry out full release testing. Instead, a control strategy is proposed in which the release is carried out in two stages, where results from stage 1 testing will be possible to generate prior to administration, whereas stage 2 results will not be available until after administration.

***Disease transmission** due to presence of bacteria, fungi, mycoplasm and viral or non-viral adventitious agents has been identified as a potential risk for XXX. Test results ensuring absence of such contaminants will not be available prior to administration. No end-product sterilisation will be possible due to sensitivity of the cells.*

***Treatment failure** due to absence of a sufficient number of viable edited xxx cells has been identified as a potential risk. Test results ensuring presence of edited cells will not be possible to generate prior to administration, either qualitatively or quantitatively.*

In Table xxx a Control Strategy is presented. Release testing at stage 1 (prior to administration) will ensure that the Quality Attributes are met. Where testing can only be performed at stage 2 (following administration in the clinic) details are provided how it is ensured that the attributes are met with high likelihood to minimise the risks listed above.

Quality attribute	***Stage****	***Control strategy***
IDENTITY	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Identity' on the DS specification (S.4.1)*
QUANTITY	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Total cell concentration' on the DS specification (S.4.1)*
PURITY (product related impurities)	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Dead cells' on the DP specification (100%-viable cells) (P.5.1)* *Characterisation test for presence of other cells (S.3.1)*
PURITY (process related impurities)	*2*	*Acceptance criteria for 'Residual <protein, enzymes>' and 'Residual <DNA/RNA>' on the DS specification (S.4.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated capability of the process to remove impurities (S.2.6).*
POTENCY	*1*	*Acceptance criteria for 'Viability' on the DP specification (P.5.1)*
POTENCY	*2*	*Acceptance criteria for 'X activity' on the DP specification (P.5.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated presence of edited cells (S.2.6).* *<Reference to relevant non-clinical experiments>*
POTENCY	*2*	*Acceptance criteria for 'Editing efficiency' on the DS specification (S.4.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated presence of edited cells (S.2.6).* *<Reference to relevant non-clinical experiments>*
PURITY (microbial contamination)	*2*	*Acceptance criteria for 'PhEur 2.6.27' on the DS specification and DP specification (S.4.1 and P.5.1). The approach is justified in S.4.5 and P.5.6.* *All input materials comply with compendial standards for injectables (S.2.3)*

Quality attribute	***Stage****	***Control strategy***
IDENTITY	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Identity' on the DS specification (S.4.1)*
QUANTITY	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Total cell concentration' on the DS specification (S.4.1)*
PURITY (product related impurities)	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Dead cells' on the DP specification (100%-viable cells) (P.5.1)* *Characterisation test for presence of other cells (S.3.1)*
PURITY (process related impurities)	*2*	*Acceptance criteria for 'Residual <protein, enzymes>' and 'Residual <DNA/RNA>' on the DS specification (S.4.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated capability of the process to remove impurities (S.2.6).*
POTENCY	*1*	*Acceptance criteria for 'Viability' on the DP specification (P.5.1)*
POTENCY	*2*	*Acceptance criteria for 'X activity' on the DP specification (P.5.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated presence of edited cells (S.2.6).* *<Reference to relevant non-clinical experiments>*
POTENCY	*2*	*Acceptance criteria for 'Editing efficiency' on the DS specification (S.4.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated presence of edited cells (S.2.6).* *<Reference to relevant non-clinical experiments>*
		Aseptic PV including equipment in contact with the product (media fill) conducted (S.2.5/P.3.5) *Engineering runs with surrogate materials demonstrate acceptable microbial quality of the product (S.2.5/P.3.5)*

Quality attribute	***Stage****	***Control strategy***
IDENTITY	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Identity' on the DS specification (S.4.1)*
QUANTITY	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Total cell concentration' on the DS specification (S.4.1)*
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PURITY (process related impurities)	*2*	*Acceptance criteria for 'Residual <protein, enzymes>' and 'Residual <DNA/RNA>' on the DS specification (S.4.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated capability of the process to remove impurities (S.2.6).*
POTENCY	*1*	*Acceptance criteria for 'Viability' on the DP specification (P.5.1)*
POTENCY	*2*	*Acceptance criteria for 'X activity' on the DP specification (P.5.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated presence of edited cells (S.2.6).* *<Reference to relevant non-clinical experiments>*
POTENCY	*2*	*Acceptance criteria for 'Editing efficiency' on the DS specification (S.4.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated presence of edited cells (S.2.6).* *<Reference to relevant non-clinical experiments>*
PURITY (adventitious agents)	*2*	*Materials of human or biological origin controlled for viral and TSE agents contamination (CoA, certificates of origin).* *Adventitious agents safety evaluation conducted (A.2)* *No risk for viral and TSE agents contamination considered for the cells due to their autologous nature.*

Quality attribute	***Stage****	***Control strategy***
IDENTITY	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Identity' on the DS specification (S.4.1)*
QUANTITY	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Total cell concentration' on the DS specification (S.4.1)*
PURITY (product related impurities)	*1*	*Acceptance criteria for cells prior to editing - starting materials (S.2.3)* *Acceptance criteria for 'Dead cells' on the DP specification (100%-viable cells) (P.5.1)* *Characterisation test for presence of other cells (S.3.1)*
PURITY (process related impurities)	*2*	*Acceptance criteria for 'Residual <protein, enzymes>' and 'Residual <DNA/RNA>' on the DS specification (S.4.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated capability of the process to remove impurities (S.2.6).*
POTENCY	*1*	*Acceptance criteria for 'Viability' on the DP specification (P.5.1)*
POTENCY	*2*	*Acceptance criteria for 'X activity' on the DP specification (P.5.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated presence of edited cells (S.2.6).* *<Reference to relevant non-clinical experiments>*
POTENCY	*2*	*Acceptance criteria for 'Editing efficiency' on the DS specification (S.4.1)* *Acceptance criteria consistently met in 3 independent simulation runs demonstrated presence of edited cells (S.2.6).* *<Reference to relevant non-clinical experiments>*
GENERAL QUALITY	*1*	*<Standard attributes>*
GENERAL QUALITY	*2*	*<Standard attributes>*

S.3 Characterisation

Characterisation include a wide range of physicochemical, biological and/or immuno-chemical methods applied to establish attributes that are relevant for the control of the active substance, including also impurities. As such the purpose of characterisation is to justify that relevant tests are

applied in the specification. Furthermore, the level of characterisation of the active substance/drug product form the basis for a comprehensive analytical evaluation of changes made to the manufacturing process during development (i.e. comparability)

S.3.1 Elucidation of structure and other characteristics

Adequate characterisation is performed in the development phase prior to Phase I/IIa and, where necessary, following significant process changes. Sufficient characterisation to define the product profile should be performed in the development phase prior to FiH clinical trials and, where necessary, following significant process changes. This section is typically rather comprehensive and presented in narrative text rather than as data tables.

The set of characterisation methods will typically comprise both the tests that are included in the specification and performed on every batch, and additional orthogonal methods to further characterise the substance (so called extended characterisation). The latter may not be expected to be performed on every batch and may have no acceptance criteria associated with them. Prior to initiation of Phase I studies, the biological activity should be determined (relevant, reliable and qualified method). The extent of characterisation data will further increase in later phases.

Consider the following:

- Describe each characterisation method under a separate subheading, including a brief description and a brief justification of the relevance. However, avoid duplication of information presented in S.4. In particular avoid stating in this section which tests are included in the specification and why, as that is to be addressed in S.4.
    - Characterisation of the ATMP can be defined in (number of batches): identity, evidence that phenotype and biological activities are maintained throughout the process, tabulation of growth kinetics (including senescence), population doubling level calculations and yields.
- Avoid presenting data from multiple batches as this is presented in S.4.4 for tests included on the specification.
- Non-cellular components are starting materials that should be characterised on their own in the context of their required function. This includes biomaterials, proteins or chemical entities which may supply structural support, a suitable environment for growth, biological signalling or other functions.

S.3.2 Impurities

Describe the processes for identifying the purity of the material. Impurities are defined as any component present in the DS or DP which is not the desired product, a product-related substance or excipient, including buffer components. An impurity may be either process- or product-related.
It may be difficult to decide which components are impurities or belong to the active, and it is recommended to have a rationale prior to the start of authoring of this section, e.g. a variant of the desired product which exhibits similar biological activity as the active may not necessarily be an impurity but just a variant of the active.
This section is about characterization of potential and actual impurities, not about their control. analytical procedures used in the characterization process, should be demonstrated to be suitable to detect, identify, and quantify biologically significant levels of impurities. Describe potential impurities under subheadings and consider the following:

- Potential process related impurities (e.g. residues of materials and equipment used in the process, such as media, proteins, enzymes, leachable, contaminants)
- Potential product related impurities (e.g. precursors, degradation products, unwanted by-products related to the product – e.g. other cell types)
- Describe what has been observed in batches. However, avoid duplication, e.g. batch data

which are presented in S.4.4

- Make sure conclusions of what might be actual impurities are consistent with the specification. However, avoid stating what is controlled on the specification as this is presented in S.4
- Make sure impurities which are a potential safety concern are not left open ended, i.e. these either should be dismissed as not likely to be present or controlled
- Use literature references where helpful
- For impurities not controlled provide an risk assessment based on actual levels expected in the DS.

S.4 Control of the active substance

Describe the process for controlling the active substance. Normally there is no need to write anything here but rather under the subheadings S.4.1-3, etc. It may be helpful though to detail any special arrangements for sampling for release testing. In that case describe the sampling procedure for controlling the active substance. During the clinical trial phases, where PV data are incomplete, the quality attributes to control the active substance are important to demonstrate pharmaceutical quality, product consistency and comparability after process changes. Therefore the quality attributes controlled throughout the development process should be more comprehensive than the tests included in the specification for which preliminary acceptance criteria have been set.

S.4.1 Specification – drug substance

Specify the method for each parameter and include a specification based on Ph.Eur. criteria, if available, or based on the limited amount of data from development batches. Due to the diverse nature of ATMP products, it is also appropriate to detail whether atypical testing or sampling will be performed e.g. testing performed solely on the DP for continuous processes or samples taken at drug substance only due to lack of material later on at the drug product stage. For example, if there is no hold time between DS and final fill into the drug product vials, it is important to note that some testing (such as sterility testing) maybe performed after final fill. Another example would be diluting a sample with final formulation buffer due to very small sample sizes during autologous ATMP processes.
For in house methods it is necessary to include SOP or method number.

List all tests conducted for release testing. Consider the following:

- Safety studies for setting acceptance criteria e.g. for impurities.
- Microbiological quality should be specified.
- Tests for identity, purity and quantity are mandatory. The convention is to list the tests in order as per ICH Q6B (description/appearance, identity, purity and impurities, potency, quantity, other tests, microbiological tests)
- A test for biological activity should be included unless absence is justified.
- Acceptance criteria should be set for all tests unless justified. These may be wide for initial trials and tightened/amended later on during development.
- Specify the method for each parameter, e.g. the methodology used. Make sure this is consistent throughout the dossier wherever this method is mentioned. Pharmacopoeia procedures are referenced as such.

Parameter	Method	Specification
Appearance	*As applicably*	
Endotoxin	*Ph.Eur.2.6.14 (on medium)*	*<0.25EU/mL*
Identity	*e.g. Flow cytometry, PCR*	*CDxx >95%*
		CDzz>90%
Mycoplasma	*PhEur2.6.7 or PCR*	*None detected*
Potency (may not be applicable for early phase)	*e.g. transduction efficacy, functionality assays*	
Purity	*Ph.Eur.2.7.29*	*<10%non-viable cells*
Sterility	*Ph.Eur.2.6.1 (on medium) or rapid detection method*	*No growth*
Viability	*Ph.Eur.2.7.29*	*>80%*
Yield	*Ph.Eur.2.7.29*	*100 x 106cells/mL* *50 vials/batch*

Table S.4.1.a. An example of a List of parameter for specification of the drug substance. Most of the parameters are applicable for all ATMPs, but methods for analysis may be different. CD: Cluster of differentiation

S.4.2 Analytical procedures

In the same order as in the specification, briefly describe all analytical methods (i.e. RT-PCR and flow cytometry) on the specification. There is no need to describe all experimental details. Methods described in a pharmacopoeia and listed as such on the specification do not have to be described unless they have been modified. It is worthwhile stating this for clarity.

S.4.3 Validation of analytical procedure

It is recognized that full validation will be updated during the clinical trial. However, test methods need to be qualified to ensure results are reliable. However, Sterility and microbial assays should be validated. In addition, other assays that are intended to ensure patient's safety should also be validated (*e.g.* when retroviral vectors are used, the analytical methods for testing for replication competent retrovirus should be validated). Throughout the clinical development, the suitability for the intended use of analytical methods used to measure critical quality attributes (*e.g.* inactivation/removal of virus and/or other impurities of biological origin) should be established but full validation is not required. Potency assays are expected to be validated prior to pivotal clinical trials.

In the same order as in the specification, briefly describe the validation of all analytical methods in the specification. Provide evidence that the methods are suitable for their intended use.
For Phase I/IIa: List at least parameters to be validated (specificity, accuracy, precision, linearity, range, detection/quantification limits), and their acceptance limits and, e.g. in a tabular form. Alternatively, and if available, results from these experiments should be listed.
Pharmacopoeia procedures which are not modified are considered as validated. It is worthwhile stating that these validations are omitted, for clarity. Suitability of compendial tests for your product should be verified (such as for sterility and microbial assays).

S.4.4 Batch analyses

In the same order as in the specification, tabulate available data from relevant batches. For quantitative parameters, actual values should be presented. Additional parameters can also be presented in the table, where appropriate.
Include information on the batches, such as

- Indicate the use of the batch and include at least batches used in non-clinical and stability studies.

- Batch size, e.g. cell number or concentration
- The date of manufacture
- If batches were manufactured by different processes, this should be indicated.

Unexpected results or results not compliant with the specification should be explained.

Parameter	***Method***	***Specification***	*Batch 1 – dev. 10% scale*	*Batch 2 – dev. 10% scale*	*Batch 3 –dev. full scale*	*Batch 4 – clinical full scale*
Sterility	*Ph.Eur.2.6 .1*					
Endotoxin	*Ph.Eur.2.6 .14*					
Mycoplasma	*Ph.Eur.2.6 .7 or PCR*					
Identity	*Flow cytometry*					
Purity	*Ph.Eur.2.7 .29*					
Functionality	*Flow cytometry , INFg*					
Viability	*Ph.Eur.2.7 .29*					
Yield	*Ph.Eur.2.7 .29*					

Table S.4.4.a. List of parameters and data from 3 development batches and one clinical batch presented as an example for a cell therapy product.

S.4.5 Justification of specification

In the same order as in the specification, provide justification of acceptance criteria. For early clinical studies, the justification may be very brief and just state that the acceptance criteria have been chosen based on development data, batches tested so far, analytical capability, stability properties etc. However, for any quality attributes associated with patient safety, limits should carefully consider available knowledge. The relevance of the selected potency assay and its proposed acceptance criteria should be justified. Absence of acceptance criteria should be justified, e.g. if insufficient data are available to establish a meaningful functionality specification it may be stated that information is being gathered for later potency assay development. Indicate which parameters are stability indicating.

- Standard pharmacopoeia requirements for microbiology
- If insufficient data to set functionality specification – information being gathered for later potency assay development
- Yield and viability

S.5 Reference standards or materials

The reference standard may be any well-characterized batch (or pharm/tox batches). The characterization of the reference material should be performed with reliable state-of-the-art analytical methods, which should be adequately described. Information regarding the manufacturing process used to establish the reference material should be provided. If the characterization tests described in S.3.1 were performed on the same batch this should be stated.

For some products a reference std may not be possible. Standards used for calibration of tests methods should be included as well (e.g. standardisations of FACS analysis, Elisa etc). For infectivity assays of GTPs international reference standardisation could be available).

S.6 Container closure system

Describe the container for the drug substance. Information on the sterilization procedures of the container should be provided. A possible interaction between the immediate packaging and the active substance should be considered (covered by stability). Include type of container and materials of construction. Avoid details such as dimensions or brands/suppliers unless critical.

S.7 Drug Substance Stability

Depending on the manufacturing process from drug substance to drug product, this section may not be applicable. When the cell product is manufactured continuously it is not applicable. However, if production is not continuous, i.e. the active substance is stored frozen, it is applicable. Progressive requirements will need to be applied to reflect the amount of available data and emerging knowledge about the stability of the active substance during the different phases of clinical development. The use of stability indicating methods should be justified.
For Phase III, the applicant should have a comprehensive understanding of the stability profile or the active substance.

S.7.1 Protocol and methods, results, shelf life

Stability summary and conclusion
Describe the process to verify the stability of the drug substance. Consider the following:

- Provide a protocol for stability testing of the drug substance (storage conditions, testing intervals (see ICH Q5C for guidance)).
- Detail the tests to be performed on stability. If these are the same as release tests, state that.
- The container closure system to be used in the stability study should be the same as the one used for storage of the drug substance or representative (e.g. same material, smaller dimensions).
- Present data already generated on batches representative of the actual clinical batches.

Conclude the shelf life based on available data and the rules for extrapolation. Describe the process to verify the stability of the drug substance.

P. INVESTIGATIONAL MEDICINAL PRODUCT

P.1 Description and composition of the medicinal product

As a matter of principle for ATMP most information regarding the drug will be found in the DS section. It is only the final procedures that should be described in this section. If necessary, a cross-reference to the DS section can be made.
Wherever possible address the drug product by using EDQM standard terms. Typical standard terms for ATMP formulations are “solution for injection”, “solution for infusion”, suspension for injection” or “suspension for infusion”.

P.1.1 Composition of the drug product

Describe the drug product qualitative and quantitative composition (suggested in a table with the following heading: Component, quantity, quality standard reference and function. Include a brief description of the diluents and container closure.

P.2 Pharmaceutical development

P.2.1 Product development

Phase I – limited (probably) – short description. For Phase II and III, more extensive data should be available.

For early product development this could include some changes in manufacturing which are clinically beneficial due to safety reasons, as well as research and development projects that have resulted in an optimized and more efficient process. For products requiring additional preparation of the medicinal product (e.g. reconstitution), the compatibility with the used materials (e.g. solvents, diluents, matrix) should be demonstrated and the method of preparation including the equipment used should be summarised (reference may be made to a full description in the clinical protocol or in a separate document). Through appropriate studies it should be demonstrated that the specified reconstitution process is sufficiently robust and consistent to ensure that the product fulfils the specifications and can be administrated without negative impact on quality/safety/efficacy profile of the ATMP.

P.2.2 Manufacturing process development

Any changes in the formulation during the clinical phases should be documented and justified. The same principles to demonstrate comparability throughout development that apply to the active substance also apply to the finished product.

P.3 Manufacture

P.3.1 Manufacturers

Describe the name, address and responsibilities for manufacturing and testing the product. List all site performing manufacturing activities on the DP, such as manufacturing, testing, packing, labelling and release. Address the different authorizations for manufacturing e.g. production permit.

P.3.2 Batch formula

In a table state the composition of one batch, the quantity could be defined in a range. Alternatively state that quantities can be changed on a pro rata basis to achieve different batch sizes (possibly within a reasonable range).

P.3.3 Description of manufacturing process and process controls

Depending on how the DS and DP are defined, the manufacture of the DP could be very brief.

- Detailed flow chart – overview of processes
- Identify test points and samples taken
- Detailed description of non-standard processes (**for ATMPs, this is generally all processes!**)

P.3.4 Control of critical steps and intermediates

Tests and acceptance criteria – may be quite minimal at Phase I/IIa:

- If Hold-times are applied, storage conditions and times should be detailed and substantiated with data.
- If no holding times are applied, it should be stated that the process is performed in a continuous manner with no extended holding times.

P.3.5 Process validation and /or evaluation

Formal PV is not required at early stages (Phase I/II) however aseptic PV is required. Validation before FiH trial shall comprise a full process for DP with process simulated in stages – 3 broth fills according to GMP Annex 1. Depending on how the DS and DP are defined, the PV can also be described in S.2.5.

For non-standard sterilisation processes not described in the Ph. Eur. and for non-standard manufacturing processes (refer to current EU guidance), the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described. Processes to ensure sterility shall be covered, e.g. describing filter validation and media fill trials of aseptic processes. However, it is not necessary to present the actual data. State, for example: "the aseptic filling process has been validated by media fill to simulate worst-case production conditions"

In addition, evidence should be provided to support consistencet production, i.e. prior development runs for process optimisation included to support evidence of consistency. This is typically done by presenting batch data in P.5.4. However, in the case of reduced release testing, e.g. due to limited stability of the product more detail should be presented here, e.g. a rationale for critical steps (those with a potential impact on safety of the product) and description of appropriate controls to ensure consistent quality. Reconstitution activities can be performed at the administration site. This covers activities required after batch release and prior to the administration of the ATMP to the patient, and which cannot be considered as manufacturing steps, e.g. thawing or mixing with other substances added for the purposes of administration (including matrices). The reconstitution process has to be qualified and needs to be described.

P.4 Control of excipients

Generally, excipients for ATMP are Ph. Eur. or injectable grade (i.e. SmPC) and all required data are found in the monographs. For excipients not covered by any Ph. Eur. an in-house specification should be provided. For excipient(s) used for the first time, reference is made to part I, Annex I of Directive 2001/83/EC and at minimum the quality, manufacturing and safety requirements should be addressed.

P.4.1 Specification

Injectable grade materials (or highest grade available of the materials) are expected, especially for human serum albumin (HSA) to ensure the excipients are appropriate for injection.

P.4.2 Analytical procedures

All excipients are approved for GMP production according to Ph. Eur. If not provided, describe the rationale, and process to ensure quality under 2.P.4.3-4.

P.4.3 Validation of the analytical procedures

Not applicable, if Ph. Eur. materials. If not, explanation on qualification to show suitability of use.

P.4.4 Justification of specification

Not applicable, since all excipient are approved according to Ph. Eur. Not all excipients are Ph. Eur compliant. For non-compendial excipients, the in-house specifications should be justified.

Care with e.g. DMSO if product not washed

P.4.5 Excipients of human origin

If applicable, describe the excipient of human origin, i.e human albumin or any other plasma derived medicinal product. information should be provided in line with Chapter 10 of the *Guideline on Plasma-Derived Medicinal Products* HSA. Detailed control of adventitious agents should be described in Appendix A.2.

P.4.6 Novel excipients

If applicable, describe the novel excipient. For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation and controls, with cross references to supporting safety data (non-clinical and/or clinical), should be provided according to the active substance format

P.5 Control of Investigational Medicinal Drug Product

P.5.1Specifications

Specification for a Phase I are usually less strict compare to the late phase. In the late phase, more clinical data is available to justify more strict specification (listed in a table).

The assay demonstrating the biological activity should be based on the intended biological effect which should ideally be related to the clinical response. Moreover, potency is the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties.

It is important to be aware of possibly potency issue for ATMP, such as

- Assay qualitative instead of quantitative
- Mechanism of action unknown (consequence: e.g. no surrogate markers available)
    - Surrogate markers etc. are not appropriate read-out for biological activity
    - Reference standard can be difficult to obtain
    - Inherent variability of reference standard unknown, i.e. comparison to fresh cells
- Not up-to-date with most recent scientific knowledge
- Assay does not reflect all relevant biological properties
    - Assay is not specific enough (effect may also be caused by impurities). If possible, develop a specific potency assay as early in clinical development as possible to ensure ability to compare manufacturing changes over time and to assess clinical trial results from pre-clinical through Phase III. For ATMPs with a short shelf life, i.e. not cryopreserved, it is important to note any tests that will be available after or close to the time of the treatment.

Generally, consider the following:

- The analytical methods and the limits for content and bioactivity should aim to ensure a correct dosing. Upper limits, taking safety considerations into account, should be set for the impurities.
    - In some specific cases (for example due to the short shelf-life), it may be needed to release the drug product batch prior to all results of specification testing are available. This approach needs to be justified and supported by performed risk analysis.
- Discuss and justify the testing strategy if this differs between DS and DP, i.e. if testing is only performed on DS due to lack of volume to test DP
- Clearly identify test substrates and reference standards – fresh product, frozen then thawed, medium / rinse solution, ATMP produced for pharm/tox study
- Identify results available prior to administration
- Describe level of control / consistency expected from the process to justify not testing DP

- Describe release and QP certification process
- Briefly describe of procedure in the event of OOS results post-administration (detail in protocol)
- Phase II/III – review limits critically vs batch data as experience increases

P.5.2 Analytical procedures

This section describes the analytical methods employed for DP. For some complex or innovative methods, a higher level of detail may be required. Describe the method, sampling procedure and acceptance criteria.
Example of analytic procedures: potency assay and dose.

P.5.3 Validation of analytical procedures

State the different analytical procedures for the product:

- Phase I/IIa – evidence of method suitability. Sterility and microbial assays should be validated from FIH and exploratory clinical trials (as stated in the GMP for ATMPs)
- Phase III – full analytical validation
- Summarise validation approach
- Results
- Statement of validation status. The requirements for the DS validation of analytical methods, see section S4.3.

P.5.4 Batch analysis

As for the DS, there is no formal requirement for full validation but appropriate monitoring and control measures should be implemented to ensure compliance with the requirements in the clinical trial authorisation. Additionally, it is expected that the aseptic processes have been validated. However, it is important to know the product and the process.

When validation batches have been completed in the GMP facilities that meets the requirements outlined in the specification, that should be presented in:

- Tabulation of results as for DS results
- Clear identification what has been tested – product, medium etc.

Batch	*Sterility In process*	*Sterility*	*Myco-plasma on DS*	*Endotoxins*	*Cell count (10^6)*	*Viability*	*CDX*	*CDY*	*Karyotype on DS*
Specification	*ND*	*ND*	*ND*						
#001	*ND*	*ND*	*ND*						
#002	*ND*	*ND*	*ND*						
#003	*ND*	*ND*	*ND*						

Table P.5.4.a. An example of impurities in culture medium. All results except 'Sterility in process' are results from the finished product after filling. ND not detected.

P.5.5 Characterisation of impurities

Describe the possible impurities and characterize for DP. Describe the expected amount of impurity in the product based on the amount in the process and purification steps or the DP. An example of an impurity could be media supplements.

P.5.6 Justification of specification (release criteria)

Describe the release criteria for the product. It is important to note and justify tests results that will not be available at the time of release/transplant and/or testing that is performed on representative/ auxiliary samples (formulation buffer, DS, pre-fill of the container/closure, etc).

P.6 Reference standards or materials

Describe the references material saved.
Sometimes, depending on the DP no reference standard is available for example for fresh DP. A sample of the product can be stored frozen as a reference, but it will not be identical to the DP.

P.7 Container Closure System

Describe the container closure system for the product. If the container closure is not a CE-marked medical device, then include testing information to ensure it meets pharmacopeia standards for safety, i.e. biocompatibility.

P.8 Stability, storage conditions, transport and logging

Progressive requirements will need to be applied to reflect the amount of available data and emerging knowledge about the stability of the drug product during the different phases of clinical development. The same requirements as for the active substance are applied to the medicinal product, including the stability protocol, stability results, shelf-life determination, including extension of shelf-life beyond the period covered by real-time stability data and stability commitment. For preparations intended for use after reconstitution, dilution or mixing, a maximum shelf life needs to be defined and supported by in-use stability data.

For Phase III, the applicant should have a comprehensive understanding of the stability profile.
Describe the process for logging the product from manufacture to clinical site.

P.8.1 Protocol and methods, results, shelf life

Describe the process for verifying the stability of the DP against the specifications, including the functional criteria to justify the shelf life. For a frozen product, the thawing and recovery methods should be standardized. For a fresh DP it is important to take transportation into account and also consider the worst case scenario.

3. Appendices

3.A.2 Adventitious agents safety evaluation

All biological material of human or animal origin used in the manufacturing process, or such materials coming into contact with the active substance/ drug product should be identified as they have potential capacity to be contaminated with adventitious agents. Therefore, information assessing the risk with respect to potential contamination with adventitious agents of human or animal origin should be provided in this section. The overall risk with each material is related to its biological source, traceability (e.g. culturing history) and the relevance of testing being performed or risk minimisation strategies applied during procurement of materials

The contamination of a medicinal product could originate from raw materials, starting materials or being unintentionally introduced during manufacturing process.

TSE
The risk for agents Transmissible Spongiform Encephalopathy (TSE) should be evaluated. As such these agents cannot be tested for, thus, evaluation of TSE risks relies on the traceability as well as certification of materials used. Further information on required documentation is provide in Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01).

3.A.1.1 Non-viral adventitious agents

Describe the process to control the non-viral adventitious agents: mycoplasma testing, sterility testing**.** Contamination by bacteria and/or fungal contamination is usually considered the most likely type of contamination. Controlling the absence of bacterial or fungal contamination should be monitored throughout the process, starting with the starting material and several in-process control before testing the DP.

In cases where the short shelf life of your product does not allow for the full testing of sterility (e.g. Ph.Eur. 2.6.1), alternative validated testing methods (as in Ph.Eur 2.6.27) are recommended.

3.A.1.2 Viral adventitious agents

Describe the process for controlling the viral adventitious agents. As for contamination of viral adventitious agents, the most likely source of contamination is the starting material and the risk of introducing viruses anywhere in the manufacturing process is in comparison limited. Qualification of the starting material therefore includes extensive testing for the absence of various viruses. Risk assessment should be performed according to Ph.Eur 5.1.7. General Text on Viral Safety. The documentation should also follow, when applicable, the requirements outlined in the Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products.

The risk assessment takes into consideration relevant factors. As example the following factors are of relevance:

- Species of origin;
- The organ, tissue, fluid of origin;
- The potential contaminants in view of the origin of the raw material and the history of the donor(s), preferably including epidemiological data;
- The potential contaminants from the manufacturing process (for example, from risk materials used during manufacture);
- The infectivity and pathogenicity of the potential contaminants for the intended recipients of the medicinal product, taking account of the route of administration of the medicinal product;
- The amount of material used to produce a dose of medicinal product;
- Controls carried out on the donor(s), on the raw material, during production and on the final product;
- The manufacturing process of the product and its capacity to remove and/or inactivate viruses.

The risk assessment can be based mainly on the manufacturing conditions if these include rigorous inactivation steps (for example, for gelatin etc., and products terminally sterilised by steam or dry heat

4. Substantial amendments

Usually not applicable in early phase.