Federal agency for medicines and health products

Hospital Exemption for Advanced Therapy Medicinal Products

Administrative and scientific guidance for initial applications and applications for substantial modification

Federal agency for medicines and health products
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GENERAL

The present document provides guidance to applicants regarding the applications for Hospital Exemption (initial applications or applications for substantial modification).

Part I (administrative guidance) deals with procedural and technical aspects of the submission.

Part II (content of the dossier and scientific guidance) describes the structure of the application file and provides scientific guidance on its content.

Relevant guidelines are listed at the end of the document.

PART I: ADMINISTRATIVE GUIDANCE

1) Application procedure

The timelines of the procedure, as described in art. 8, 9 and 10 of the RD of 08.01.2017, are outlined below:

Validation phase:

After receipt of the application dossier, the FAMHP will contact the applicant by email within 20 calendar days, to confirm the admissibility and completeness of the application. If the application is not complete, this is notified to the applicant (invalidation notification), who will have to submit the missing items within 20 calendar days. After receipt of the missing items, the FAHMP will decide on the admissibility and completeness of the application within 20 calendar days.

Assessment phase:

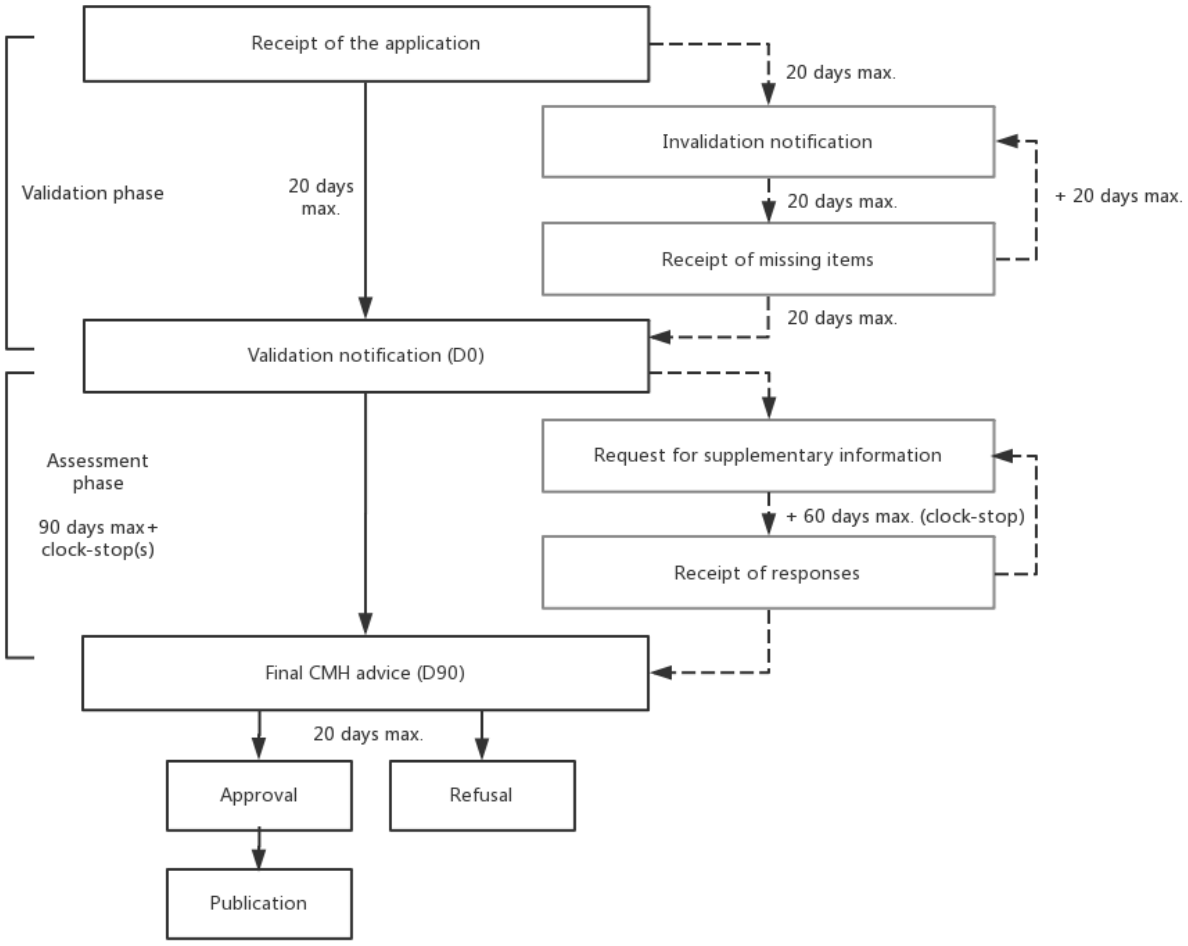
After confirmation of the admissibility of the application (Day 0 – validation notification), the Committee for Medicines for Human use (CMH) will issue an advice within 90 calendar days. This 90-day delay can be suspended, 60 days at most within each clock-stop, to allow the applicant to answer the request(s) for supplementary information issued by the CMH.

In practice, a maximum of 2 "rounds" of questions and answers is foreseen.

Final decision and publication:

Once the CMH issues a final advice (by Day 90), the Hospital Exemption will be refused or granted within 20 calendar days: an approval or a refusal letter will be sent to the applicant.

In case of approval, the decision (including the informed consent form template, see part II) will be published through the agency's website.



2) Submission of an application for Hospital Exemption for Advanced Therapy Medicinal Products

Prior to submission, please contact atmp@fagg-afmps.be: a procedure number will be allocated, which should be used for all subsequent communication.

The initial application should preferentially be submitted by electronic means, either:

- through CESP (Common European Submission Portal): https://cespportal.hma.eu/Account/Login (no maximum upload size),
- through EudraLink to atmp@fagg-afmps.be: you can request access to this service to EMA* at https://servicedesk.ema.europa.eu/ (no maximum package size)
- or as Zip (compressed) files by email to atmp@fagg-afmps.be (attachment size should not exceed 16MB).

*you will be asked to provide information on a "referee person" from the Member State's Agency: you can mention the name and contact details of the dossier manager in charge of your future application. If not yet known, please contact atmp@fagg-afmps.be.

Alternatively, the initial application can be submitted by registered mail, or delivered personally against a receipt, to the following address :

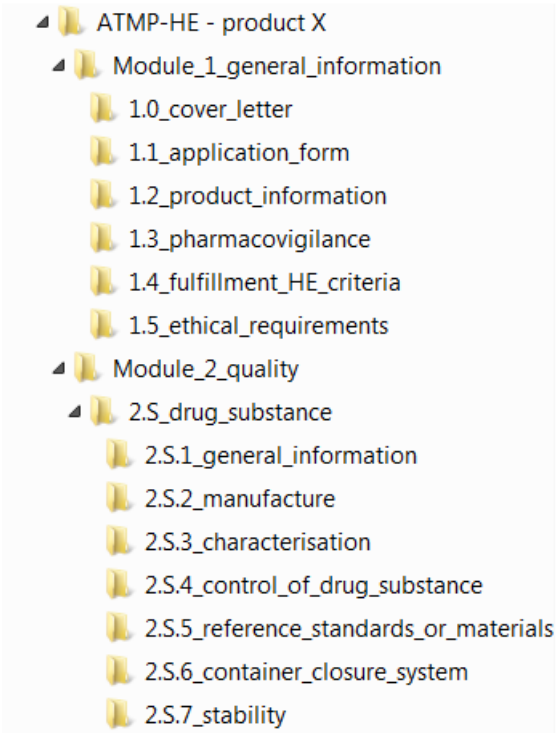
FAGG-AFMPS
DG Pre - Division Marketing Authorisation
Place V. Hortaplein 40/40
1060 Bruxelles/Brussel

In the latter case, a CD/DVD or other suitable electronic carrier (e.g. USB key) is expected, together with a paper cover letter.

Subsequent submissions (responses to invalidation notification or responses to request for supplementary information) can be sent through the same channels.

3) Format and structure of the dossier

The submitted documents should preferably be provided in pdf format, within folders organised according to the following tree view:



etc…

NB: in case of an application for a substantial modification, only the relevant sections should be provided, indicating the changes that have been made.

4) GMP certification

At the time of the submission of the application for hospital exemption, the certificate of good manufacturing practices for the preparation of advanced therapy medicinal products is not mandatory, however the holder of the Hospital Exemption should have a certificate available before starting the preparation of the ATMP (Art. 14. §1. 1° of RD of 08.01.2017).

The necessary measures should be undertaken simultaneously to the application for hospital exemption: please take contact with the DG Inspection (olivier.pauwels@fagg-afmps.be).

PART II: CONTENT OF THE DOSSIER AND SCIENTIFIC GUIDANCE

The content of the application dossier is described in art. 7 of RD of 08.01.2017 and is detailed in the following sections:

MODULE 1: GENERAL INFORMATION

1.0. Cover letter

1.1. Application form

[Please fill in the document "APPLICATION FORM FOR HOSPITAL EXEMPTION FOR ADVANCED THERAPY MEDICINAL PRODUCTS" and include it as Module 1.1 of the dossier]

1.2. Product information

1.2.1. Summary of product characteristics

[The Summary of Products Characteristics (SmPC) should follow the Annex II to Regulation (EC) No 1394/2007 of the European Parliament and of the council of 13 November 2007 on advanced therapy medicinal products.

Link: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf

If some sections do not apply, the absence of data should be justified.

The words « Marketing authorisation holder » should be read as meaning « holder of the hospital exemption authorisation ».

1. Name of the medicinal product.

2. Composition of the product:

2.1. General description of the product, if necessary with explanatory drawings and pictures,

2.2. Qualitative and quantitative composition in terms of the active substances and other constituents of the product, knowledge of which is essential for proper use, administration or implantation of the product. Where the product contains cells or tissues, a detailed description of these cells or tissues and of their specific origin, including the species of animal in cases of non-human origin, shall be provided,

For a list of excipients, see point 6.1.

3. Pharmaceutical form.

4. Clinical particulars:

4.1. Therapeutic indications,

4.2. Posology and detailed instructions for use, application, implantation or administration for adults and, where necessary, for children or other special populations, if necessary with explanatory drawings and pictures,

4.3. Contra-indications,

4.4. Special warnings and precautions for use, including any special precautions to be taken by persons handling such products and administering them to or implanting them in patients, together with any precautions to be taken by the patient,

4.5. Interaction with other medicinal products and other forms of interactions,

4.6. Use during pregnancy and lactation,

4.7. Effects on ability to drive and to use machines,

4.8. Undesirable effects,

4.9. Overdose (symptoms, emergency procedures).

5. Pharmacological properties:

5.1. Pharmacodynamic properties,

5.2. Pharmacokinetic properties,

5.3. Preclinical safety data.

6. Quality particulars:

6.1. List of excipients, including preservative systems,

6.2. Incompatibilities,

6.3. Shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,

6.4. Special precautions for storage,

6.5. Nature and contents of container and special equipment for use, administration or implantation, if necessary with explanatory drawings and pictures,

6.6. Special precautions and instructions for handling and disposal of a used advanced therapy medicinal product or waste materials derived from such product, if appropriate and, if necessary, with explanatory drawings and pictures.

7. Marketing authorisation holder.

8. Marketing authorisation number(s).

9. Date of the first authorisation or renewal of the authorisation.

10. Date of revision of the text.

1.2.2. Labelling of outer/immediate packaging

[The labelling should follow the Annex III to Regulation (EC) No 1394/2007 of the European Parliament and of the council of 13 November 2007 on advanced therapy medicinal products.

Link: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf

If some sections do not apply, the absence of data should be justified.

The words « Marketing authorisation holder » should be read as meaning « holder of the hospital exemption authorisation ».]

(a) The name of the medicinal product and, if appropriate, an indication of whether it is intended for babies, children or adults; the international non-proprietary name (INN) shall be included, or, if the product has no INN, the common name;

(b) A description of the active substance(s) expressed qualitatively and quantitatively, including, where the product contains cells or tissues, the statement 'This product contains cells of human/animal [as appropriate] origin' together with a short description of these

cells or tissues and of their specific origin, including the species of animal in cases of nonhuman origin;

(c) The pharmaceutical form and, if applicable, the contents by weight, by volume or by number of doses of the product;

(d) A list of excipients, including preservative systems;

(e) The method of use, application, administration or implantation and, if necessary, the route of administration. If applicable, space shall be provided for the prescribed dose to be indicated;

(f) A special warning that the medicinal product must be stored out of the reach and sight of children;

(g) Any special warning necessary for the particular medicinal product;

(h) The expiry date in clear terms (month and year; and day if applicable);

(i) Special storage precautions, if any;

(j) Specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place;

(k) The name and address of the marketing authorisation holder and, where applicable, the name of the representative appointed by the holder to represent him;

(l) Marketing authorisation number(s);

(m) The manufacturer's batch number and the unique donation and product codes referred to in Article 8(2) of Directive 2004/23/EC;

(n) In the case of advanced therapy medicinal products for autologous use, the unique patient identifier and the statement 'For autologous use only'.

1.3. Pharmacovigilance

1.3.1. Summary of the Pharmacovigilance System Master File (PSMF)

[The Applicant of an hospital exemption should implement a Pharmacovigilance system to collect efficacy and safety data related to the innovative therapy. This information should be gathered in the Pharmacovigilance System Master File which should follow the recommendations outlined in the last update of the "Guideline on good pharmacovigilance practice (GVP) Module II – Pharmacovigilance System Master File" available on the EMA website at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp. In line with the recommendation outlined in this document, a "Summary of the Pharmacovigilance system" should be submitted with the application for an hospital exemption.]

1.3.2. Risk Management Plan

[When an innovative therapy involves significant safety concerns, the Applicant of the hospital exemption should identify and characterize the risks that are associated with the preparation and the administration of the innovative therapy. The information outlined in this section should be structured in accordance with the recommendations described in the "Guideline on safety and efficacy follow-up-risk management of advanced therapy medicinal products" (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006326.pdf), exception made of the considerations regarding Detailed Description of the Pharmacovigilance System (DDPS) that are presently obsolete following the Directive 2010/84/EU. Missing information regarding the use of the innovative therapy in specific populations and all measures to prevent or minimize the risks should be discussed as well. In this respect, the need for additional educational material for healthcare professionals/patients should be examined.

As outlined in the Royal decree of 8.01.2017, the Holder of a hospital exemption for an innovative therapy will implement a Registry to collect cumulative data for each patient exposed to the innovative therapy during 30 years. Details regarding the measures and means used to collect the Registry data should also be included in this section, and comply with the "Guideline on good pharmacovigilance practice (GVP) Module VIII – Post authorisations safety studies" available on the EMA website at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp.]

1.4. Fulfilment of Hospital Exemption criteria

[In this section, the applicant is invited to explain why the product falls under the scope of the Hospital Exemption, especially regarding the non-routine basis of the preparation (expected number of treated patients per year, production frequency…). Please refer to Art. 5. and Art. 6. of RD of 08.01.2017 for the detailed criteria.]

1.5. Ethical requirements

1.5.1. Positive opinion of the consulted ethics committee

[Please provide in this section the positive opinion obtained from a fully recognised ethics committee as referred in the law of 7 May 2004 on experiments on the human person, regarding the use, in the proposed indication, of a medicine for which a marketing authorisation is not required.]

1.5.2. Informed consent form

[Please provide in this section a template of the informed consent form, approved by the ethics committee, containing at least the nature, the scope, the purpose, the consequences, the expected benefits and the risks of the treatment.

Please note that this document will be made publicly available through the FAMHP website once the hospital exemption will be granted. As such, the informed consent form will have to be available in NL and FR at the end of the procedure.]

MODULE 2: QUALITY DATA REQUIREMENTS

2.S DRUG SUBSTANCE

2.S.1 General information

2.S.1.1 Nomenclature

Information on the nomenclature of the drug substance must be given, if any:

- trade name
- proposed INN-name (international non-proprietary name)
- description
- descriptive name :

- cell-based active ingredients: information on the cell type and its origin [Human (autologous/allogeneic) and xenogeneic (directive 2001/83, part IV; 2]
- In vivo gene therapy: name and origin of the therapeutic gene and/or the vector used.
- ex vivo gene therapy: information on the in vitro genetically modified cells including the DNA or RNA starting materials
  - Short description
  - Firm or lab code

2.S.1.2 Structure

A summarised description of the biological and physiochemical properties of the active substance is to be given in this section.

For cell-based therapy:

Brief description of the physical and biological characteristics of the substance (e.g. origin, phenotype, specific cell markers), including a description of any other materials such as bioactive molecules (e.g. growth factors, etc.) and/or structural components (e.g. scaffolds, medical devices, etc.), when these are an integral part of the active substance. The purpose of adding these other materials should be explained.

For gene therapy:

Brief description and schematic representation of the major functional genetic elements of the vector that will be transferred (e.g. transgene, regulatory *Cis*-elements, vector sequences and selection markers).

Detailed information on the vector used and the complete sequence of the gene and the vector to be transferred should be listed under 2.S.3.1.

2.S.1.3 General Properties

The biological activity and properties of the drug substance, relevant for the intended clinical use, are to be described here including the proposed mechanism of action. Further information is given in 2.S.3.1.

For cell-based therapy:

A short description of the composition, biological properties, and where appropriate, the physicochemical and other relevant properties of the drug substance should be provided. A description of the biological activity (potency) of the cells, should also be included.

For gene therapy:
For viral vectors and where appropriate, information on particle number, titer and tropism, as well as the tissue-specificity and strength of transgene expression should be provided.

2.S.2 Manufacture

2.S.2.1 Manufacturer(s)
The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site or facility involved in manufacture, testing, and batch release should be provided.

2.S.2.2 Description of Manufacturing Process and Process Controls
A summarised description of the manufacturing process and process controls needs to be submitted.
A flow-chart of the entire process covering all stages of the process, including the extraction of cells, tissues or biological fluids or the use of cell banks, as well as information on starting materials, intermediates (e.g. intermediate cell batches), and reagents should be provided. Any process control carried out should be indicated, together with the step where it is performed including appropriate acceptance criteria.

Critical process steps are described in detail in 2.S.2.4. When Matrixes/devices/scaffolds or medical devices are used during the manufacture of the drug substance, the corresponding production step must be specified. When such a product is used during the production of the final drug, a cross reference shall be made to the medicinal product manufacturing section.

Raw materials that have been added during the process should be identified and, where applicable, a statement on the elimination of these raw materials should be added.

Information on the scale of production should be provided. If the batch size of the substance cannot be defined, information on the amount of starting material needed to produce a certain amount of substance has to be provided.

2.S.2.3 Control of Materials
Materials used in the manufacture of the substance (e.g. raw materials, starting materials, reagents) should be listed and information on the source, quality and control of these materials shall be provided.

A listing of impurities (e.g. residual bovine serum, feeder cells, other cell populations not for the intended action, dead cells, etc.) should be included.

Primary cells and tissues
The specific quality and safety requirements for donation, procurement and testing, laid down in Directives 2004/23/EC and 2006/17/EC10, and the traceability system as required by Regulation (EC) No 1394/2007 should be considered. In conjunction with this, the applicant is requested to read the guideline on Human Cell-based Medicinal Products (EMEA/CHMP/410869/2006).

Cell banking systems

Information on the source, history, establishment and characterisation/qualification of the cell bank systems that are used, including information about all raw and starting materials and other adjuvant used during establishment should be provided.

The phenotypic and genotypic characterisation should also be documented, especially with regard to the identity, viability and purity. In addition, documentation for safety evaluation of biological agents (control of bacteria, fungi, mycoplasma, viruses, endotoxins) is required. The tests conducted for the characterisation and the release, including specifications, can be tabulated. The analysis of the tumorigenic potential should also be performed.

Virus banks

Data on virus identity, titer, purity, nucleotide sequence of the genetic material to be transferred is required. The presence of replicative competent viruses should be excluded. In addition to these requirements, documentation of the safety evaluation (control of bacteria, fungi, mycoplasma, viruses, endotoxins) is required. The tests conducted to characterise and release the seed banks, including specifications, can be tabulated.

Bacterial cell banks

Information on viability, identity (possibly by biochemical or physiological parameters), genotyping/phenotyping, and verification of the plasmid structure (e.g. by restriction analysis) are required. Tests for adventitious agents and endogenous viruses should be carried out.

Other starting materials

All the raw materials used in the production process are to be listed in tabular form. Information on their quality (eg EP, USP, JP) should be provided. If pharmacopoeia quality is not available, the applicant should demonstrate their suitability and qualification for the manufacture of the drug substance. For starting materials of human and/or animal origin, details of their origin and safety with regard to contamination by foreign substances (e.g. mycoplasma, bacteria, TSE-risk virus safety) are required.

2.S.2.4 Control of Critical Steps and Intermediates

Tests and acceptance criteria for in-process control of critical manufacturing steps and the specifications of intermediate products should be briefly summarised. If holding times are foreseen for process intermediates, periods and storage conditions should be justified and supported by data on physicochemical and biological characteristics/properties.

2.S.2.5 Process Validation and/or Evaluation

Data on process validation should normally be collected throughout the development by the applicant although they are not required to be submitted in the HE dossier. However the applicant should provide evidence that the process is reproducible and that the quality of the active substance is consistent from batch to batch.

2.S.2.6. Manufacturing Process Development

This section should be documented if the manufacturing process significantly differs from that used for the production of the batches used previously during non-clinical studies, during administration into humans during authorized clinical trials or during transitional period. It should contain summarised information on the historical development of the manufacturing process.

Major changes to the manufacturing process should be described and justified. The impact of the respective changes in the manufacturing process on the efficacy and/or safety of the drug product should be investigated.

2.S.3 Characterisation

2.S.3.1 Elucidation of Structure and other Characteristics

Characterisation of the drug substance (i.e. adequate description of the active substance) by appropriate techniques is necessary to allow relevant specifications to be established. Reference to the literature data only is not acceptable.

For cell-based therapy:

A description of the active cellular substance and possibly other non-cellular components is necessary. It should encompass all the components in the product (e.g. scaffolds, matrices, bio-materials, bio-molecules or other components), if applicable.

Adequate Cell characterisation including in particular identity, purity and impurities, viability and biological activity testing are necessary and should be performed. For purity, tests should be applied to provide information on product and process related impurities including microbial (bacterial and fungal) and adventitious viral safety. Depending on the manufacturing process, when differentiation, activation and/or ex vivo expansion are taking place, data demonstrating the genetic stability of cells is required.

For gene therapy:

Detailed information on the structure and properties of the gene transfer vector, including the gene of interest, the regulatory sequences, the packaging signals, the selection marker and the vector backbone should be made available (i.e. in the form of a schematic representation of the individual genetic elements). In addition, a brief description of the intended function of the transferred genes(s) is to be given.

If a replication-incompetent vector is used, analysis that excludes the presence of replication-competent viruses is to be presented. Moreover, if genetically modified cells are used, data demonstrating the genetic stability of cells following transgene integration is required.

2.S.3.2 Impurities

Details and specifications of process-related impurities (e.g. serum, medium components, growth factors, antibiotics) and product-related impurities of cellular origin (e.g. unwanted cell types and non-viable cells) are required and should be discussed in the light of their risk that is related to the clinical dose. Product related impurities of non-cellular origin (e.g.

degradation products from structural components) identified should be characterized and their impact on the cellular components should be addressed.

2.S.4 Control of the Drug Substance

2.S.4.1 Specification(s)

The specifications that define the acceptance criteria for the drug substance's batches to be used during hospital exemption procedure together with the used test to exert sufficient control of the quality of the active substance are required and should be provided. Quality attributes including quantity, identity, purity and impurities and biological activity are mandatory; unless otherwise justified. Upper limits for contaminants need to be set, taking safety considerations into account. In addition, the microbiological quality of the active substance should be specified.

2.S.4.2 Analytical Procedures

A brief description of the analytical methods used for the testing of the drug substance should be given. It is not necessary to provide a detailed description of all the analytical procedure, but the documentation should include principle of the method, reagents, assay controls and test procedures for each of the assay used.

Analyses that are carried out in accordance with European or other monographs (USP, JP) can be referenced and will be acceptable. Additional tests that are performed for information gathering only (FIO) should be also disclosed.

2.S.4.3 Validation of Analytical Procedures

In this section the suitability or the qualification of the analytical method used should be presented. If available, validation data (e.g. validation parameters and acceptance limits) should be submitted and listed in tabular form.

For GTMP: For assays that are used to detect replication-competent viruses potentially present, at least data on detection and determination limit should be presented.

2.S.4.4 Batch Analyses

The focus of this section is to demonstrate the quality of the batches (i.e. conformance to established specifications) to be used during the HE procedure. Data on all the products manufactured with the current process should be presented in tabular form including, where applicable, the batch number, batch size, manufacturing site, manufacturing date, test methods, acceptance criteria and the test results.

It could be acceptable to have a limited number of representative batches, if manufactured using the equipment and methodology described in 2.S.2.2 and appropriately justified. Drug substance batches produced with a different manufacturing process and possibly used in non-clinical studies and/or used to treat patients outside a formal clinical trial during transitional period could be used as supporting data, if relevant.

2.S.4.5 Justification of Specification(s)

A justification for the quality attributes included in the specification and the acceptance criteria should be provided.

Any changes to previously defined specifications (e.g. addition or removal of parameters, widening of acceptance criteria) should be indicated and justified.

2.S.5 Reference Standards or Materials

Where applicable, reference can be made to reference materials or "in-house" standards. For "in-house" standards, information on preparation, characterisation and analytical methods is required.

2.S.6 Container Closure System

This contains a description of the immediate packaging material that is used for the drug substance.

2.S.7 Stability

If the drug substance is not immediately used, information on storage times and conditions should be provided and justified. The stability of the active ingredient for the storage period and storage conditions must be supported on the basis of product-specific parameters. Stability data should be presented for representative batch(s) of the manufacturing process of the active substance under the HE procedure.

The claimed shelf life of the active substance under the proposed storage conditions should be stated and accompanied by an evaluation of the available data that can be presented in tabular form. Any observed trends should be discussed.

2.P DRUG PRODUCT

2.P.1 Description and Composition of the Medicinal Product

This section details the dosage form and the qualitative and quantitative composition of the finished medicinal product. Identity, cell number and viability purity and biological activity/potency should be provided. In addition, details of the excipients (e.g. name, concentration, properties, function) and their impact on the medicinal product in terms of function and effectiveness need to be provided and discussed.

For combined-ATMP, the choice and the suitability of the medical device for the intended use should be justified.

2.P.2 Pharmaceutical Development

This section will describe any relevant information on the current pharmaceutical development, unless they are described in 2.S.2.6.

A short description of formulation development, including justification of any new pharmaceutical form or excipient, should be provided.

For products requiring additional preparation of the finished product, the compatibility with the used materials (e.g. matrix/scaffold/device, medical device, solvents, diluents) should be demonstrated and the method of preparation should be summarised.

2.P.3 Manufacturing Process Development

Any changes in the manufacturing process including changes in formulation and dosage form compared to previous experience with the medicinal product during or outside a formal clinical trial should be described.

2.P.4 Manufacture

2.P.4.1 Manufacturer(s)

The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site or facility involved in manufacture, testing, and batch release of the medicinal product should be provided. In case of multiple manufacturers contributing to the manufacture of the finished medicinal product, their respective responsibilities need to be clearly stated.

2.P.4.2 Batch Formula

Where applicable, information on how a batch is defined is given, specifying the various components and a designation of the range within which the batch size varies.

2.P.4.3 Description of Manufacturing Process and Process Controls

In case the manufacturing process of the active substance and the finished product are similar, information on the manufacturing process should be included in the relevant section for the active substance (i.e. section 2.S.2.2) and a cross reference to this section

should be made for the finished product. In addition, a flow chart and a summarised description of the manufacturing process detailing the individual successive production steps including in-process controls and the components used for each step should be provided.

Where a component such as a matrix/scaffold or medical device is added to the substance, this step should be identified.

For all ATMPs, the strategy for ensuring the microbiological quality of the product should be described in detail in Section 2.A.2

2.P.4.4 Controls of Critical Steps and Intermediates

In case of critical steps in the manufacture, their identification and strategies for their control should be briefly summarised.

If holding time is foreseen, storage time and conditions, if relevant, should be provided and justified by data in terms of physicochemical, biological and microbiological properties.

2.P.4.5 Process Validation and/or Evaluation

If different from 2.S.2.5, information on process validation may be provided but are not required.

2.P.5 Control of Excipients

2.P.5.1 Specifications

References to the Ph. Eur., the pharmacopoeia of an EU Member State, United States Pharmacopeia (USP) or Japanese Pharmacopeia (JP) should be indicated if applicable. For excipients not covered by any of the aforementioned standards, it is necessary to list the specifications and provide relevant certificates of analysis.

2.P.5.2 Analytical Procedures

In cases where reference to a pharmacopoeial monograph listed under 2.P.5.1 cannot be made, the analytical methods used to determine the specifications must be described briefly.

2.P.5.3 Validation of the Analytical Procedures

The suitability of the analytical method is briefly described. Available data for validation (validation parameters and acceptance limits) are to be listed in tabular form.

For GTMP: For assays that are used to detect replication-competent viruses potentially present, at least data for detection and quantitation limits should be presented.

2.P.5.4 Justification of Specifications

For excipients not covered by any of the aforementioned standards, the chosen specifications should be justified. If available, certificates from the manufacturer can be added as required under 2.P.5.1.

2.P.5.5 Excipients of Animal or Human Origin

A list of the concerned excipients should be provided. For their safety assessment, see section 2.A.2 APPENDICES.

2.P.5.6 Novel Excipients

For novel excipients, information on the manufacturing process, characterisation and control and product safety should be described. Where relevant, the interaction between the excipient and the cells/tissues should be discussed.

2.P.6 Control of the Medicinal Product

2.P.6.1 Specifications

The same principles are described for the active substance specification should be applied for the final product.

For GTMP: When replication-deficient viruses are used, a test to detect replication-competent viruses (RCV) has to be in place, if not already performed for the substance.

2.P.6.2 Analytical Procedures

The analytical procedures should be described for all tests included in the specification.

2.P.6.3 Validation of Analytical Procedures

At least the suitability or qualification of the analytical methods used should be addressed as described under 2.S.4.3.

2.P.6.4 Batch Analyses

Quality characteristics or certificates of analysis that are representative for the medicinal product are to be provided. If applicable, the batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.

2.P.6.5 Characterisation of Impurities

Additional impurities observed in the medicinal product, but not covered by section 2.S.3.2, should be identified and quantified as necessary.

2.P.6.6 Justification of Specification(s)

A justification for the quality attributes included in the drug product specification should be provided mainly based on the drug substance specifications as described under 2.S.4.1.

2.P.7 Reference Standards or Materials

If applicable, details of reference material standards should be provided. When "in-house" standards are used, information on preparation, characterisation and analytical methods are expected.

2.P.8 Container Closure System

Information on the immediate (i.e. primary) packaging material for the medicinal product should be provided. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If applicable, a CE mark for an additional medical device should be confirmed.

2.P.9 Stability

The same requirements as for the active substance are applied to the finished product. When applicable, the parameters known to be critical for the stability of the medicinal product need to be identified and summarised in a tabular format.

The presented data should justify the proposed shelf-life of the product from its release to its administration to patients.

2.A APPENDICES

2.A.1 Facilities and Equipment

A brief description of the facilities and equipment should be provided. Appropriate authorizations or certificates attesting that all institutions involved in the process have a valid permit authorizing the manufacture and/or testing should be provided.

2.A.2 Adventitious Agents Safety Evaluation

All materials of human or animal origin used in the manufacturing process of both substance and medicinal product (starting materials, excipients and reagents), or other materials coming into contact with substance or medicinal product during the manufacturing process, should be identified and their use at production should be described.

Control of bacteria, mycoplasma, fungi and parasites

Detailed information regarding adventitious agents, such as bacteria, mycoplasma, and fungi should be provided in appropriate sections within the application. This relevant information can also be provided in this section and the measures to minimize microbial contamination by proper sourcing/sampling of the starting material and raw materials should be addressed.

TSE safety

This section concern all starting and/or raw materials from animal species susceptible to present a TSE risk or related substances that came into contact with the with the active substance or the medicinal product during their manufacturing process. The note for guidance on minimizing the risk of Transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products [Official Journal of the European Union (2011/C 73/01) (EMA/410/01 rev.3)] in its current version is to be applied. This can be supported by an appropriate European Directorate for the Quality of Medicines (EDQM) certificate for TSE.

Viral Safety

Where applicable, information assessing the risk with respect to potential viral contamination should be provided in this section.

Testing of substances of biological origin

All biological raw materials or substances of biological origin coming into contact with the active substance or the medicinal product during their manufacturing process should be identified and their use at production should be described (including additives and auxiliary agents). The potential risk of introduction of viruses by these substances should be evaluated. For this purpose, the applicant is requested to fulfill, where applicable, the requirements as outlined in the Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products (EMEA/CHMP/BWP/398498/2005) and in the Note for Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal origin (CPMP/ICH/295/95).

Testing of donors and starting materials of biological origin

When using material from human blood or other human tissues, careful selection and testing of the donor should be described (see Section 2.S.2.3). When using materials from animal blood or tissues, the epidemiology of the geographical region, the animal husbandry, veterinary supervision and the specific testing of the animals or materials is to be described.

Studies on virus inactivation / removal

An effective method for reducing (inactivation or removal) of viruses (known and unknown) represents a major aspect of the safety of ATMP, and should therefore, wherever possible, be applied; unless otherwise justified. To assess the viral reduction processes, the applicant is requested to present study reports in accordance with the guideline CPMP/BWP/268/95.

2.A.3 Other information

This section should include all relevant information on medical devices in combined ATMP. In the case where a Notified Body has evaluated the device part, the result of this assessment shall be included in this section. Information on other structural components, bio-materials, scaffolds or matrices shall also be included in this section (see also Section 2.S.2.3).

2.R REFERENCES

MODULE 3: NON-CLINICAL DATA REQUIREMENTS

Non-clinical data submitted in an application for hospital exemption should be appropriate to contribute to the proof of concept/principle of the ATMP, and for a preliminary safety evaluation of the ATMP. The extent of non-clinical data to be submitted should be determined by a risk-based approach as defined in the Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products (EMA/CAT/CPWP/686637/2011) read in conjunction with the guidelines relevant to the product.

It is expected that non-clinical data are obtained with the product produced and tested as described in Module 3 which take into consideration the minimum requirements for Quality data. Batch analysis data for batches used in non-clinical studies should be provided. The safety and suitability of all structural components for their intended function must be demonstrated, taking into account their physical, mechanical, chemical and biological properties.

The required minimal set of non-clinical data is described below. Any deviation or lack of data should be scientifically justified.

3.1 Pharmacology

3.1.1. Proof of concept (Primary Pharmacodynamics)

The non-clinical pharmacodynamic "proof of concept/principle" including *in vitro* studies and if feasible, at least one study in a relevant *in vivo* animal model reflecting the intended clinical use. Relevance of the models should be discussed.

3.1.2. Safety pharmacology

Safety pharmacology should be considered on a case-by-case basis depending on the characteristics of the product.

3.2 Biodistribution (pharmacokinetics)

Biodistribution data (kinetics, migration and persistence) are normally essential to support the pharmacodynamics and the safety of ATMP (e.g. engineered stem cells, or genetically modified cells). Relevant data should be included in order to support the assessment of the concomitant NC data. These data could be derived from dedicated biodistribution studies or they could be generated through endpoint integration in other type of studies, e.g. "proof of concept" or toxicity studies. The absence of biodistribution data should be justified. On a case by case basis, risks of germinal transmission should be assessed in the biodistribution study.

3.3 Toxicology

Toxicology studies are expected to be of appropriate quality and reliability and to follow relevant guidelines where appropriate. They are not required to be GLP studies but are expected to be conducted in accordance to GLP principles and standards.

3.3.1. Single and repeated dose toxicity studies

Toxicity studies should be performed in relevant animal models. If the human cells are not immediately rejected, the studies may be combined with safety pharmacology, local tolerance, or proof of concept and efficacy studies. Sufficiently characterized analogous animal-derived cells may be used for some allogeneic CBMP when not immediately rejected.

The duration of observations in such studies might be much longer than in standard single dose studies, since the cells are supposed to function for long times, or induce long term effects, which should be reflected in the design of these studies. The route and dosing regimen should reflect the intended clinical use. Repeated dose toxicity studies are only relevant if the clinical use includes multiple dosings.

3.3.2. Local tolerance studies

Local tolerance studies may be required in an appropriate species. Most often, local tolerance, tissue compatibility and tolerance to excreted substances can be evaluated in single or repeated dose toxicity studies.

3.3.3. Other toxicity studies

The risk of inducing tumourigenesis due to neoplastic transformation of host cells and cells from the CBMP should be considered, as appropriate, on a case-by-case basis. Conventional carcinogenicity studies may not be feasible. Tumourigenesis studies should preferably be performed with cells that are at the limit of routine cell culturing or even beyond that limit. Tissues found to contain applied cells or expressed products during the biodistribution studies should also be analysed with special emphasis during tumourigenicity studies.

Genotoxicity studies are not considered necessary for human CBMP, unless the nature of any expressed product indicates an interaction directly with DNA or other chromosomal material.

The need for reproductive studies is dependent on the CBMP and should be considered on a case-by-case basis.

MODULE 4: CLINICAL DATA REQUIREMENTS

The clinical section should contain the following:

4.1. Rationale for the Hospital Exemption

A short description of the indication to be treated and the conditions of use should be provided.

Available treatments and ongoing clinical trials for the same indication in Belgium should be described.

The need for the hospital exemption with the advanced therapy medicinal product should be justified. Reasons why clinical trials cannot be initiated or applied with this particular treatment should be given.

4.2. Relevant clinical data on efficacy and safety (clinical trial data phase I-II-… and clinical experience outside clinical trials)

For advanced therapy medicinal products for which a hospital exemption application is considered, the available clinical data may be limited. The content of the supportive data package should be justified. All clinical experience with the product and the expected benefit for the patient should be discussed.

For products under development, preliminary safety data collected at least during phase I clinical trials are deemed necessary (of note: the hospital exemption cannot be granted if the same ATMP has not been previously administrated to humans).

Only exceptionally, the clinical data on efficacy may be based on the clinical experience with the product in a different therapeutic indication.

Clinical experience with similar products could also be described if considered relevant regarding efficacy and safety.

4.3. Relevant literature references

Relevant bibliography and clinical guidelines should be cited and provided to support the Applicant's claims about the usefulness and the safety of the product in the specified indication, or similar indications if considered relevant.

4.4. Discussion including benefit-risk analysis of the clinical data

The Applicant should justify that the proposed medicinal product is likely to have a clinical benefit for the patient.
Unresolved issues and uncertainties should also be discussed.

4.5. Overall benefit-risk discussion (including quality, nonclinical, and clinical data)

Within the overall benefit-risk discussion (including all available data: quality, nonclinical and clinical data), the Applicant should discuss the importance of the favourable and unfavourable observed effects, and the impact of the uncertainties and limitations associated with the available data on their translation into clinical practice.

4.6. Specific requirements for all advanced therapy medicinal products (Directive 2001/83/EC Module 5)

When the clinical application of advanced therapy medicinal products requires specific concomitant therapy and involves surgical procedures, the therapeutic procedure as a

whole shall be investigated and described. Information on the standardisation and optimisation of those procedures during clinical development shall be provided.

When medical devices used during the surgical procedures for application, implantation or administration of the advanced therapy medicinal product may have an impact on the efficacy or safety of the advanced therapy product, information on these devices shall be provided.

Specific expertise required to carry out the application, implantation, administration or follow-up activities shall be defined. When necessary, the training plan of health care professionals on the use, application, implantation or administration procedures of these products shall be provided.

4.7. Description of the monitoring plan of the safety and effectiveness

A plan for monitoring the safety and effectiveness of the product is highly recommended to be included in the Risk Management Plan (Cf. Module 1.3 – Pharmacovigilance).

RELEVANT GUIDELINES

Guidelines relevant for ATMPs can be found on EMA website at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000298.jsp&mid=WC0b01ac05800862bd

1. Cell and Tissue Engineered Products:

1.1. Overarching Guideline

Guideline on human cell-based medicinal products (Doc. Ref. EMEA/CHMP/410869/2006) Q NC C Adopted
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003894.pdf

Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products (EMA/CAT/CPWP/686637/2011)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139748.pdf

1.2. Multidisciplinary guidance pertaining to subgroups of cell-based products

Reflection paper on stem cell-based medicinal products (Doc. Ref. EMA/CAT/571134/2009) *Q NC C Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500101692.pdf

Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (Doc. Ref. EMA/CAT/ GTWP/671639/2008) *Q NC C Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500126836.pdf

Guideline on xenogeneic cell-based medicinal products (Doc. Ref. EMEA/CHMP/CPWP/83508/2009) *Q NC C Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500016936.pdf

1.3. Quality-specific guidance

Guidance on the Use of Bovine Serum in the Manufacture of Human Biological Medicinal Products (EMA/CHMP/BWP/457920/2012 rev 1) *Q Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500143930.pdf

Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01 Rev. 3) *Q Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf

CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products" (EMA/CHMP/CAT/BWP/353632/2010) *Q Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2011/06/WC500108069.pdf

Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006) *Q Adopted*.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003382.pdf

Potency testing of cell based immunotherapy medicinal products for the treatment of cancer (Doc. Ref. EMEA/CHMP/BWP/271475/2006) *Q Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003814.pdf

Guideline on the use of porcine trypsin used in the manufacture of human biological medicinal products (EMA/CHMP/BWP/814397/2011) *Q Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162147.pdf

2. Gene therapy medicinal products:

2.1. Overarching guideline:

Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products" (CPMP/BWP/3088/99) Q NC C Adopted
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003987.pdf

And its revision:
Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products - Draft (EMA/CAT/80183/2014)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/05/WC500187020.pdf

Questions and answers on gene therapy" (EMA/CHMP/GTWP/212377/2008) *Q NC Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500059111.pdf

Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products (EMA/CAT/CPWP/686637/2011)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139748.pdf

2.2. GMO/Environmental risk:

Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2006):
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003964.pdf

Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms (GMOs) (EMEA/CHMP/BWP/473191/2006-corr):
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003805.pdf

2.3. Gene therapy products with modified somatic cells:

Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (CHMP/GTWP/671639/2008) *Q NC C Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500126836.pdf

Live recombinant viral vectored vaccines (principles can be applied):
Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines (EMA/CHMP/VWP/141697/2009) *Q NC C Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC500094345.pdf

3. Viral safety related guidelines (for biological and biotechnological products):

Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP/BWP/268/95 or 3AB8A) *Q Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003684.pdf

ICH Topic Q5A: Note for guidance on quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin (CPMP/ICH/295/95) *Q Adopted*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002801.pdf