Regulation 19/12/2014
Rec. no. 002646/00.01.00/2014

5/2014

Regulation of the Finnish Medicines Agency Fimea

PREPARATION OF ADVANCED THERAPY MEDICINAL PRODUCTS (ATMP) FOR THE TREATMENT OF INDIVIDUAL PATIENTS (HOSPITAL EXEMPTION)

Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency
P.O. Box 55, 00034 FIMEA | Tel. 029 522 3341 | kirjaamo@fimea.fi | www.fimea.fi | Business ID 0921536-6

Authorising provisions

Medicines Act (395/1987), section 15 c, subsection 3, as amended by Act 773/2009

Target group

Units manufacturing advanced therapy medicinal products

Period of validity

This regulation will enter into force on 01/01/2015 and will remain in force until further notice.

Applicable EU legislation

Directive 2001/83/EC (3200IL0083) of the European parliament and of the Council, Official Journal L311, 28/11/2001, p. 67, as amended by the Regulation (EC) No 1394/2007 of the European Parliament and of the Council (32007R1394)
Official Journal L 324, 10/12/2007 p. 121.

CONTENTS

1 GENERAL

1.1 Purpose of the Administrative Regulation

This Administrative Regulation provides the more detailed regulations referred to in section 15c, subsection 3, of the Medicines Act concerning the non-industrial preparation of advanced therapy medicinal products referred to in Regulation No 1394/2007 of the European Parliament and of the Council (the so-called national ATMP manufacturing licence).

1.2 Applicability of the Administrative Regulation

This Administrative Regulation applies to any advanced therapy medicinal products (ATMPs), which are prepared on a non-routine basis according to special quality standards and used on prescription of a physician in a hospital located within the same Member State, under the exclusive professional responsibility of a medical practitioner for the individual hospital treatment of a single patient.

2 DEFINITIONS

In this regulation, the following terms shall have the following meanings:

1) ATMP – Advanced Therapy Medicinal Product
2) GMP – Good Manufacturing Practice
3) EMA – European Medicines Agency
4) TSE – Transmissible spongiform encephalopathy

3 REQUIREMENTS FOR PREPARATION AND USE

3.1 General requirements

The preparation of any advanced therapy medicinal product based on cell or gene therapy or tissue modification requires a licence by the Finnish Medicines Agency, hereinafter referred to as Fimea. The application for a licence must include the information stated in this regulation, and must be submitted by using the Fimea form attached to this regulation or other form contain the same information.

The granting of a licence to manufacture an ATMP requires that the quality and safety of medicines meet the requirements specified for the particular preparation. The preparation must conform to GMP when applicable. Procedures for monitoring adverse reactions and adverse incidents must be in place, and the materials used must be traceable.

The application must contain a risk assessment of the preparation, based on known risk factors (for example infections and infestations, immunogenicity, tumorigenicity, loss of cell function, replicable viruses contained in gene therapy products and integration of viruses into the genome. The risk assessment must present information concerning any non-clinical studies and/or the clinical use of the preparation based on which the safety of the preparation has been assessed. In particular, safety studies might be needed for preparations that have never been used on humans before.

If it is not certain whether the regulations concerning advanced therapy medicinal products can be applied to the preparation, a Fimea classification must be requested for the preparation before submitting an application for a national licence.

3.2 Preparation-specific requirements

3.2.1 Quality requirements

The preparation-specific quality requirements must contain reports of the following:

- Manufacturing according to GMP
- Pharmacochemical and biological properties of the preparation

The reports must meet the requirements of the EU, EMA and the European Pharmacopoeia. The preparation must be characterised so as to make it possible to evaluate its composition, identity and purity.

The quality documentation must, at a minimum, provide the following information:

- Testing results for starting materials or the manufacturer's analysis certificate
- Testing of donors
- Suitability of materials (in particular the viral and TSE safety of materials of animal origin)
- Compatibility of non-cell-based components of combination products with cells and related testing (matrices, growth factors)
- Description of the production process and validation of the aseptic process
- Key process controls (microbiological control, cell growth control)
- Sufficient characterisation tests

The quality requirements (specifications) for the active ingredient and end product must always be presented accompanied by analysis results for one or several lots. The tests on the active ingredient and end product must address at least the following parameters:

- Identity test
- Microbiological purity / sterility
- Toxic / detrimental impurities
- Dose determination and testing
- Cell viability
- Evaluation of the tumorigenicity of stem cells and other cells grown for an extended period of time
- Gene therapy products: viruses capable of replication and the percentage of infective viruses of the entire virus population

An adequate description is to be provided of all the analytical methods used in product testing, and the main analytical methods must be validated.

If the product is stored before being administered to the patient, the research findings on the shelf life of the product in the proposed storage conditions must be provided.

3.2.2 Preparation

The preparation and packaging of a drug manufactured with a national ATMP manufacturing licence must follow the Good Manufacturing Practice (GMP) of medicinal products, described in more detail in the EU GMP publication "Guide to Good Manufacturing Practice for Medicinal Products". Packaging must be labelled in compliance with the requirements presented in Annex III to the Regulation (EC) No 1394/2007.

3.2.3 Adverse drug reactions and adverse incidents

In the event that human tissue or cells are used in the preparation of an ATMP, the recording and processing of adverse incidents and reactions related to the quality and safety of the products and the reporting procedures for serious adverse incidents and reactions must satisfy the provisions of the Act on the Medical Use of Human Organs and Tissues (101/2001; hereinafter referred to as the Tissue Act), and the regulations issued under said Act.

In the event that human blood or its components are used in the preparation of an ATMP, the recording and processing of adverse incidents and reactions related to the quality and safety of the products and the reporting procedures for serious adverse incidents and reactions must satisfy the provisions of the Blood Service Act (197/2005) and the regulations issued under said Act.

The manufacturing licence holder must report to Fimea within 15 days of any serious adverse incidents related to the preparation of the drug and of any serious adverse drug reactions related to the use of the drug.

The holder of the national ATMP licence must submit to Fimea annually a PSUR of the drug prepared, a report on adverse incidents associated with the manufacture of the drug and any adverse drug reactions caused by the drug. The deadline for submitting these documents is the end of March of the following year. The report must provide the data identifying the medicine, the production volumes, the number of patients treated with the preparation, the name of the physician prescribing the medicine and responsible for care, as well as any serious adverse incidents in the preparation of the medicine and any adverse reactions caused by it.

3.2.4 Traceability

In the event that human tissue or cells are used in the preparation of an ATMP, they must satisfy the traceability requirements of the Act on the Medical Use of Human Organs and Tissues and the more detailed regulations issued under said Act.

In the event that human blood or its components are used in the preparation of an ATMP, they must satisfy the traceability requirements of the Blood Service Act and the regulations issued under said Act.

The traceability requirement also applies to other starting materials or precursors, products or materials affecting the safety or quality of the product that are used in the preparation of an ATMP.

3.2.5 Other legislation regulating the national preparation and use of an ATMP

In the event that human tissues or cells are used in the preparation of medicinal products, their donation, collection and testing must comply with the provisions of the Tissue Act.

In the event that human blood or its components are used in the preparation of medicinal products, their donation, collection and testing must comply with the provisions of the Blood Services Act.

In the event that living genetically modified organisms (GMOs) are used in the preparation of medicinal products or contained in a medicinal product, the preparation and use of such a medicinal product must satisfy the provisions of the Gene Technology Act (377/1995).

Processing of personal data must follow the Personal Data Act (523/1999).

4 APPLYING FOR A NATIONAL ATMP LICENCE AND SUPERVISION OF THE LICENCE HOLDERS

A national ATMP licence is applied for from Fimea by using the application form in the appendix of this regulation. The same form is also available in an electronic format on the Fimea website. The processing of the application will include a quality assessment of the preparation and an inspection of the manufacturing site to verify that the GMP guidelines are met. Pursuant to section 15, subsection 1, the licence may contain conditions to be met, and it may be temporary or remain in force until further notice.

After the manufacturing licence has been granted, the manufacturing location will be inspected according to an inspection programme based on Fimea's risk assessment.

5 INFORMATION AND ADVICE

On request, Fimea will offer information and advice on the application of this regulation.

6 PERIOD OF VALIDITY

This regulation will enter into force on 01/01/2015 and will remain in force until further notice.

Director General	Sinikka Rajaniemi
Senior Pharmaceutical Inspector	Pirkko Puranen

DISTRIBUTION

Units that prepare advanced therapy medicinal products for individual patients

FOR INFORMATION

Ministry of Social Affairs and Health
National Supervisory Authority for Welfare and Health
National Institute for Health and Welfare
Board for Gene Technology
The Office of the Data Protection Ombudsman
Provincial State Offices
Provincial Government of Åland
Finnish Patients Association
Finnish Association of Municipalities and Regional Authorities
Association of Finnish Pharmacies
The Finnish Pharmacists' Association
Pharmaceutical industry
Generic medicine industry
Hospital districts
Helsinki University Central Hospital
Kuopio University Hospital
Oulu University Hospital
Tampere University Central Hospital
Turku University Central Hospital
Universities
Tissue services providers

Appendix to the Finnish Medicines Agency Regulation 5/2014
Manufacturing licence application for an advanced therapy medicinal product
Form 19/12/2014

1. Manufacturer (licence applicant) information

1.1 Manufacturer (licence applicant)	
1.2 Corporate form (appendix) ☐ company ☐ association ☐ other community	
1.3 Mailing address	
1.4 Street address	
1.5 Invoicing address (if different from manufacturer's address)	
1.6 First and last name of the contact person for the application	E-mail @
Phone	Mobile phone

2. Description of the preparation and its safety for the patient being treated

2.1 Class of preparation ☐ Gene therapy ☐ Cell therapy ☐ Tissue engineering
2.2 Detailed description of the preparation and name of preparation
2.3 Safety of the preparation (appendix)
2.4 Manufacture of the preparation following the Good Manufacturing Practices (appendix)
2.5 Pharmacochemical and biological properties of the preparation (appendix)

3. Identification of the prescriber and the medical practitioner responsible for the treatment

3.1 First and last name of the physician	E-mail @
3.2 Qualifications / specialty of the physician	
3.3. Site name	
3.4 Street address of the site (if different from the manufacturer's address)	
Phone	Mobile phone

4. Description of the manufacturing process

4.1 Description of the manufacturing process (appendix)
4.2 Product packaging

5. Persons in charge of manufacture

5.1 First and last name of the person in charge of manufacture	Qualification / profession (appendix)
5.2 First and last name of the person releasing the preparation	Qualification / profession
5.3 Other persons in charge of manufacture	Qualification / profession

6. Persons participating in manufacture

First and last name of the person	Qualification / profession (appendix)
First and last name of the person	Qualification / profession
First and last name of the person	Qualification / profession
First and last name of the person	Qualification / profession

7. Quality system

7.1 Overview of the quality system
7.2 Standard operating procedures of the quality system (appendix)

8. Manufacturing premises

8.1 Report on manufacturing premises (appendix)

9. Devices and equipment used in the manufacture

9.1 Report on critical devices and equipment, and their supervision, service and maintenance (appendix)

10. Traceability

10.1 Report on the implementation of traceability of cells, human blood or its components, other ingredients and raw materials affecting quality and safety (appendix)

11. Serious adverse incidents

11.1 Description of the procedures used for addressing any serious adverse incidents occurring during the manufacturing process (appendix)

12. Pharmacovigilance

12.1 Report on the processing and reporting of adverse reactions and severe adverse reactions (appendix)

13. Data security and confidentiality

13.1 Processing of personal data; description of the file (appendix)

14. Ethics

14.1 Report on the ethics of the therapy
14.2 Authorisation from the ethics committee or equivalent body (if applied for) (appendix)

15. Environmental effects

15.1 Description of the environmental effects of the preparation (if applicable)

16. Signature of the person in charge

Place and date	
Signature	
Name in block letters	

Please submit the application and its appendices to the registry office of the Finnish Medicines Agency Fimea:

Finnish Medicines Agency Fimea
Kirjaamo
P.O. Box 55 (Mannerheimintie 103b)
FI-00034 FIMEA, Finland

Appendices to the application

1. Manufacturer information

☐ if the applicant is a company, a copy of the Articles of Association and an extract of the Trade Register

☐ if the applicant is a company, a copy of the rules of the association and an extract of the Associations Register

☐ if the applicant is a community, a copy of the rules of the community

2. Description of the preparation and its safety for the patient

2.2 ☐ Description safety of the preparation for the patient being treated

2.3 ☐ Description of the manufacture of the preparation according to good manufacturing practices

2.4 ☐ Pharmacochemical and biological properties of the preparation

3. Information of the physician in charge of the therapy

☐ description of the qualification and role of the physician in charge of the therapy, an extract from a personal file or a copy of his/her diploma

4. Description of the manufacturing process

4.1 ☐ Description of the manufacturing process

5. Persons in charge of manufacture

5.1 ☐ Description of the qualification of the person in charge of manufacture, an extract from a personal file or a copy of his/her diploma

6. Persons participating in manufacture

6.1 ☐ List of persons participating in manufacture, their competencies and responsibilities

7. Quality system

7.2 ☐ List of standard operating procedures

Copies of the following standard operating procedures:

☐ ensuring traceability

☐ handling of serious adverse incidents

☐ pharmacovigilance procedures

8. Manufacturing premises

8.1 ☐ Manufacturing premises, floor plans with space classifications

9. Devices and equipment

9.1 ☐ List of the critical devices and equipment in the manufacturing process

10. Traceability

10.1 ☐ Report on the implementation of traceability of cells, human blood or its components, other ingredients and raw materials affecting quality and safety

11. Serious adverse incidents

11.1 ☐ Description of the procedures used for addressing any serious adverse incidents occurring during the manufacturing process

12. Pharmacovigilance

12.1 ☐ Report on the processing and reporting of adverse reactions and severe adverse reactions

13. Data security and confidentiality

13.1 ☐ Processing of personal data; description of the file

14. Ethics

14.2 ☐ Copy of the authorisation granted by the ethics committee

Any other appendices (such as other licences granted by an authority)

Regulation
ISSN-L 1798-6567
ISSN 1798-6567

Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency
P.O. Box 55, 00034 FIMEA | Tel. 029 522 3341 | kirjaamo@fimea.fi | www.fimea.fi | Business ID 0921536-6