HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

# Guide to
# Hospital-Based Advanced Therapy Medicinal Products

**AUT-G0091-1**
**28 FEBRUARY 2013**
This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

## CONTENTS

## 1 PURPOSE

This document has been written to provide regulatory information to hospital-based manufacturers of advanced therapy medicinal products (ATMPs) and to clarify the Health Products Regulatory Authority (HPRA) requirements for the manufacture and use of these medicines.

## 2 SCOPE

This guideline only applies to ATMPs as defined in Article 28 of Regulation EC No. 1394/2007 (the 'ATMP Regulation').

*Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.*

This class of ATMP will largely be manufactured on a hospital or university campus for use within a Member State. These types of ATMPs can be referred to as 'hospital-exempt' ATMPs and are exempt from the formal requirement for a marketing authorisation from the European Commission. Thus this guidance does not apply to ATMPs that will be authorised under the ATMP Regulation for which a marketing authorisation is required.

This guidance does not apply to the human application of tissues and cells or organs, as defined by European and national legislation, nor does it apply to ATMPs supplied as investigational medicinal product for use in clinical trials.

## 3 INTRODUCTION AND BACKGROUND

The ATMP Regulation came into force on 30 December 2008. Subject to the exemption outlined in the paragraph below, the Regulation requires all substances that fulfil the definition of a medicinal product as defined in Directive 2001/83/EC, and are classed as ATMPs, to be regulated through the centralised European marketing authorisation (MA) route.

However, this Regulation does make provisions (Article 28) to exempt, from MA requirements, ATMPs manufactured in hospitals, universities or start-up companies where the medicine is prescribed for patients under the care of a medical practitioner. This manufacture should occur on a non-routine basis according to specific quality standards and the ATMP should be used in a hospital within the Member State.
Article 28 requires Member States to have certain control measures in place namely:

- Donation and procurement of tissue and cells and donor testing must comply with national and European tissues and cells legislation (Directive 2004/23/EC),
- Manufacture of the ATMP requires a manufacturing/importation authorisation,
- National traceability and pharmacovigilance requirements apply,
- Specific quality standards apply.

## 4 MANUFACTURING REQUIREMENTS

Article 28 of the Directive requires that hospital-exempt manufacture of ATMPs be carried out under a national authorisation. In Ireland, each site must be authorised for compliance with:

- The tissue and cell legislation for donation, procurement and testing (of donors) when such tissues and cells are used as starting materials for ATMP manufacture (European Communities (Quality and Safety of Human Tissues and Cells) 2006 (S.I. No. 158 of 2006))
- The blood legislation for collection and testing (of donors) when such blood components are used as starting materials for or used in the production processes of ATMP manufacture (European Communities (Quality and Safety of Human Blood and Blood Components) Regulations, 2005 (S.I. No. 360 of 2005)).
- The requirements of Good Manufacturing Practice for the processing of the tissues and cells after procurement i.e. a manufacturing / importation (MIA) authorisation in accordance with the Medicinal Products (Control of Manufacture) Regulations 2007, as amended (S.I. 539 of 2007, as amended).

The requirement for an MIA for manufacture of a hospital-exempt ATMP is stated in the Medicinal Products (Control of Placing on the Market) Regulations, 2007 – 2010 and specifically as amended by S.I. No. 3 of 2009).

## 5 TRACEABILITY AND SAFETY MONITORING REQUIREMENTS

Traceability

Manufacturers of hospital-exempt ATMPs are required to maintain traceability mechanisms as defined in Article 15 of the ATMP Regulation. These traceability systems should be compatible with those defined in the Tissues and Cells Directive 2004/23/EC and when relevant the Blood Directive 2002/98/EC. The traceability systems should ensure traceability of tissues, cells and derived ATMPs from the donor to the receipt/patient. Traceability is also required for starting materials or precursors or any materials of human origin used in the manufacture of the ATMP.

Safety Monitoring Requirements

For ATMPs that are centrally-authorised under the Regulation, the pharmacovigilance requirements laid down in Articles 21 to 29 of Regulation (EC) No. 726/2004 (as well as Article 14 of the ATMP Regulation) shall apply. While meeting the requirement in the Regulation for appropriate pharmacovigilance standards, it is recognised that certain requirements cannot readily be applied to hospital=exempt ATMPs. In particular, it would not be appropriate to apply the requirement for periodic safety update reports for hospital-exempt ATMPs that are produced on a non-routine basis. In addition, as an authorised indication for hospital-exempt ATMPs does not exist, it is proposed that follow up of efficacy should be viewed in the context of the normal professional obligation for clinicians to closely monitor the effects on patients of these innovative, complex or high risk treatments.

As such, the pharmacovigilance requirements for hospital-exempt ATMPs should ensure appropriate recording and reporting of suspected adverse reactions and events, in the context of the relevant legislative requirements for medicinal products, tissues and cells, or blood as applicable. In addition, any need for a risk management plan will be considered on a case-by-case basis. Initial consideration of the need for such a plan will be initiated at the point that a manufacturer's authorisation is sought to operate under the exemption and will reflect the nature of the proposed activity. In addition, the HPRA may request a risk management plan from the manufacturer at any point (if, for example, safety concerns were raised about a product which was not known at the point that the application was made for a manufacturer's authorisation).

## 6 QUALITY STANDARDS

The above requirements place an onus on hospital-based manufacturers to manufacture ATMPs in compliance with GMP requirements and ensure that all starting materials comply with the Tissues and Cells Directive and, where relevant, the Blood Directive. These requirements focus on the manufacturing facility and do not define product-specific quality requirements.

There is no legal requirement for the HPRA to perform an assessment of quality, safety and efficacy of these types of products as no procedure exists for a national marketing authorisation.

However, in accordance with the Article 28 of Regulation EC No. 1394/2007 specific quality standards are required. Thus, the application for a manufacturing authorisation must be accompanied by relevant product-specific quality requirements to ensure their quality and safety.

The following is a (non-exhaustive) list of examples of the quality documents that should be provided, unless otherwise justified:

- Risk assessment of known risk factors (e.g. potential infectious agents, immunogenicity, tumorigenicity, loss of cell functionality, non-cellular impurities, viruses contained in the gene therapy product capable of replication, retro-/lentiviral genome integration).
- Specifications and test results for starting materials or the manufacturer's analysis certificate.
- Confirmation that donors are tested for presence of viruses in accordance with blood and tissues legislation and where relevant for other infectious agents that may compromise the quality of the manufactured product.
- Suitability of starting materials of human/animal origin (in particular with respect to viral and TSE safety).
- Compatibility of non-cell-based components of combination products with cells (bioscaffolds, matrices, growth factors etc).
- Description of the production process and validation of aseptic processes.
- Description of the key process controls during production (e.g. microbiological control, cell growth/ viability control).
- Demonstration that there are sufficient characterisation tests to ensure adequate control of product quality and batch to batch consistency.

The release specifications for the active substance and end product should be presented and accompanied by batch analysis results for all available lots. Specifications for the active substance and end product should address, as a minimum, the following quality parameters:

- identity
- dose determination
- cell viability
- freedom from adventitious agents (viruses, mycoplasma, bacteria, fungi)
- potential impurities
- cell based medicinal products: evaluation of tumorigenicity of cells grown for an extended period of time
- gene therapy products: viruses capable of replication and the percentage of infective viruses relative to the entire virus population

A description of proposed analytical methods used in product testing should be provided, and the main analytical methods should be validated or qualified as suitable for use.

For autologous ATMPs which cannot be stored prior to use, a two step release approach may be acceptable. This approach requires that rapid release tests e.g. sterility, viability and dose determination tests are conducted prior to administration of the product and that additional batch release tests are completed following product administration. The risks associated with this approach would need to be considered and, in the event of an out-of-specification result(s) being determined following product administration, appropriate follow-up actions implemented. Such a two-step release approach would need to be scientifically justified and details of follow-up actions to be taken in the event of an out-of-specification result provided.

Proposed packaging materials should be described e.g. in terms of pharmacopoeial quality, and demonstrated as being suitable for intended use (e.g. compatibility with the active substance or medicinal product).

If the product is intended to be stored before administration to the patient, available information in support of the proposed shelf life of the product in the proposed storage conditions should be provided. Similarly if the active substance is intended to be stored prior to formulation of the finished medicinal product, information on stability over the intended storage period should be provided if available.

## 7 ANNUAL REPORT OF ACTIVITY

An annual safety review report concerning the hospital-exempt manufactured ATMP is required one year on from when the manufacturing / importation authorisation (MIA) is granted. The report should provide the following:

- number of ATMPs manufactured,
- number of patients treated with each ATMP,
- name of the physician prescribing the ATMP and having responsibility for care of that patient,
- any serious adverse incidents in the preparation of the ATMP,
- any adverse reactions caused by the ATMP.

## 8 CLINICAL TRIALS

Clinical trials on hospital-exempt products or any ATMPs should be conducted in accordance with the principles laid down in the Clinical Trials Directive (2001/20/EC) transposed into Irish law by the European Communities (Clinical Trials on Medicinal Products for Human use) Regulations, 2004, S.I. No. 190 of 2004 as amended. The HPRA is responsible for authorising clinical trials in Ireland. For further information please view the HPRA clinical trials webpage.

## 9 CONSULTATION WITH THE HPRA

In order to provide added assurance as to the quality and safety of products used through the hospital-exempt route, manufacturers can discuss issues with the HPRA in relation to the product(s) they wish to manufacture. It is expected that this advice would be sought at the same time as an application for manufacturing / importation authorisation is submitted. Interested parties wishing to seek such advice should contact the HPRA at info@hpra.ie.

## 10 ADDITIONAL INFORMATION

Additional information on ATMPs can be found on:

- HPRA website www.hpra.ie
- EMA website
- European Commission website
- ICH website
- European Pharmacopoeia website

## APPENDIX 1: LEGISLATION


1 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official Journal of the European Union 10.12.2007. L324/121-137 (2007)*.

2 European Union, Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. *Official Journal of the European Union*, *2001;L311:67–128*.

3 The European Parliament and the Council of the European Union. Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/ EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products. *Official J. Europ. Union 15.9.2009, L242/3–L242/12 (2009)*.

4 European Union, Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. *Official Journal of the European Union, 2004;L104:48*.

5 Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Community and of the Parliament as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

6 Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Community and of the Parliament as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

7 European Union, Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. *Official Journal of the European Union, 2003;L33:30*.

8 Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Community and of the Parliament as regards certain technical requirements for blood and blood components.

9 Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Community and of the Parliament as regards traceability requirements and notification of serious adverse reactions and events.

10 Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Community and of the Parliament as regards Community standards and specifications relating to a quality system for blood establishments.

11 Medicinal Products (Control of Manufacture) Regulations 2007 – 2010 (S.I No. 539 of 2007, as amended)

12 Medicinal Products (Control of Placing on the Market) Regulations 2007 – 2010 (S.I. No. 540 of 2007, as amended)

13 European Communities (Quality and Safety of Human Blood and Blood Components) Regulations 2005. (S.I. No. 360 of 2005)

14 European Communities (Human Blood and Blood Components Traceability Requirements and Notification of Serious Adverse Reactions and Events) Regulations 2006. (S.I. No. 547 of 2006)

15 European Communities (Quality System for Blood Establishments) Regulations 2006 (S.I. No. 562 of 2006)

16 European Communities (Quality and Safety of Human Tissues and Cells) Regulations 2006. (S.I. No. 158 of 2006)

17 European Communities (Human Tissues and Cells Traceability Requirements, Notification of Serious Adverse Reactions and Events and Certain Technical Requirements) Regulations 2007 (S.I. No. 598 of 2007)