

# Advanced therapy medicinal products in clinical trials



Lennart Åkerblom  
Medical Products Agency

# Outline of presentation

- Proposal for a Regulation on Advanced Therapy Medicinal products (ATP)
- Cell-based Medicinal Products (CBMP)
- Gene Therapy Medicinal Products (GTMP)
- Critical issues prior to first clinical trial in man
- Updates on guidelines, directives and national legislation

# **Proposal for a Regulation on advanced therapy medicinal products**

The proposed Regulation lays down specific roles concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

The provisions of this Regulation will apply to advanced therapy medicinal products which are industrially produced and intended to be placed on the market in Member States in accordance with article 2.1 of Directive 2001/83/EC

# Scope

- Scope of the proposal:

*“products intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process”*

- Explicit exclusion:

The proposal does not apply to *“any advanced therapy medicinal product which is both prepared in full and used in a hospital, in accordance with a medical prescription for an individual patient”*.

# Scope

Other explicit exclusions:

- Products prepared in a pharmacy in accordance with a medical prescription for an individual patient
- Products prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy
- Products intended for research and development trials, without prejudice to Directive 2001/20/EC

# Definitions

- Advanced therapy medicinal products:
  - Gene therapy (*already defined*)
  - Somatic cell therapy (*already defined*)
  - Tissue engineered products (*new*)
- Tissue engineered products:
  - Contains or consists of engineered cells or tissues;
  - is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue.
- Engineered cells or tissues

# Concrete examples

Following products are considered within the definition of advanced therapy medicinal products:

- Human autologous chondrocytes in bovine collagen matrix
- Engineered skin composed of autologous keratinocytes and allogeneic fibroblasts embedded in a plasma matrix.
- Autologous epidermis expanded in vitro on irradiated murine cells
- Suspension of isolated/purified human allogeneic liver cells for treatment of acute liver failure

# GUIDELINE ON HUMAN CELL BASED MEDICINAL PRODUCTS

Cell-based medicinal products (CBMP) have the following characteristics:

- They contain viable human cells of allogenic or autologous origin;
- They did undergo a manufacturing process;
- They may be combined with non-cellular components;
- The cells might be genetically modified.

# CELLS

Human cells and tissues used as starting materials should be donated, procured and tested in accordance with the Directive 2004/23/EC. The quality criteria for the sourcing must meet the requirements of Directive 2006/17/EC.

# IN-PROCESS CONTROLS

The manufacturing process needs to be controlled by several in-process controls at the level of critical steps or intermediate products.

# Adventitious agents

A critical aspect is to establish that CBMP are free from adventitious microbial agents (viruses, mycoplasma, bacteria, fungi).

A risk assessment should be performed to evaluate the possibility of reactivation of cryptic (integrated, quiescent) forms of adventitious agents should be performed.

# POTENCY

The assay demonstrating the biological activity should be based on the intended biological effect which should ideally be related to the clinical response.

# Release criteria

The release specifications of the active substance and finished product should be selected on the basis of parameters defined during the characterisation studies.

# FINAL PRODUCT

The key parameters for performance testing of the completed product should be justified in relation to the development data and the final quality requirements.

# Classification of potential cell therapy medicinal products

- Stem/progenitor cells derived from ex vivo expansion of allogeneic umbilical cord blood;
- Allogeneic, ex-vivo cultured human mesenchymal stem cells;
- Autologous dendritic cells charged with autologous tumour antigen;

# Non-clinical development

The goals of these studies include the following:

- to provide information to select safe doses for clinical trials,
- to provide information to support the route of administration and the application schedule,
- to provide information to support the duration of exposure and the duration of the follow-up time to detect adverse reactions,
- to identify target organs for toxicity and parameters to monitor in patients receiving these therapies.

# Ethics

Advanced therapy products may be based on human cells, they can raise important ethical issues.

Decisions on the use or non-use of any type of cells, including embryonic stem cells, are a national responsibility.

# GTMPs

Gene therapy medicinal products (GTMPs) include a combination of a coding region of a transgene(s) and expression vector - plasmid DNA, viral and non-viral vectors, genetically modified viruses and genetically modified cells that are developed for treatment or prevention of a variety of human diseases.

# Non-clinical studies of GTMPs

Due to the specific characteristics of each single GTMP, final decisions on the non-clinical study program prior to first clinical use and its adequacy should be made on a case-by-case basis.

# Gene therapy guidelines: pharmaceutical

- GMP production permit
- Developmental genetics
  - design: origin, description
  - function
  - vector characteristics
  - fidelity in replication
- Production
  - raw material & quality
  - selection markers
- Purification
  - virus removal
- Batch control
  - Data for 3 batches: consistency, identity, purity, potency
- Specific delivery systems
  - Plasmids: sequence homology/ recombination risk
  - Liposomes: size, charge, stability
  - Virus: origin, biology, tropism, package/recombination, insertion mutagenesis, pathogenicity
  - Cells: source, viral screen, manipulation, proliferation, stability

# Gene therapy guidelines: pre-clinical

- Gene construct safety
  - recombination
  - (retro)viral sequences
  - extracellular vector
  - **no germ line transfer!**
- Cell line safety
  - latent virus activation
  - immune responses
  - transformation
  - cell persistence
  - other products
- Gene expression efficacy
  - site
  - level
  - persistence
  - functional activity
- (Device characteristics)
  - appropriate design, durability
  - tissue compatibility/toxicity
- Final product characteristics
  - pharmacology, GLP toxicology

# Pharmaco-toxicological requirements - prior to human subjects

- Safety evaluation based on safety studies identifying
- target organs & -thresholds:
  
- Safety Pharmacology studies - GLP
  - vital organs: cardiovascular; respiration, (CNS?)
  
- Toxicological basal data - GLP
  - repeat dose toxicity mimicing intended clinical use (max 6m):
    - full histopathology
    - investigation of immune responses

# Take home message

- The technical basis - useless without them.
  - Could you reproduce the process - every time?
- The reason - from probable to proven.
  - Could you show effect in controlled trials?
- The denominator – being the terminator?
  - Is the Efficacy/Safety ratio acceptable to all?