Advanced Therapy in Retinal Disease
Regulatory View CAT

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27-28 October 2011

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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Outline of Presentation

- **Regulatory Framework**
- **Safety considerations**
- **Potency**
- **Biodistribution**
- **Risk based approach**
- **ATMPs as Combination Products**
- **Take home message**

Regulatory framework for ATMPs

- **Directive 2001/83/EC, Annex I, Part IV (revised through 2009/120/EC)**

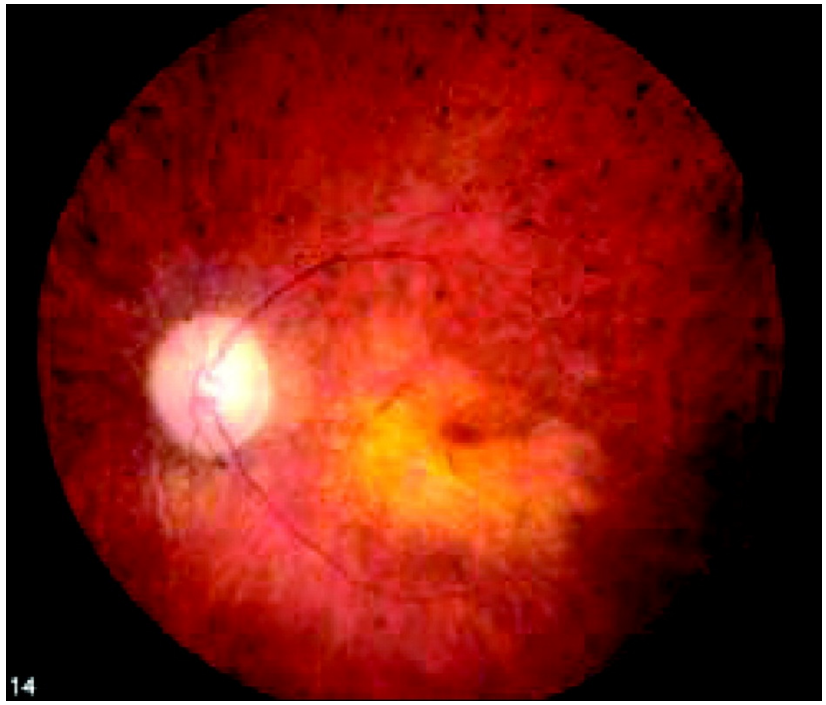
  - new definitions for somatic cell therapy and gene therapy MPs

  - updated technical requirements (Q, NC, C) for all ATMPs
- **Directives 2004/23/EC, 2006/17/EC, 2006/86/EC**

  - requirements for donation, procurement and testing of tissues and cells
- **Regulation on Advanced Therapy Medicinal Products (ATMPs) 1394/2007/EC**
- **Directive 93/42/EEC on medical devices and Directive 90/385/EEC on active implantable medical devices (revised 2007)**
- **EMA guidelines for CBMPs and GTMPs**

Type of ATMPs

- Cell-based MP
- Gene Transfer MP
- Genetically modified cells
- Combined ATMPs



Sieving P A et al. PNAS 2006;103:3896-3901

Technical requirements

- **Specific pre-clinical and clinical requirements**
- **Compliance with 'Essential Requirements' for products incorporating medical devices**
- **Specific guidelines on**

  - GMP (Good Manufacturing Practice)

  - GCP (Good Clinical Practice)
- **Post-authorisation aspects**

  - Risk management

  - Traceability

Consistency in Production

- **Manufacturing process should be able to produce consistent product**
- **Product characterisation should provide information on critical parameters of the cells/ product and tools for IPC/ release and stability testing, setting limits for composition, dose and level of impurities**
- **Change in manufacturing process during or after the pivotal clinical studies, comparability of the product before and after the change(s) has to be demonstrated**

Specific challenges with ATMPs

- **Upscale of manufacturing process**
- **potency testing**
- **non-clinical challenges**

  - animal models

  - proof of concept

  - safety aspect
- **factors limiting clinical studies**

  - possibilities for masking, availability of comparators

  - feasibility of dose finding and biodistribution studies in humans

Specific risks with ATMPs

- **microbial contamination**
- **tumourigenicity**
- **dedifferentation**
- **immunogenicity**
- **ectopic engraftment**
- **shedding**

- **lack of proper animal models**

Potency of ATMPs

- Bioassays measure potency by evaluating a product's active ingredients within a living biological system. Bioassays can include in vivo animal studies or cell culture systems.
- Analytical assays can provide extensive product characterization data by evaluating molecular attributes of the product. These attributes may be used to demonstrate potency if the surrogate measurement(s) can be substantiated by correlation to a relevant product-specific biological activity(s).

Biodistribution

- Biodistribution is a complex issue that relates to cell localization and migration as well as survival and differentiation status.
- The design of biodistribution studies conducted in animals must include a consideration of multiple factors:

  - the methods applied to cellular detection and their sensitivity,

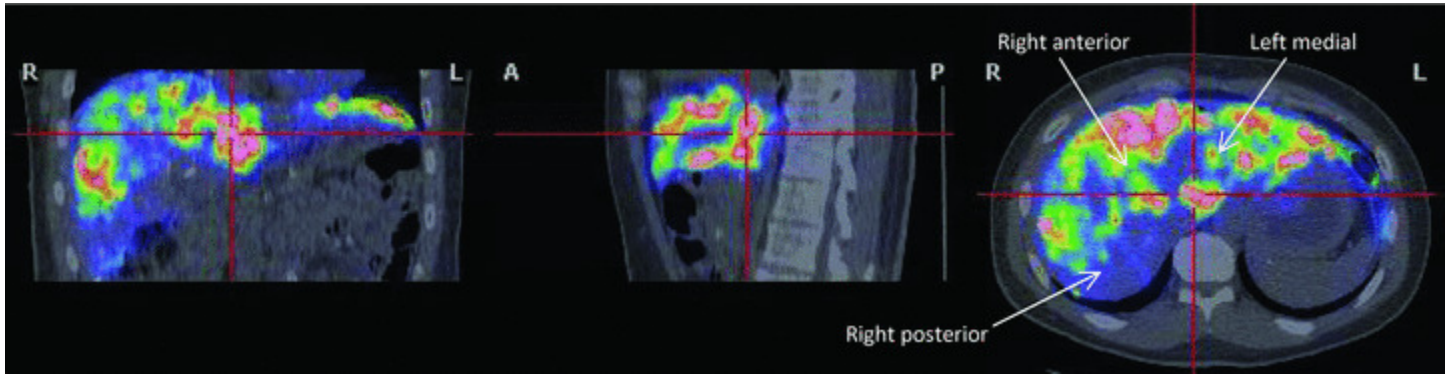
  - is single species adequate? will xenogenic cells (ie human cells) migrate in a relevant way in an animal model? Homologous model?

  - route of administration.

Biodistribution

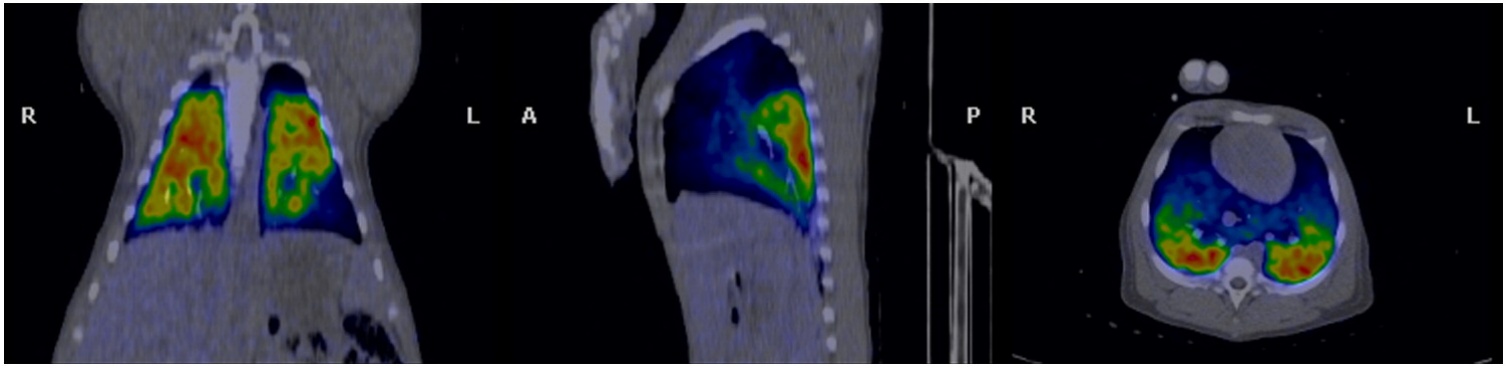
Positron Emission Tomography in Clinical Islet Transplantation

O. Eriksson et al, 2009



Positron Emission Tomography in adoptive T cell therapy in a porcine preclinical model

O. Eriksson et al, 2011



Gene therapy

Different types of viruses used as gene therapy vectors:

- Retroviruses/ Lentiviruses - A class of viruses that can create double-stranded DNA copies of their RNA genomes. These copies of its genome can be integrated into the chromosomes of host cells.
- Adeno-associated viruses - A class of small, single-stranded DNA viruses that can insert their genetic material at a specific site on chromosome 19.

Clinical trials:

- Results of world's first gene therapy for inherited blindness show sight improvement (2008). Results from the world's first clinical trial to test a gene therapy treatment for a type of inherited blindness.

Risk-based approach

- **Concept paper provide background & rationale of guideline on Risk-based approach**
- **Drafting of guideline is currently ongoing in CPWP & GTWP**
- **Risks are determined by various risk factors which are related to the quality, biological activity and administration of the ATMP.**
- **Guideline is intended to support the Applicant to identify the risks and associated risk factors, and to establish a risk profile of their ATMP under development.**
- **With the use of the identified risk profile the Applicant will be able to justify the extent of data to be included in the MAA dossier.**

ATMPs - Combined vs. Not combined

Definition :

Combined ATMPs means:

- it must incorporate, as an integral part of the product, one or more medical devices or one or more active implantable medical devices, and

- its cellular or tissue part must contain viable cells or tissues, or

- its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to."

ATMPs classification

1. MD already CE mark:

Does the ATMPs incorporate as an integral part this MD?

Where the medical device or active implantable medical device is combined with the cells **at the time of the manufacture or application or administration of the finished products**, they shall be considered as an integral part of the finished product.

Combined ATMP

Not Combined ATMP

(examples alginate matrix will be considered as excipients)

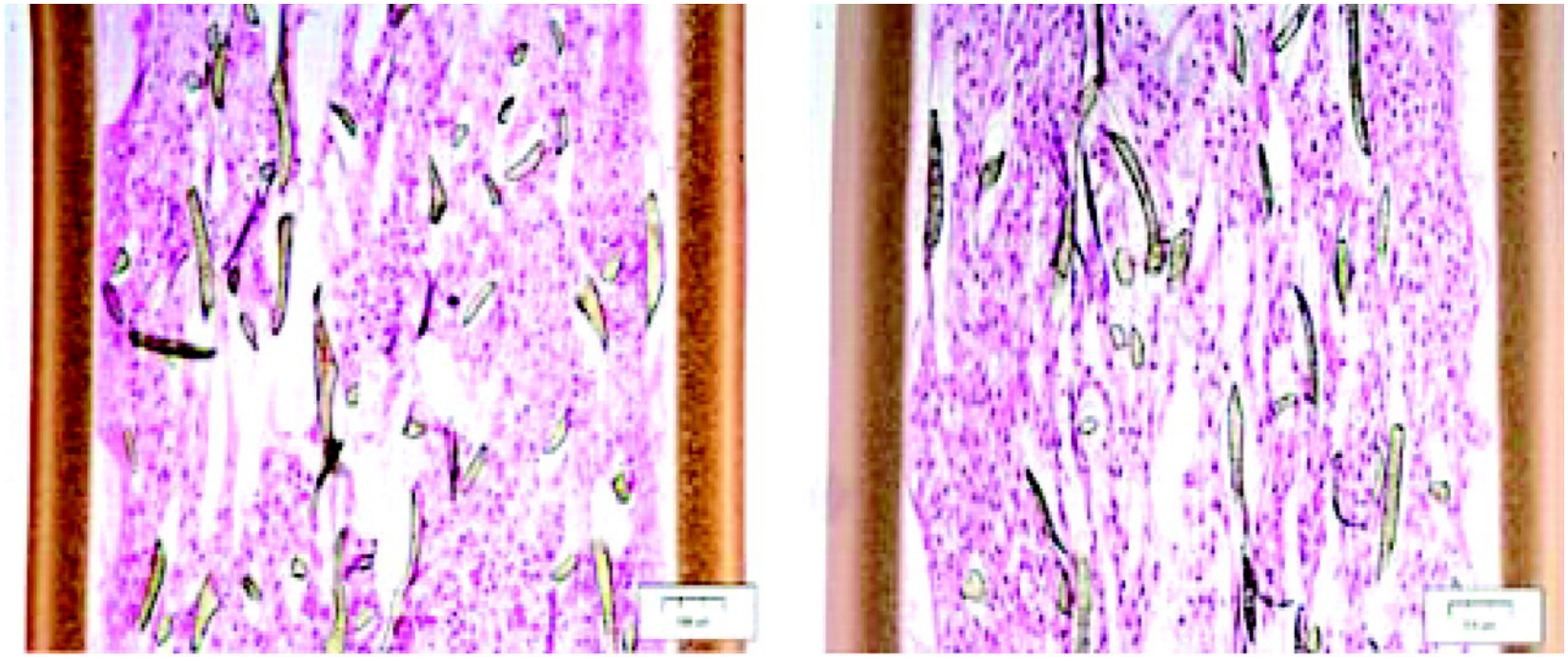
ATMPs classification

2. Structural component not CE mark:

This structural component:

- Can be an integral part of the finished product
- Can be considered as a support to contain/preserve biological characteristics and functional activities of the cells
- **should be inert**

Cell therapy device in clinical trial



Before Implantation

After Removal

Sieving P A et al. PNAS 2006;103:3896-3901

Take home message

- **Technical requirements of ATMPs**
- **Requirements of Combination ATMPs**
- **New guideline on Risk based approach**
- **Need for consistency in manufacture**
- **Need for risk assessment of stem cell-based products**