Advanced Therapy Medicinal Products (ATMPs)

European Experience and Challenges

ASEAN training. Kuala Lumpur. 31 May 2011

Presented by: B. Brake and A. Ganan Jimenez
European Medicines Agency
Content

- European Medicines Network
- Definition of ATMPs
- Guidance on Cell products
- Development of a (stem) cell-based MP
- Case study of an approved ATMP: ChondroCelect
- EMA Regulatory procedures for ATMPs
European Medicines Network
EMA and ATMPs

To foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health

- Network of European experts (+3500)
- 6 Scientific Committees (CHMP, CAT, COMP, PDCO, CVMP, HMPC & ...)
- Over 15 working parties (human unit)
- Centralised Procedure (for ATMPs): 1 single market
- Motto: Science, Medicines, Health
- Values: Europe, public health, innovation, sense of purpose, quality, transparency, integrity, honesty, objectivity, impartiality (CoI)
CHMP, CAT and working parties

CHMP
Chair: E. Abadie

CAT
Chair: C. Schneider

Scientific Advisory Groups (i.e. Oncology, Diagnostics…)

Pediatric Committee, Committee for Orphan Medicinal Products

Coordination Group

5 double members
Definitions of Advanced Therapy Medicinal Products
**Gene Therapy Medicinal Product**

Biological medicinal product with the following characteristics:

a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

Annex I, part IV of Dir. 2001/83/EC
Cell-based products

Somatic cell therapy medicinal products:

- **substantially manipulation** cells or tissues **or not intended** to be used for the same essential function(s);

- administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action.

Tissue engineered product:

- **engineered** cells or tissues, and

- administered to human beings with a view to regenerating, repairing or replacing a human tissue.

Non-substantial Manipulation

- cutting
- grinding
- shaping
- centrifugation
- soaking in antibiotic or antimicrobial solutions
- sterilization
- irradiation
- cell separation, concentration or purification
- filtering
- lyophilization
- freezing
- cryopreservation
- vitrification

Everything else is considered as substantial

ATR 1394/2007, Annex I
**Combined ATMPs**

**Definition:**

Incorporates a medical device (according to Article 1(2)(a) of Dir. 93/42/EEC)

**and**

Includes viable cells or tissue parts

**or**

In case of non-viable cellular/tissue part, the primary mode of action is attributed to the cell component as either pharmacological, immunological, metabolic or as repair, replacement, regeneration
Summary of definitions

**Gene therapy medicinal product:**
- recombinant nucleic acid \(\rightarrow\) to regulating, repairing, replacing, adding or deleting a genetic sequence

**Somatic cell therapy medicinal products:**
- substantially manipulated cells/tissue \(\rightarrow\) to treat, prevent or diagnose a disease
  (pharmacological, immunological, metabolic action)

**Tissue engineered product:**
- substantially manipulated cells/tissue \(\rightarrow\) to regenerate repair or replace a human tissue

**Combined ATMP:**
- medical device + cell/tissue part
### ATMP Classification examples

<table>
<thead>
<tr>
<th>TISSUE ENGINEERED PRODUCT</th>
<th>SOMATIC CELL THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult skeletal muscle derived cells: female stress urinary incontinence</td>
<td>Human allogeneic fibroblasts and keratinocytes + fibrin (structural component): chronic venous leg ulcers</td>
</tr>
<tr>
<td>NOT COMBINED</td>
<td>COMBINED</td>
</tr>
<tr>
<td>Frozen, cultured allogeneic keratinocytes on a silicone dressing material: acute burn wounds</td>
<td>Autologous osteoprogenitor cells in 3D biodegradable scaffold: regenerating and replacing bone defects in OdontoStomatology</td>
</tr>
</tbody>
</table>
ATMP Classification examples

GENE THERAPY PRODUCT

Genetically modified Lactococcus lactis secreting human IL-10: inflammatory bowel disease

Salmonella typhi strain genetically modified to secrete a fusion protein of the prostate specific antigen (PSA) and a protein leading to an increased antigenicity: prostate cancer
Guidance for (stem) cell-based medicinal products
What is special about ATMPs?

- **Classification** is dependent not only on the product (substantial manipulation), but also on the application (heterologous use)
- **Risk-based approach** – Data requirements related to the nature of the product
- **Balance between standardisation and case-by-case approach**
- **Innovative field in rapid progression** – Further knowledge required, standards established and guidance developed
- **Medicinal products containing/consisting on genetically modified organisms an environmental risk assessment** on the risks to human health and the environment is requested.
Risk-based approach

- A risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data for a MAA.

- The risk analysis may cover the entire development.

  Relevant factors: the origin of cells, ability to proliferate and/or differentiate and to initiate an immune response, level of cell manipulation, combination products, nature of gene therapy medicinal products, extent of replication competence of viruses or micro-organisms used *in vivo*, the level of integration, long time functionality, risk of oncogenicity and mode of administration or use.

- Relevant available non-clinical and clinical data or experience with other, related ATMPs may also be considered in the risk analysis.
Product Traceability – Coding System

The ATMP Regulation (art. 15) defines a two tiered system connecting the required traceability from cell donation and procurement to the manufacturer and user:

- At the tissue establishment: link between donor and donation
- At the manufacturing site: link between donation and product
- Hospital/practice: link between product and recipient
- The systems should allow full traceability from donor to recipient through anonymous coding systems.
- Manufacturers should establish their coding systems in a rational way, building from the coding system of the tissue establishment, and designing it to facilitate the tracing of the donation to the product and to the patient.

![Diagram of traceability system](image)
Genetically Modified Organisms (GMO)

Directive 2001/18/EC: Definitions (paraphrased)

An organism is a biological entity capable of replication or of transferring genetic material

- A genetically modified organism is one in which the genetic material has been altered in a way that does not occur naturally by mating or natural recombination.

Environmental risk assessment means evaluation of the risks to human health and the environment. (Module 1.6.2 of the CTD dossier).

Guidance: Environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs) (Module 1.6.2). EMEA/CHMP/BWP/135148/2004

Guidance on cell products

Guideline on cell-based medicinal products (2008)

- Potency testing of cell-based immunotherapy MPs for treatment of cancer (2007)
- Reflection paper on stem-cell based MPs (2010)
- Reflection paper on Xenogeneic CBMPs (2009)
- Guideline on MPs containing genetically modified cells
- Guideline on Safety & Efficacy Follow-up – Risk Management of ATMPs

Reflection paper on Chondrocyte containing MPs for cartilage repair (2009)
Guideline on human cell-based medicinal products

‘Mother guideline’

Human Cell & Tissue engineered products

- Quality + manufacturing aspects
- Nonclinical development
- Clinical development
Draft Reflection paper on stem cell-based medicinal products

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**Reflection paper on stem cell-based medicinal products**

*Disclaimer: Please note that the present reflection paper has been developed to communicate the current status of discussions and to invite comments in the area of stem cell-based medicinal product development, where scientific knowledge is fast evolving and regulatory experience is limited.*

The reflection paper shall be further discussed at the European Medicines Agency’s public workshop on stem cell-based therapies to be held on 10 May 2010.

| Draft Agreed by Cell Products Working Party | March 2010 |
| Adoption by Committee For Advanced Therapies (CAT) for release for consultation | 12 March 2010 |
| End of consultation (deadline for comments) | 30 June 2010 |
| Agreed by <WORKING PARTY> | <month year> |
| Adoption by <COMMITTEE> | <day month year> |
Scope

- Embryonic stem cells

- Adult or somatic stem cells including
  - Haematopoietic progenitor /stem cells
  - Mesenchymal/stromal stem cells
  - Tissue-specific progenitor cells with restricted differentiation capacity

- Induced pluripotent stem cells and/or their intermediate stages

- relevant to all MPs using stem cells as starting material.

- Finished product: terminally differentiated cells, pluripotent stem cells or mixture of cells with varying differentiation profiles
Risk-based approach

- EU legislation (Annex I, part IV of Dir. 2001/83/EC)

- Guidance under development (Concept paper CHMP/CPWP/708420/09)

**Approach:**

- Use to justify amount of data needed for Q, NC & C

- cover the entire development

- discuss risk profile of product (risk factors) and implication on extent of data in MAA dossier
Development of a (stem) cell-based medicinal product
Quality issues I

✓ Starting material tested/documented for viral, TSE safety?
✓ Excipients, reagents and structural components qualified?
✓ Product consistent and well characterised
✓ Active moiety identified and quantified?
  ✓ Manufacturing process validated?
✓ Potency assay available?
✓ Comparability issues?
Quality issues II

**Control & validation of the manufacturing process**
- Critical steps & limits (i.e. population doublings)
- Control via relevant markers, mRNA, protein expression

**Purity**
- Maximise active moiety
- Eliminate and control undesired dedifferentiated cells
  - Minimum requirement: consistency

**Tumourigenicity**
- Limit amount of dedifferentiated cells
- Demonstrate genotypic / phenotypic stability during process
Potency assay

- To utilise quality attributes of the cells to measure biological activity relevant for efficacy/safety in the patient
Potency assay & comparability

Aim: control manufacturing & finished product, to bridge to the new product following process changes
- Scale – up
- Site transfer
- New/amended starting material (i.e. primary cell culture)
Potency assay

should be in place for clinical development but absolutely for pivotal data
Potency assay

Biological activity

• Cell number
• Differentiation status
• Relevant gene/protein expression (i.e. microarray, flow cytometry, immuno-fluorescence, cell cloning, PCR)

• Functional performance \textit{in vivo}
  – tissue regeneration, repopulation (e.g. ectotopic model)
  – Metabolic activity (e.g. secretion of growth factors, metabolites)
  – Immunological activity (e.g. measurable immune response)
Potency test – practical aspects

• *in vivo* assays
  – tissue regeneration
  – Metabolic activity
  – Immunological activity

• *in vitro* assays
  – Gene/protein expression
  – viability
  – Other cell characteristics

• Time consuming
  • functional correlation
    ➢ Validation of process/comparability

• Can be quick
  • Based on surrogates
  • Should be correlated to functional assays
  ➢ Batch release
Preclinical issues

Animal models

✓ Species specificity on a molecular, cellular and tissue level
✓ Animal model suitable & predictive of safety?
✓ Homologous model / disease model (efficacy/ proof of concept)
✓ Non-homologous model (immunocompromised?) to test human product
✓ Biologically relevant animal model available (concomitant treatment immunogenicity, delivery)?

Large animal model necessary (surgical procedure, tissue regeneration)
Preclinical issues

**Biodistribution and Niche**
- Important for systemic applications
- Methods for tracking cells *in vivo* to be developed/employed
- Safety requirements

**Tumourigenicity & chromosomal stability**
- Thorough evaluation before first clinical use
- Study differentiation process / migration *in vivo*
- Manipulated/extensively cultured cell products
- Extent of testing dependent on route of administration, intended clinical use.
Clinical Issues

2 main clinical concerns: Safety
                      Long-term efficacy

✓ Non-clinical data available to justify B/R for clinical use?

✓ Clinical control available/feasible/ethical?

✓ Standardised collection & delivery procedure?

✓ Dose available & justified?

✓ Suitable endpoint (clinical indication, TEP specific)?

✓ Duration of follow-up (efficacy/safety)
Clinical criteria

Dose finding

- Minimally effective dose i.v. applied stem-cell products

Clinical efficacy

- common endpoints recommended in the studied indication (common guidance)
- Additional endpoints: specific structural endpoints

Clinical safety

- caution if stem cell products developed solely using non-clinical homologous model endpoints
- Safety FU combined with Efficacy FU
Pharmacovigilance

Follow-up of safety and lack of efficacy

Duration of follow-up → intended therapeutic effect and identified safety risks

Specific surveillance plan for long-term safety

Guideline on the safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008)
Follow-up of efficacy & safety post-marketing

- Efficacy as part of Risk-management

Positive

- Benefit-risk (clinical trials)
- MA
- Benefit-risk (post-marketing)

Long-term efficacy (tissue regeneration)

Life cycle management

Shift/extension of review procedure
Combined ATMP

Definition:

Incorporates a medical device according to Article 1(2)(a) of Dir. 93/42/EEC

and

Includes viable cells or tissue parts

or

In case of non-viable cellular/tissue part, the primary mode of action is attributed to the cell component as either pharmacological, immunological, metabolic or as repair, replacement, regeneration
Combined ATMPs

Validation of cell culture process with respect to integrity of cells/scaffold

- Effect of device on cell growth and activity
- Effect of cells on device function and integrity

✓ Characterisation and testing of cell-device combination
✓ Impurities and degradation products from device component
✓ CE mark of device component, if possible
Challenges for cell products

- Autologous product → limited amount of material for testing
- Short shelf-life → limited possibilities for batch release testing
- Difficulties to find a suitable potency test → correlation of cell quality to clinical outcome?
- No suitable animal models → non-clinical testing cannot be performed; clinical evidence?
- Wide clinical experience already → not necessary to conduct non-clinical studies?
- Administration of the cells impacts the final outcome / rare diseases / unmet medical need / proper comparator not available → open-label, single arm, non-controlled study with minimal number of patients enough? No clinical trial conducted?
Case study of an approved ATMP
Tissue Engineering - ChondroCelect

Articular cartilage regeneration with ChondroCelect®
Characterised Chondrocyte Implantation (CCI)

healthy knee

implantation

sealing of the defect

rehabilitation

defect

biopsy

marker analysis

cell expansion

TiGenix
Autologous Chondrocyte product approved as first ATMP

EPARs for authorised medicinal products for human use - ChondroClect - Microsoft Internet Explorer

Product Overview
Name of the Medicinal Product
ChondroClect

Marketing
Authorisation Holder
Tigenix NV
Romensestraat 12 bus 2
BE-3001 Leuven
Belgium

Active Substance
characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins

International
Nonproprietary Name or Common Name
characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins

Pharmacotherapeutic Group
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ATC Code
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Therapeutic Indication
Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present. Demonstration of efficacy is based on a randomised controlled trial evaluating the efficacy of ChondroClect in patients with lesions between I-10.9

European Public Assessment Report

ChondroClect

Published 16/11/09

Summary for the public
Public assessment report (6)

All Authorised Presentations
Procedural steps taken and scientific information after authorisation (6)

Conditions imposed on member states for safe and effective use

05/10/2000 ChondroClect-H-C-070-00-00

This document includes:

Annex I - Summary of product Characteristics
Annex IIa - Manufacturing Authorisation Holder responsible for Batch Release
Annex IIb - Conditions of the Marketing Authorisation
Annex IIIa - Labelling
Annex IIIb - Package Leaflet

Please note that the size of the above document can exceed 50 pages. You are therefore advised to be selective about which sections or pages you wish to print.

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Send all queries regarding the Web functionality to: EMAwebServices
ChondroCelect

- characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins.

**Therapeutic indication**

*Repair of single symptomatic cartilage defects of the femoral condyle of the knee in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present.*

*Demonstration of efficacy based on a randomised controlled trial evaluating the efficacy of ChondroCelect in patients with lesions between 1-5 cm².*

- CHMP positive opinion: June 2009, Commission decision October 2009
Quality data

- A series of functional tests for cell characterise, validation the manufacturing process
  - Cell culture (3D cell culture assay),
  - Functional assay in animal models,
  - Test of cellular expression patterns of genes relevant for cartilage and chondrocyte biology
- Validation of manufacturing process has been adequately performed.
- Comparability and consistency of lots manufactured were adequate

Preclinical data

- Combined pharmacodynamic / pharmacokinetic (distribution) / toxicological studies were performed in ectopic mouse and in orthotopic models in sheep and goats

- studies in goats adequate to demonstrate proof of principle in a clinically relevant setting

Clinical efficacy
- Study TIG/ACT/01/2000

- phase III, multicentre, randomized, controlled trial to compare ChondroCelect to microfracture in the repair of symptomatic single cartilaginous lesions of the femoral condyles of the knee

- 4-year extension phase

- Clinical non-inferiority in KOOS (patient-based outcome measure)

- Clinical superiority in a structural endpoint (structural assessments (histology and MRI))

Clinical safety

- total of 463 patients exposed
- Safety profile comparable to Microfracture
- Increased joint swelling related to the open knee surgery
- Cartilage hypertrophy reduced by use of biomembrane
- treatment failure was higher in the microfracture arm requiring subsequent surgical intervention.
- acceptable RMP including proposal for confirmatory randomized controlled trial and observational follow-up study

Conclusions

• ATMPs (stem cell products) authorised via centralised procedure involving the CAT

• Scientific Advice!

• ‘Mother guideline’ Human Cell-based medicinal products (EMEA/CHMP/410869/2006)

• **Quality:** characterisation, consistency, potency and comparability

• **Nonclinical:** adequate animal models, mechanism of action, biodistribution, safety

• **Clinical:** safety, long term efficacy, general endpoints + TEP-specific endpoint, duration of follow-up
EMA Regulatory procedures for ATMPs
EU Regulation for Advanced Therapies

Legislation

Medical Devices 93/42/EEC

Regulation EC (No) 1394/2007

Medicinal Products 2001/83/EC

Advanced Therapies

Medical Devices

Tissue Engineering

Cell Therapy

Gene Therapy

Biotech (e.g. insulin)

Pharmaceuticals (e.g. aspirin)

Committee for Advanced Therapies (CAT) expertise

CHMP expertise
‘Advanced Therapies’ Regulation EC (No) 1394/2007

- Definitions for gene therapy, cell therapy & tissue engineered products
- Mandate to EMA/EC to develop guidance
- Combined ATMPs
- Initial Marketing Authorisation Procedure + Requirements for ATMPs
- Post-authorisation requirements including efficacy FU
- Incentives (Scientific Advice, Certification procedure, Fee reductions)

Committee for Advanced Therapies

- Transitional period until 2011/2012
EMA Regulatory procedures for ATMPs

- Early Development
- Certification
- Scientific Advice
- Evaluation

- Quality
  - Quality, Non Clinical
  - Quality, Clinical
Advanced Therapies

Introduction

Advanced therapy medicinal products (ATMP's) are medicinal products for use, and are based on gene therapy, somatic cell therapy or tissue engineering. They offer groundbreaking new treatment opportunities for diseases and injuries of the human body. The regulatory framework for ATMPs is established by Regulation (EC) No 1394/2007 on advanced therapy medicinal products which is designed to ensure the free movement of these medicines within the European Union (EU), to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies in the field, while guaranteeing the highest level of health protection for patients. Regulation (EC) no 1394/2007 also establishes the new expert Committee on Advanced Therapies (CAT).

- Questions and answers on the regulation of advanced therapy medicinal products

Further information relating to EU legislation on advanced therapies is available on the European Commission's Pharmaceuticals website.
Early exploration

quality/preclinical
development

clinical trials I – III

MAA filing

Innovation task force
Briefing meetings

Orphan designation*

Letter of intent

Scientific Advice

Certification of Q / NC data

Regulatory Classification as ATMP

Clinical trial application at member states

CE marking of medical device

Paediatric development plan

EMA guidelines

* Orphan designation can be applied for at any time
Is the product an ATMP?

- To define Borderline e.g. with medical device, transplant, cosmetics.
- Incentive for applicants, not legal requirement
- Fast procedure (max 60 days)

Info on EMA website


Procedural advice
Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products

Previous cases
Summaries - Summaries of CAT scientific recommendations on ATMPs classification
How we advice on ATMP development

► Scientific Advice can be given on ANY scientific question: Quality, non-clinical and clinical

► At any time point of the development
  • Pre and Post-marketing advice

► Broad advice, Conditional approval and Exceptional circumstances

► Confidential

Info on EMA website


How to apply
Guidance for companies requesting Scientific advice and protocol assistance
Regulatory strategy: save time

**Scientific advice:** Complying with SA/PA is significantly associated with positive outcome

Evaluation of data generated during ATMP development

- Incentive for Small and medium enterprises (SME)
- Assessment of early quality and non-clinical data
- Fast procedure (90 days)
- Certificate may attract investments

Info on EMA website

www.ema.europa.eu -> Home / Regulatory / Human medicines / Advanced therapies / Certification procedure for SMEs

Procedural advice
Procedural advice on the certification on Q, N/C data for SMEs developing ATMPs

Scientific guidance
Guideline on the minimum quality and non-clinical data for certification of ATMPs
What it is

- Scientific evaluation of manufacturing, non-clinical data generated during development of an ATMP (not on a full Module 3/4)
- EMA evaluates compliance with scientific and technical requirements of Annex I Assessment of early quality and non-clinical data
- A CERTIFICATE is issued of those parts/studies that are performed finalised (in line with scientific standards for a MAA)

What it is not

- No assessment of benefit/risk
- No statements on appropriateness to enter into clinical trials
- No prospective statements pertaining to the further development of the product
The product development is completed!

► Principles of existing legislation on medicines apply to advanced therapies

► Centralised procedure mandatory

► A Committee with specific expertise evaluate MAAs

► Special features:
  • Risk based approach
  • Risk management Plan and follow-up of safety and efficacy
Related documents

Procedural advice


General Advanced therapies: Regulatory and procedural guidance

European Medicines Agency - Guidance - Advanced therapies: Regulatory and procedural guidance
Where to find information?

**EMA website:** [www.emea.europa.eu](http://www.emea.europa.eu)


**Cell therapy guidelines:**


**Regulatory & Procedural guidance:**

Who to contact

General Enquiries: info@ema.europa.eu

Advanced Therapies (including certification of ATMPs):
AdvancedTherapies @ema.europa.eu

Informal ITF Briefing meeting: ITFsecretariat@ema.europa.eu
Thank you for your attention

European Medicines Agency
brigitte.brake@bfarm.de
alberto.ganan@ema.europa.eu