Advanced therapy medicinal products

Overview of the current approach to regulation of Advanced therapy medicinal products (ATMPs)

Chances and Challenges

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Overview

1. Introduction

2. Implementation and key features of the ATMP regulation

3. CAT composition and tasks

4. Summary and conclusion
Definition of ATMPs

The European definition of advanced therapy medicinal products is comprised of three subcategories:

- Gene Therapy Medicinal Products (GTMPs)
- Somatic cell therapy medicinal products (SCMPs)
- Tissue engineered products (TEP)
Complexity of ATMPs

Differences in quartenary structure and Post translational modifications (ie glycosylation profiles) were main factors which led to the biosimilar discussion =>

Impact of manufacturing process on efficacy/safety profile

Adopted from: Dr. Christian K Schneider, MD, Are regulators up to speed to address the challenges of biotechnological medicinal products? EMA, December 15th, 2010
Scientific challenges and regulatory Consequences with ATMPs

Scientific challenges

• Non-uniform starting materials for autologous cell therapies
• Cells depend on their (micro) environment and react to it
• Cells may dedifferentiate and become heterogeneous during culturing processes or in-vivo after application
• Cells may migrate from their designated location
• ATMPs are often aimed at restoring physiological functions which last for a lifetime with a single or very few interventions
• Preclinical toxicity (animal) studies often are not applicable
• Current approaches for dose dependency / efficacy studies don’t work for cell-based therapies

Regulatory consequences

Difficulties in demonstrating pharmaceutical quality

Need for adequate characterization but also necessity to accept limitations (e.g. karyotyping, expression patterns for various marker gens)

Difficulties to demonstrate Efficacy and Safety in initial MAA based on trial designs / endpoints for non-ATMPS Necessity to establish long term safety / efficacy follow-up protocols

Need to develop new tests, accept surrogate models (use of immuno-deficient animals e.g. nude, SCID or Rag1 Mice models or use of a homologous model in an animal species)
Regenerative medicine cell therapies currently on the market

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Year of approval</th>
<th>Agency</th>
<th>Patients treated**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carticel®</td>
<td>symptomatic cartilage defects of the femoral condyle</td>
<td>1997</td>
<td>FDA</td>
<td>17000</td>
</tr>
<tr>
<td>Apligraf®</td>
<td>venous leg ulcers</td>
<td>1998</td>
<td>FDA</td>
<td>250000</td>
</tr>
<tr>
<td></td>
<td>diabetic foot ulcers</td>
<td>2001</td>
<td>FDA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>chronic Ulcers and soft-tissue defects</td>
<td>2008</td>
<td>Reimbursement in Switzerland</td>
<td></td>
</tr>
<tr>
<td>Dermagraft®</td>
<td>diabetic foot ulcers and other chronic wounds</td>
<td>2010</td>
<td>SFDA*</td>
<td>&gt;50000</td>
</tr>
<tr>
<td>Orcel®</td>
<td>mitten-hand deformity</td>
<td>2001</td>
<td>FDA</td>
<td>&gt;200</td>
</tr>
<tr>
<td></td>
<td>donor site wounds burn patients</td>
<td>2001</td>
<td>FDA</td>
<td></td>
</tr>
<tr>
<td>Epicel®</td>
<td>burn wounds</td>
<td>2007</td>
<td>FDA</td>
<td>1653</td>
</tr>
<tr>
<td>Chondrocelect®</td>
<td>symptomatic cartilage defects of the femoral condyle</td>
<td>2009</td>
<td>EMA</td>
<td>500</td>
</tr>
</tbody>
</table>

**Total patients treated**: >320000

* Saudi Food and Drug Authority ** cumulative number of patients until March 2010

Unique composition of ATMP sponsors*

* Source: Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive
R. Maciulaitis, L. D’Apote, A. Buchanan, L. Pioppo and C. K. Schneider, Molecular Therapy, vol. 20, no. 3, march 2012
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Definition of Gene Therapy Medicinal Products*

A Gene Therapy Medicinal Product is defined as:

- 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

- 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

Regulation of cell based and gene therapy medicinal products before 2008:

- **Gap in Regulation**
- Regulation depending on the member state as:
  - **Medical Device**
  - **Medicinal product**
  - **Tissue preparation**
- No GMP requirement across all MS

- **Gap in Expertise**

- **Medical devices according to 93/42/ECC**
- **Varying degrees of expertise across MS agencies**

- **Medical products according to directive 2001/83/EC**
- **Somatic cell therapy**
  - defined as biological MPs as early as 2003 via 2003/83/EC
- **Gene therapy**
  - Little specific expertise within the CHMP

- **Devices**
  - **Tissue engineering**
  - **Biologics**
  - **Small molecule entities**
Harmonized rules are needed:

- ensure a high level of scientific evaluation of these medicinal products in the Community, preserve the confidence of patients and medical professions in the evaluation and facilitate Community market access for these innovative technologies

- Clear definition of ATMPs (in conjunction with Dir. 2009/120)
- Mandatory MA via centralized procedure for all ATMPs
- Establishment of a specialized Committee (CAT)
- Incentives for SMEs to foster innovation
Regulation of cell based and gene therapy medicinal products after introduction of the ATMP regulation

- Medical devices according to 93/42/ECC
- ATMPs as defined in Regulation 1394/2007
- Medicinal products according to directive 2001/83/EC

<table>
<thead>
<tr>
<th>Devices</th>
<th>Tissue engineering</th>
<th>Somatic cell therapy</th>
<th>Gene therapy</th>
<th>Biologics</th>
<th>Small molecule entities</th>
</tr>
</thead>
</table>

Regulatory / Scientific expertise is provided by the CAT

a single scientific evaluation of the quality, safety and efficacy of ATMPs carried out to the highest possible standard available

Reg. 1394/2007 introduced additional provisions to those laid down in Directive 2001/83/EC
Regulation of cell based and gene therapy medicinal products after introduction of the ATMP regulation

- **ATMP Regulation 1394/2007**
  - Modern biological MPs
  - Based on human Cells or tissues
  - Combined ATMPs Device requirements

- **Directive 2001/83/EC**
  - Community code relating to all medicinal products for human use
  - Requirements with a view to MA

- **Directive 2004/23/EC**
  - standards of quality and safety for the donation, procurement, testing, human tissues and cells

- **Directive 2006/17/EC**
  - technical requirements for the donation, procurement and testing

- **Directive 2006/86/EC**
  - technical requirements for traceability requirements, notification of SA-reactions and events

- **Directive 93/42/EEC**
  - concerning medical devices

- **Directive 90/385/EEC**
  - relating to active implantable medical devices

- **Regulation 726/2004**
  - Centralized procedure via EMA
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Composition of the Committee for advanced therapies (CAT)

5 Members and alternates nominated from within the CHMP “CAT/CHMP Double members”

1 Member and alternate appointed by each EU member state (27) except for those which are included in the CHMP nominees

2 Members and alternates appointed by the European Commission to represent patient associations

2 Members and alternates appointed by the European Commission to represent clinicians

61 CAT Members and their respective fields of expertise

1 Member and alternate appointed from national CA by each EU member state (27) except for those which are included in the CHMP nominees

1Source: Challenges with advanced therapy medicinal products and how to meet them, Nature Reviews Drug Discovery 9, 195-201 (March 2010)
Primary tasks of the Committee for advanced therapies (CAT)

• **Scientific evaluation of ATMP marketing authorization applications**
  Draft adopted by the CAT – Final opinion adopted by the CHMP

• **Classification procedure**
  Clarification whether your product falls within the scope of the ATMP regulation

• **Scientific Advice**
  Provide scientific advice for ATMPs / provide input on ATMP related questions form other committees (CHMP / PDCO)

• **Certification procedure**
  Assessment of early quality and non-clinical data
Primary tasks of the Committee for advanced therapies (CAT)

COMP = Committee for Orphan Medicinal Products
CHMP = Committee for medicinal products for human use
PDCO = Pediatric committee
CAT = Committee for Advanced Therapies

GTWP = Gene Therapy WP
CPWP = Cell-based products WP
BWP = Biologics WP
QWP = Quality WP
SWP = Safety WP
PhVWP = Pharmacovigilance WP

EMA/CAT-NB = EMA/CAT and Medical Devices’ Notified Body Collaboration Group
Evaluation of ATMP MAAs

**CAT**
- Scientific Assessment (incl. Day 80/150 AR, Adoption LoQ, LoOI)
- Adopt draft opinion (Day 200)

**CHMP**
- Appoints Rapporteur
- Adopts Final CHMP opinion (Day 210)

Clockstop

Day 0 Evaluation Start
Day 80 AR
Day 120 LoQ
Day 121 Response
Day 150 AR
Day 170 LoOI
Day 171 CAT O.E.
Day 171 Grounds for approval/refusal Transmission To CHMP
Day 200 CAT Adopts draft opinion
Day 210 CHMP Adopts final opinion

Day 120 LoQ to CHMP
Highlights
M.O. / divergence
Evaluation of ATMP MAAs

What is different for ATMPs?

- Rapp/CoRapp are from CAT, not CHMP
- Scientific discussion on LoQ/LoOI/OE at CAT
- CAT adopts LoQ, LoOI and draft opinion
- CHMP fully informed of progress of CAT evaluation
- Circulation of Rapps AR to CHMP, discussion of LoQ/LoOI etc.
- CHMP will adopt the final opinion at Day 210

ATMP evaluation procedure builds on full transparency between CAT and CHMP to avoid divergent views
Tasks of the assessment team members

CAT (Co) Rapporteur

• coordinates the procedure & discussions at CAT

• preparation of assessment reports

CHMP (Co) Coordinator

• responsible for flow of information between CAT & CHMP

• discussion/adoption of opinion

Peer review by one CHMP member and at least one CAT member

There should be adequate and sufficient interaction and communication between the two Committees, CAT and CHMP, via the Assessment Team members*

*CAT RULES OF PROCEDURE, EMEA/CAT/EMEA/454446/2008
Classification Procedure

The CAT provides a recommendation:

- as to whether the product in question falls within the ATMP definition
- And if so, to which ‘subclass’ of ATMP it belongs (GTMP, SCMP, TEP)
- Takes up to 60 Days, possibility of ‘clockstop’ at day 30

Available to all applicants

- Gain understanding of required regulatory pathway at an early stage of development
- Widely adopted => approximately 90 classification requests finalized since coming into force of the ATMP regulation
Thus the CAT offers a certificate regarding the quality and/or preclinical data of an ATMP in order to support SMEs when they are:

- Rallying for new investors
- Looking for support from bigger pharmaceutical companies
- Try to obtain approval for a CTA from national competent authorities

ATMPs are mostly developed by small to medium sized enterprises (e.g. university spin-offs) which:

- largely depend on venture capital
- often lack the resources to conduct ‘full scale’ clinical trails
- Do not know how to successfully navigate the regulatory landscape

Thus the CAT offers a certificate regarding the quality and/or preclinical data of an ATMP in order to support SMEs when they are:

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Not widely adopted => only two applications for certification procedure

- In 2012 EMA conducted a survey to assess the reasons for the slow adoption among stakeholders
- Main points identified were
  - limited added value as compared to scientific advice
  - Certification only available to SMEs
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Problems identified

• Since coming into force of the ATMP regulation in December 2008 until November 2013 only 10 initial MAAs have been received at the EMA and only five positive opinions have been issued by the CAT resulting in approval of four ATMPs

• During the same period the number of positive opinions for new chemical entities (excluding ATMPs) was approximately 35 per year

• Incentives in the ATMP regulation are specifically tailored to and exclusively available for small to medium sized enterprises

• The EMA has engaged in a consultation with relevant stakeholders in order to revise the current ATMP regulation. The consultation was finalized in 2012.
EMA consultation –
Major points identified

MAA Dossier requirements are still designed for conventional medicinal products
Any tailoring for ATMP specific requirements would be beneficial

• Especially the drug substance requirements for autologous cell based therapeutics should be clarified

• Hospital exemption deters the pursuit of an MAA in certain circumstances
  • Should not be available in indications where an ATMP is already approved

• Incentives for any ATMP related regulatory procedure should be opened to non-commercial entities such as academia and charity organizations to better reflect the actual stakeholders in the ATMP field

• Further clarification on applicability / necessity of animal models in pre-clinical development is required
In summary

• Stakeholders appreciate the establishment of the regulatory framework for ATMPs as the regulatory processes and requirements to obtain a MAA are now clearly mapped out.

• The current framework is in need to adopt some of the previously outlined changes in order to better accommodate the characteristics specific to ATMPs and to better recognise the resource constraints of the involved stakeholders.

• The upcoming revision of the ATMP regulation is a chance to keep Europe at the heart of biotech innovation.

• If however the identified gaps are not addressed properly a stifling of innovation is likely to occur.