The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CAT or reflecting the position of the CAT.

Margarida Menezes Ferreira
Senior Assessor at INFARMED
PT expert at the Biologics Working Party - BWP/CHMP – EMA
PT member at the Committee for Advanced Therapies - CAT – EMA
(margarida.menezes@infarmed.pt)

EUROPEAN REGULATION OF CELL BASED MEDICINAL PRODUCTS
ADVANCED THERAPY MEDICINAL PRODUCTS - ATMP


- Somatic cell therapy
- Gene therapy

TEP not defined

Somatic cell therapy and DE, IT, FR


Centralised marketing authorisations (MA) from 1/2009

Tissue engineered

TEP / regenerative medicine
Combined products
Non-substantial manipulation
Long term efficacy follow up
Hospital exemption...


ATMP specific
Dossier requirements
for MA

NEW DEFINITIONS for GeneTherapy and Somatic Cell Therapy

Directive 2001/83/EC revised

GOVERNO DE PORTUGAL
of 13 November 2007
on advanced therapy medicinal products and amending Directive 2001/83/EC
and Regulation (EC) No 726/2004

- Definitions supporting regenerative medicine TEP / Combined - medical devices
- Clarifying fronteers - Non-substantial manipulation to separate from transplantation
- Centralised MA from Jan 2009 / new Committee CAT
- Traceability – flow between cell donation vigilance - pharmacovigilance
- National system for hospital exemption for named patient and non routine
- Specific GMP requirements
- Long term efficacy follow up
- hESC - national prohibitions apply
- Incentives for SME
- Revise Annex 1 of Directive 2001/83/EC to establish new dossier requirements

Directive 2009/120/EC – specific requirements for MA of an ATMP
NOT substantial = NOT medicinal product:

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

heterologous use = medicinal product

Regulation 1394/2007/EC
New Commission Regulation determines:
EUROPEAN CENTRALIZED PROCEDURE
FROM 30 December 2008

Gene Therapy
Somatic Cell Therapy
Tissue Engineered Products

new Committee for Advanced Therapies - CAT
at the European Medicines Agency - EMA
AUTHORISATION UNDER HOSPITAL EXEMPTION

Applies to:

- Any **ATMP**, 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, following an individual medical prescription
- **custom-made product** for an individual patient.

How:

- Competent **authority authorises manufacturing** of these products
- Requires **traceability and pharmacovigilance**
- + **specific quality standards equivalent** to Community MA of ATMP
The normal path of an authorised medicinal product: 

1. **R&D**
2. **Non clinical**
3. **Clinical Trials**
   - 2001/20/EC
4. **Market Authorisation**
   - 2001/83/EC amended

---

**Manufacturing Authorisation**

- **GLP (tox)**
- **GCP**
- **GMP**
Risk-based approach: a strategy to determine the extent of quality, non-clinical and clinical data to be included in the Marketing Authorisation Application dossier.

- identify the risks and associated risk factors,
- establish a risk profile
- With the identified risk profile possible to justify the extent of data to be included in the MAA dossier

**Risk**: an unfavourable effect that can be attributed to the ATMP and is of concern to the patient and/or to third parties.

**Risk factor**: a qualitative or quantitative characteristic that contributes to a specific risk following administration of an ATMP.

**Risk profiling**: a methodological approach to systematically integrate all available information on risks and risk factors in order to obtain a profile of each individual risk associated with a specific ATMP.
Consequences for the dossier

- Risk based approach not mandatory

- Strategy for each risk and discussion on conclusions and justifications supporting the extent of data – to be included in the MAA CTD Mod 2.2.

- Result of the risk-based approach can be used as one starting point for the safety specifications as part of the Risk Management Plan.
Detailed guidelines on good clinical practice specific to advanced therapy medicinal products

ATIMP should be **traceable** through the sourcing, manufacturing, packaging, storing, transport, delivery to the hospital/institution/private practice, administration to the subjects, reconciliation and destruction or final disposition.

Subjects should be followed-up during and, if necessary, after the end of the clinical trial both for their own care and to allow data collection as needed. **Long-term follow-up** after the end of the trial should be determined based on the nature of the ATIMP.
DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

Article 13

Manufacture and import of investigational medicinal products

(b) in the case of investigational medicinal products manufactured in a third country, that each production batch has been manufactured and checked in accordance with standards of good manufacturing practice at least equivalent to those laid down in Commission Directive 91/356/EEC, in accordance with the product specification file, and that each production batch has been checked in accordance with the information notified pursuant to Article 9(2) of this Directive;

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Health systems and products
Medicinal products – quality, safety and efficacy

Brussels,
SANCO/D/6/SF/mgd1.d.6(2013)1104750

TEMPLATE FOR THE QUALIFIED PERSON'S DECLARATION EQUIVALENCE TO EU GMP FOR INVESTIGATIONAL MEDICINAL PRODUCTS MANUFACTURED IN THIRD COUNTRIES

MUTUAL RECOGNITION AGREEMENTS
Sectoral Annex on Good Manufacturing Practices
Issues related to Investigational Medicinal Products
Coverage from 1 May 2004

Information on Investigational Medicinal Products in MRA partner countries:

<table>
<thead>
<tr>
<th></th>
<th>IMPs covered by the MRA</th>
<th>limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>yes</td>
<td>Clinical trial products in phase I trials are excluded as they are not GMP regulated in Australia</td>
</tr>
<tr>
<td>Canada</td>
<td>yes</td>
<td>currently limited to sites in Canada already holding an establishment licence</td>
</tr>
<tr>
<td>Japan</td>
<td>no</td>
<td>may be in the future</td>
</tr>
<tr>
<td>New Zealand</td>
<td>yes</td>
<td>same as Australia</td>
</tr>
<tr>
<td>Switzerland</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>no</td>
<td>MRA not operational</td>
</tr>
</tbody>
</table>
## Volume 4
EU guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

### Annex 2
Manufacture of Biological active substances and Medicinal Products for Human Use


**Deadline for coming into operation:** 31 January 2013

### Table

<table>
<thead>
<tr>
<th>sources</th>
<th>enzymes, hormones</th>
<th>fluid</th>
<th>processing</th>
<th>purification</th>
<th>filling</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Human and / or animal sources</td>
<td>Gene therapy: genetically modified cells</td>
<td>Donation, procurement and testing of starting tissue / cells</td>
<td>Manufacture vector and cell purification and processing.</td>
<td>Ex-vivo genetic modification of cells, Establish MCB, WCB or cell stock</td>
<td>Formulation, filling</td>
</tr>
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<td></td>
<td>Somatic cell therapy</td>
<td>Donation, procurement and testing of starting tissue / cells</td>
<td>Establish MCB, WCB or cell stock</td>
<td>Cell isolation, culture purification, combination with non-cellular components</td>
<td>Formulation, combination, fill</td>
</tr>
<tr>
<td></td>
<td>Tissue engineered products</td>
<td>Donation, procurement and testing of starting tissue / cells</td>
<td>Initial processing, isolation and purification, establish MCB, WCB, primary cell stock</td>
<td>Cell isolation, culture purification, combination with non-cellular components</td>
<td>formulation, combination, fill</td>
</tr>
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</table>

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**Increasing GMP requirements**
GMP – Annex 2
Starting and raw materials
36. Human tissues and cells (T&C)

- EU procurement, donation and testing approved by EU T&C authorities
- Importations meet the same standards as EU T&C
- Initial processing may be conducted in Tissue Establishments (TE) under T&C Directive 2004/23/EC = T&C Responsible Person (RP) release
- Testing results available to Pharma Qualified Person (QP)
- Technical agreement between TE, manufacturer, sponsors (CT), MA holder
- Defined roles for RP and QP for, testing, transportation, traceability
Authorisation of tissues and cells procurement + donor testing

by transplantation authority

authorisation of collection and testing and tissue establishments (TE) for banking

Export / Import activities in the EU by authorised TE

✓ TE ensures that imported cells from 3rd countries allows traceability to donor and collection and testing under equivalent standards as Directive

✓ Cells exported from EU comply with this Directive
hierarchy of guidelines – for MA!
No ATIMP guidance – consult BIMP

COMMITTEE FOR MEDICINAL PRODUCT FOR HUMAN USE (CHMP)

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS

DATE FOR COMING INTO EFFECT 1 September 2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON POTENCY TESTING OF CELL-BASED IMMUNOTHERAPY MEDICINAL PRODUCTS FOR THE TREATMENT OF CANCER

DATE FOR COMING INTO EFFECT 15 May 2008

Reflection paper on stem cell-based medicinal products
Adoption by CAT 14 January 2011

Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee
Final 16 April 2010
ATIMP – 3rd country – common scenario - autologous / allogeneic - units / stocks

**HOSPITAL - US**

- **collection**
- **TE - RP** (SPONSOR QP)
- **+ Preparation**
- **Starting material** (+ biologic raw materials + HSA?)

**HOSPITAL - EU**

- **HOSPITAL PHARMACY**
  - Thawing / washing = reconstitution
  - ?
- **INVESTIGATOR**
  - administration

**MANUFACTURER - US or EU**

- **Starting material** (+ biologic raw materials )
- **SA - Manufacturing process**
  - Stabilisers ?
  - Criopreservation ?
- **EU QP**
- **/ US QP**

**IMPORTER**

- **US QP**
  - Shipping to EU

**FP - Combination / formulation**

- (+ excipients + biologic residual ? + HSA? )

**FP - Criopreservation**
### Case study: NewStem Biologics

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<th>Issue</th>
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<td>MCB / WCB are not cell substrates banking = ICHQ5D +++ starting materials</td>
<td>MCB is also under manufacturing Process control</td>
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**NewCell B and C**

- Safety data
- Clinical data
- Filiations
- Comparability – implies characterisation / potency

**NewCell A transport**

- QP verification - defined Conditions – specs temperature, timings
- QP Acceptance / rejection

**NewCell A customs in Portugal**

- Identified as ATIMP Warning as Biological specimen – IATA agreements
- Trial Authorisation by Infarmed Eudract number

**NewCell A thawing + reconstitution**

- Qualified procedure
- QP ensures training – Clear instructions
- Hospital pharmacy responsibility
## Case study: NewStem Biologics

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**Note:**

- **QP** stands for Quality保证.
- **IATA** refers to the International Air Transport Association agreements.
- **Infarmed** is the Portuguese National Medicines Agency.

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**Image Credits:**

- GOVERNO DE PORTUGAL
- **intermed**

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# Case study: NewStem Biologics

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<td>MCB + WCB + AS processes</td>
<td>Starting materials + bio raw materials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viral safety = TSE’s minimisation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Culture</td>
<td>Communications controls – cell viability</td>
</tr>
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<td></td>
<td>Asseptic process validated</td>
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<td>- Clear instructions</td>
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Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

Guidance for proteins – certain aspects not directly relevant
but
General recommendations apply

analytical validation / process validation / viral validation - required for phase III
Asseptic process validated
Control specifications built on acceptance criteria – few batches

Major concern with trials is on safety:
Viral safety / TSE’s – full consideration / risk assessment
Integrated strategy:

- **Source** of possible infectious agents:
  - Origin of the cells / tissues
  - reagents in manufacturing process

- Infectivity and pathogenicity of the infectious agent considering the use and mode of administration

- **Testing** at the level of the donation, biological raw and other starting in process / final product

- **Removal / inactivation capacity** of the manufacturing process
Raw materials: reagents

general text in the Eur Phar in preparation for 2014

- serum/medium
- cytokines / growth factors
- enzymes (such as trypsin)
- antibodies
- individual proteins
- buffers
- plasmids/ viral vectors

Identity
Purity
Biological Activity / Functionality
Specific Activity
Total Protein content
Impurities, Product-related
Impurities, Process-related
Viral Safety / TSE compliance
Microbial Contamination
Stability / Storage conditions

-GUIDELINE the use of **bovine serum** in the manufacture of human biological medicinal products (EMA/CHMP/BWP/457920/2012 rev.1) UNDER NEW REVISION

-GUIDELINE the use of **porcine trypsin** used in the manufacture of human biological medicinal products (EMA/CHMP/BWP/814397/2011) DRAFT
2.6.27. MICROBIOLOGICAL CONTROL OF CELLULAR PRODUCTS

This test has been shown to be preferable to the test for sterility (2.6.1) for certain cellular products, since it has better sensitivity, has a broader range, and is more rapid. It is applied instead of the test for sterility (2.6.1)


Variable characterisation and control

Product definition - intended function often based on multiple interactions
dynamic processes/ cell like or tissue like / immunogenic / proliferative / …

Identity – choice of phenotypic markers

Cell purity / impurities – relevant cells versus other cells = impurities, viable and non
viable / heterogeneity profile / cell debris

Impurities (process related) – adventitious agents / reagents

Potency – according to intended function – required for comparability, consistency
and stability

Tumourigenicity – proliferative capacity / genetic instability
New CT Regulation - draft

- single Clinical Trial Application (CTA) with defined and harmonized requirements
- single-EU Portal electronic submission.
- improve transparency about the recruitment of participants in a clinical trial and the results of the clinical trial.
- Member States cooperate in the assessment
- assessment is made by each Member State individually of intrinsic ethical or national/local aspects (e.g. liability, informed consent, suitability of clinical trial site etc).
- proportionality approach to risk
- changes to insurance rules and compensation
- (co) promotion and inspections.
Thank you for your attention!