Somatic Cell Therapy Medicinal Products

• This includes any type of cells, irrespective of their source (human-autologous or allogeneic- and animal), the degree of differentiation (committed cells, progenitors or stem cells) or their origin (embryo, foetus, new born or adult individuals).

• A further issue concerns the concept of somatic cell therapy products within the scope of medicinal products. This definition is also found in the Commission Directive 2009/120/EC²: “Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics: (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor; (b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.”

• For the purposes of point (a), the manipulations listed below (as they are listed in Annex I to Regulation (EC) No 1394/2007³), shall not be considered as substantial manipulations:
  - Cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation or vitrification.
Gene Therapy Medicinal Products

• From the regulatory point of view, the definition of a gene therapy medicinal product is more precise regarding the objectives and effects and it excludes vaccines from its scope. The definition is found in the Commission Directive 2009/120/EC: “Gene therapy medicinal product means a biological medicinal product which has 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.
Tissue Engineered Products

• The first idea that springs to mind when we are speaking about tissue engineered products is a scaffold, more or less complex, biological or not, in combination with cells. Although this may indeed be typical of a tissue engineered product, a scaffold does not necessarily need to be present for a product to be included in this category of ATMPs.

• The definition is set out in the Regulation (EC) Nº 1394/2007 as follows:
  - “Tissue engineered product means a product that: contains or consists of engineered cells or tissues, and 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.
  - A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.
Combined Advanced Therapy Medicinal Products

• The last category of ATMPs comprises the combined advanced therapy medicinal product. Regulation (EC) Nº 1394/2007 defines an advanced therapy medicinal product as that which “fulfils the following conditions:
  - 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.”

• As in the previous cases, the Regulation also considers that “where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product.”
Limits between ATMPs Categories

Taking these possibilities into account, some products could fall into different categories of ATMPs, but the Regulation (EC) Nº 1394/2007\(^3\) clarifies this: “A product which may fall within the definition of a somatic cell therapy medicinal product or a tissue engineered product, and a gene therapy medicinal product, shall be considered as a gene therapy medicinal product.”
Core Competency

The ability to manufacture GMP-grade human cellular therapy products
Production Overview

• Blood and tissue Establishment (CRF)-bone marrow aspirate
• CCMI:
  – Validated Facility
  – Controlled Environment
  – Validated Protocols
  – Qualified Materials
  – In-Process Control
  – Release Criteria
  – QP Release of Product
Bone Marrow Acquisition

• CCMI uses the Clinical Research Facility (CRF) in NUIG

• CRF has a tissue Establishment Licence
  – Recruitment of volunteer patients
  – Screening patients (Blood tests)
  – Physical examination of patients
  – Bone marrow aspiration by clinician
  – Labelling and documentation of BM
  – Repeat Blood tests (within 30 days)
1. Biological tests required for donors

1.1. The following biological tests must be performed for all donors as a minimum requirement:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV 1 and 2</td>
<td>Anti-HIV-1,2</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>HBsAg</td>
</tr>
<tr>
<td></td>
<td>Anti HBc</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Anti-HCV-Ab</td>
</tr>
<tr>
<td>Syphilis</td>
<td>See 1.4 (below)</td>
</tr>
</tbody>
</table>

1.2. HTLV-I antibody testing must be performed for donors living in or originating from high-incidence areas or with sexual partners originating from those areas or where the donor’s parents originate from those areas.

1.3. When anti-HBc is positive and HBsAg is negative, further investigations are necessary with a risk assessment to determine eligibility for clinical use.

1.4. A validated testing algorithm must be applied to exclude the presence of active infection with *Treponema Pallidum*. A non-reactive test, specific or non-specific, can allow tissues and cells to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a specific Treponema confirmatory test is non-reactive. A donor whose specimen tests reactive on a Treponema-specific test will require a thorough risk assessment to determine eligibility for clinical use.

1.5. In certain circumstances, additional testing may be required depending on the donor’s history and the characteristics of the tissue or cells donated (e.g. RhD, HLA, malaria, CMV, toxoplasma, EBV, *Trypanosoma cruzi*).
CCMI Starting Material

- Bone Marrow
- Production Materials:
  - Tissue Culture Flasks
  - Tissue Culture Medium
  - Foetal Bovine Serum
  - Trypsin
  - PBS
  - Other plastics...tubes, pipettes
  - Final packing material...cryobags
Raw Material for CCMI

- Bone marrow aspirate
- Donor identification and consent
- Donor assessment:
  - Physical examination and assessment
  - Medical history review
  - Selection criteria (deferral reasons)
  - Biological testing
Validations : Verifications

- Operator Gowning Qualification
- Operator Material Transfer Qualification
- Operator Aseptic Technique
- Operator Cell counting using Haemocytometer
- Viability Testing using Trypan Blue
- Cryobag Integrity Testing
- Media Fill
- Foetal Bovine Serum Qualification (Serum Screen)
- IMP Reconstitution
- Filling time
- Hold time study
- Verification Batches
In-process QC Controls

• Sampling of materials used for the process
• Sampling of reagents in process
• Sampling of ‘spent’ culture media (Sterility, Endotoxin and Mycoplasma)
• Technical staff EM monitored throughout procedures
# CCMI Production Process and QC Testing

<table>
<thead>
<tr>
<th>Manufacturing Process</th>
<th>In-Process and Final Drug Substance</th>
<th>Controls and Tests</th>
<th>Final Drug Substance Released</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation, Expansion and Cryopreservation</td>
<td>In-Process Acceptance Criteria</td>
<td>In-Process Acceptance Criteria</td>
<td>In-Process Acceptance Criteria</td>
</tr>
<tr>
<td>Bone Marrow Receipt from GSBTE</td>
<td>Patient must be free from all viruses to participate in the Clinical Trial</td>
<td>Bone Marrow Sterility must be free from microbial growth</td>
<td></td>
</tr>
<tr>
<td>Seeding of hMSC at Passage 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expansion of hMSCs until large non-overlapping colonies formed with spindle like morphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subculture to Passage 1</td>
<td>In-Process Control: Colony Size. If colonies are not formed by Day 21 of P0 the process is stopped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subculture to Passage 2</td>
<td>In-Process Control: Colony Size, cell count, viability, sterility, mycoplasma and endotoxin testing.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subculture from Passage 2 to Passage 1</td>
<td>In-Process Control: Confluence. If sufficient confluence is not observed by Day 7 of P1 the process is stopped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Process Control: Confluence, cell count and viability.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Process Control: Confluence, cell count and viability.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Release Tests: Sterility, Endotoxin, Karyology, Mycoplasma, Viability, Immunophenotyping</td>
<td>Sterility: Free from microbial growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Drug Substance Testing</td>
<td>Mycoplasma: No mycoplasma detected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Product Testing</td>
<td>Endotoxin: For information only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Drug Substance Released</td>
<td>Mycoplasma: No mycoplasma detected</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Controls and Tests

- **In-Process Acceptance Criteria**
  - Patient must be free from all viruses to participate in the Clinical Trial
  - Bone Marrow Sterility must be free from microbial growth
- **In-Process Control**
  - Colony Size: If colonies are not formed by Day 21 of P0 the process is stopped
  - Colony Size, cell count, viability, sterility, mycoplasma and endotoxin testing.
  - Confluence shall be between 80-90% for subculture to P2.
  - Confluence shall be between 80-90% for subculture to P2.
  - Confluence shall be between 80-90% for subculture to P2.
  - Confluence shall be between 80-90% for subculture to P2.

### In-Process and Final Drug Substance

- **Release Tests**
  - Sterility
  - Mycoplasma
  - Endotoxin
  - Karyology
  - Viability
  - Immunophenotyping
Final Product Packaging
Cryopreservation

Cryopreservation

Grade A Air

Quantity of hMSCs

Reconstitution of cells in Cryo-media in Cryobags

Temperature Control

Liquid nitrogen Controlled Rate Freezing

Storage
Finished Product Testing

• Sterility
• Viability
• Mycoplasma
• Endotoxin
• Immuno-phenotyping
• Karyology
Challenges

- The manufacturing of cellular products is unique in that it is not a conventional pharmaceutical product but it is a biological product which is manufactured from a living tissue source (starting material).
- Although it is nonconventional in a pharmaceutical context, the manufacturing of these still require the same level of rigor and overall GMP regulatory requirements.
- As the starting material is of a human source, this can lead to variability in the manufacturing of the product and batch to batch variation, although the same release criteria must be applied to each batch.
Challenges

• The sustainability of these manufacturing facilities is another key challenge.
• While the traditional pharmaceutical industry is driven primarily by profit and fulfilling shareholder needs, the ATMP facilities are largely funded through governmental funding at local and international levels.
• These facilities are largely focused on patient benefit and act as translational facilities from the bench to the bedside.
• The focus is not profit driven for the majority of such ATMP facilities and so the challenge of maintaining and running these pharmaceutical facilities is significant.
• The same level of rigor and compliance to GMP as in a conventional pharmaceutical facility is required in these smaller non-profit operations.
## Manufacturing Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pharmaceutical</th>
<th>ATMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw Materials</td>
<td>Chemical/Pharmac</td>
<td>Biological/Pharmac</td>
</tr>
<tr>
<td>Product</td>
<td>General</td>
<td>Allogeneic/autologous</td>
</tr>
<tr>
<td>Batches</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Labour and costs</td>
<td>**</td>
<td>****</td>
</tr>
<tr>
<td>Premises</td>
<td>Large facilities</td>
<td>Small facilities</td>
</tr>
<tr>
<td>Quality control costs/dose</td>
<td>*</td>
<td>*****</td>
</tr>
<tr>
<td>Personnel qualifications</td>
<td>**</td>
<td>****</td>
</tr>
<tr>
<td>Specificity quality controls</td>
<td>**</td>
<td>****</td>
</tr>
<tr>
<td>Good stability, long expiry date, easy shipping, etc....</td>
<td>****</td>
<td>*</td>
</tr>
</tbody>
</table>
Global Perspective

• The UK is making significant progress in manufacturing cell and gene therapies and have shown good foresight by developing the Cell and Gene Therapy Catapult. Catapult was established in 2012 as an independent centre of excellence to advance the growth of the UK cell and gene therapy industry. The vision is that the UK has the capacity and skills needed to stay globally competitive in advanced therapy manufacturing capacity and capability in cell and gene therapy.

• **Catapult** are opening their own 7,200m² cell and gene therapy facility in Stevenage next year will provide a step change to the UKs manufacturing offering that will help deliver revolutionary treatments for patients and assist companies to develop manufacturing in the UK.

• Continued increase in the number of GMP manufacturing facilities in the UK; **22 facilities in 2016**, rising from 18 in 2015 and 13 in 2014. Of this increase, 3 are gene therapy manufacturing facilities and an additional facility in cell therapy.

• An increase in the number of people employed across UK cell and gene therapy manufacturers by a further 20% – from **324 to 391**.

• A 9% increase in total clean room footprint for cell therapy facilities, now totalling nearly 1900m², whilst gene therapy clean room footprint almost trebled to more than 2400m².
Global Perspective

• **India** has 9 major organisations at present engaged in stem cell research, and the field of regenerative medicine and stem cell biology is gaining ground.

• The stem cell market in India is estimated to touch $600 million by 2017 and their government is focusing on a strategy to leverage intellectual talent and become a global leader in stem cells research and therapy.

• "The government's aim is to develop a cure for human ailments with unique stem cell based therapies, as well as regenerative medicine", said a Ministry of Health official. He added that, compared to other countries, India has more liberal regulations governing stem cell research. "The approval by the Drug Controller General of India (DCGI) for clinical trials of stem cell based drugs is proving to be a winner. Many global stem cell players are keen to work in India, and pursue their clinical trials there."
Global Perspective

• Stem cell market is predicted to be worth $330 million dollars in 2020.
• There are 5,482 clinical trials, using stem cells, in progress across the globe (ClinicalTrials.gov) at the moment.
• The global stem cell therapy market on the basis of the mode of treatment is segmented into allogeneic and autologous stem cell therapy. In addition, based on the therapeutic applications, the global stem cell therapy market is segmented into eye diseases, metabolic diseases, GIT diseases, musculoskeletal disorders, immune system diseases, CNS diseases, CVS diseases, wounds and injuries, and others.
• A number of factors such as the increasing funding from various government and private organizations, growing industry focus on stem cell research, and increasing global awareness about stem cell therapies through various organizations are stimulating the research activities for stem cell therapies.
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Global Perspective

Figure 4. Development stages for regenerative medicine approaches and investment needed.
Global Perspective

Figure 3. Number of companies, products and trials worldwide in 2014.27
Global Perspective

• Developing markets, emergence of induced pluripotent stem (iPS) cells as an alternative to embryonic stem cells (ESCs), and evolution of new stem cell therapies represent high growth opportunities for market players.

• North America hold the largest share of the global stem cell therapy market. This large share is primarily attributed to the extensive government funding and increasing fast-track approval for stem cell therapeutics by the FDA.

• However, the Asia-Pacific stem cell therapy market is expected to grow at the highest CAGR in the forecast period, owing to factors such as increasing regulatory support through favorable government policies, strong product pipelines, and increasing licensing activities in this region.

• Significant global players that are involved in the development of stem cell therapies are Mesoblast Ltd. (Australia), Aastrom Biosciences, Inc. (US), Celgene Corporation (US), and StemCells, Inc. (US).
Global Perspective

Fig 2. Cell therapy clinical trials registered worldwide.
Future

- **Stem Cell Tourism**
  - The recent growth of stem cell tourism reflects the high optimism that currently surrounds stem cell science. Stem cell treatments for various conditions are increasingly advertised over the Internet as being available at hospitals and clinics around the world. However, most are clinically unproven.

  - Only rigorous science and rigorous regulation can ensure translation of science into effective therapies rather than into ineffective market products, and mark, at the same time, the sharp distinction between the striving for new therapies and the deceit of patients.
Future

- Cost effective therapies
- Financial support from Pharma Companies (Phase III studies)
- Successful Phase III studies
- Automation and scale in manufacturing
- New technologies for isolation
- Xeno-free culture
- Delivery devices
- Induced pluripotent stem cells - insight into disease and new therapies
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Quality Policy

CCMI uses state-of-the-art technologies to manufacture hMSC in a controlled and consistent manner in accordance with GMP requirements, for the advancement of cellular therapies.
CCMI Vision Statement

ADVANCEMENT OF PATIENT CARE BY DEVELOPING NEW CELLULAR THERAPIES