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3 **DEVELOPMENT OF A CELL-BASED MEDICINAL PRODUCT:**
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5 **REGULATORY STRUCTURES IN THE EUROPEAN UNION**
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54 **Preferred short title of paper:** Cellular medicine in the European Union
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ABBREVIATURES

ATMP: Advanced Therapy Medicinal Product

sCTMP: Somatic Cell Therapy Medicinal Product

GTMP: Gene Therapy Medicinal Product

TEP: Tissue-Engineered Product

CATP: Combined Advanced Therapy Products

FDA: Food and Drug Administration

MHLW: Ministry of Health Labour and Welfare

EMA: European Medicines Agency

EU: European Union

ICH: International Conference on Harmonization

PMDA: Pharmaceutical and Medical Devices Agency

CAT: Committee for Advanced Therapies

GLP: Good Laboratory Practice

GCP: Good Clinical Practice

GMP: Good Manufacturing Practice

GVP: Good Pharmacovigilance Practice

PASS: Post-Authorization Safety Studies

ABSTRACT

Introduction: New therapies with genes, tissues and cells have taken the emerging field for the treatment to many diseases. Advances on stem cell therapy research have led to international regulatory agencies to harmonize and regulate the development of new medicines with stem cells.

Sources of data: European Medicines Agency on 15th September 2012.

Areas of agreement: Cell therapy medicinal products should be subjected to the same regulatory principles than any other medicine.

Areas of controversy: Their technical requirements for quality, safety and efficacy must be more specific and stringent than other biological products and medicines.

Growing points: Cell therapy medicinal products are at the cutting edge of innovation and offer a major hope for various diseases for which there are limited or no therapeutic options.

Areas timely for developing research: The development of cell therapy medicinal products constitutes an alternative therapeutic strategy to conventional clinical therapy, for which no effective cure was previously available.

KEY WORDS: regulatory agencies, advanced therapies and cell therapy.

INTRODUCTION

Advanced Therapy Medicinal Products (ATMP) are a new medicinal product category including: Somatic Cell Therapy Medical Products (sCTMP), Gene Therapy Medical Products (GTMP) and Tissue Engineered Products (TEP). Cells, genes and engineered tissues are regarded as new active substances in the development of medicines. Aside from the well-established bone marrow transplantation, advances in cell therapy in the last decade, have promoted the development of multiple lines of research for the development of a sCTMP.

The application of cells as pharmacological active substance has the purpose to repair, replace or recover the biological function of damaged tissue or organs. Cell therapy is an alternative for the treatment of both high prevalent chronic and rare diseases including immune¹ and cardiovascular diseases², diabetes and their complications³⁻⁶, neurodegenerative disorders⁷, inflammatory diseases such as Crohn's disease⁸, musculoskeletal diseases⁹, cancer¹⁰, etc.

Development of new medicines for the treatment of untreated disease aims to improve the patient's quality of life with new and specific therapies either addressed to the right target thus minimizing side effects or using new strategies and mechanisms of action which open new therapeutic avenues. In this context Europe has pioneered the development of advanced therapies; however most of the preclinical and clinical research is investigator-driven and less-frequently involving spin-offs and small biotech companies. Academic institutions and small and medium enterprises are not so familiar with regulatory issues as conventional pharmaceutical industry. In this manuscript we

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3 aim to describe the regulatory issues to consider during the different steps in the process
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5 of innovation for new advanced therapies as sCTMP.
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10 The design, development and authorization of a medicine are a long and complex
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12 process. Regulation needs to be applied from the early stages of development of a new
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14 medicine to ensure that it meets the requirements of quality, efficacy, and safety for
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16 administration in humans. This applies to all medicinal products whether of chemical or
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18 biological origin¹¹. In Europe, sCTMP meet the definition of a medicinal product as
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20 described in Directive 2001/83/EC¹² amended by two subsequent directives
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22 (2003/63/EC and 2009/120/EC)^{13,14} and completed by Regulation (EC) No 1394/2207¹⁵.
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24 sCTMP have a specific regulation to harmonize legal framework and to promote
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26 research in this field.
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32 This review describes and discusses the different stages in the development of a
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34 sCTMP, and both regulatory and practical requirements, from a European perspective.
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38 1. REGULATORY AGENCIES

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42 The three most important regulatory agencies that regulate the development of a
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44 medicine for human use are: European Medicines Agency (EMA) in the European
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46 Union (EU), Food and Drug Administration (FDA) in United States and Ministry of
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48 Health Labour and Welfare (MHLW) in Japan.
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54 Coordination of technical requirements at the international level is achieved through the
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56 International Conference on Harmonization of Technical Requirements for Registration
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3 of Pharmaceuticals for Human Use (ICH). Its main mission is to achieve management
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5 in the technical guidelines on the quality, safety and efficacy of new medicines¹⁶ (Table
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7 1). This organization brings together regulatory authorities, pharmaceutical industry and
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9 scientific experts from the United States, Japan and Europe.

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11 Regulatory agencies also review the indications for use, content of the package leaflet,
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13 dosage, side effects, warnings and contraindications. Finally, they also ensure post-
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15 regulatory **Pharmacovigilance**.

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23 24 25 **European Medicines Agency (EMA)** 26

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29 EMA is a decentralized agency of the EU located in London (www.ema.eu). Its main
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31 responsibility is the protection and promotion of human and animal health, through the
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33 evaluation and supervision of medicines for human and veterinary use¹⁷. This
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35 evaluation is done by experts from the national medicines agencies from the EU
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37 countries who are members of different committees within the EMA: Committee for
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39 Medicinal Products for Human Use (CHMP), Committee for Medicinal Products for
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41 Veterinary Use (CVMP), Pediatric Committee (PDCO), Committee for Orphan
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43 Medicinal Products (COMP), Committee on Herbal Medicinal Products (HMPC) and
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45 Committee for Advanced Therapies (CAT). In July 2012 a new committee **was created**
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47 at the EMA, the Pharmacovigilance and Risk Assessment Committee (PRAC).
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49 Scientific Committees also receive input from different Working Parties (experts in
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51 different areas). Through these committees, EMA provides scientific advice for the
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53 development of new medicines.
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5 The CAT started working in 2009 in order to promote the development of advanced
6 therapies and to the pursuit of innovation in new treatments with ATMP. The CAT
7 consists of experts in the field of ATMP nominated by the EU Member States, the
8 CHMP and the European Commission. Its main responsibility is to prepare a draft
9 opinion on the quality, safety, and efficacy of a product for the final approval each
10 ATMP marketing authorization application submitted to the EMA, before the CHMP
11 adopts the final opinion on the medicine concerned. CAT offers a query system for the
12 classification of ATMP. This procedure is optional, free of charge and may take place at
13 any stage of the development of a sCTMP or any ATMP in advance of applying for a
14 marketing authorization^{18,19}. CAT is involved in the certification of quality and/or non-
15 clinical data, in the development of scientific guidelines and reflection papers and in
16 regulatory procedures and scientific articles. Regulatory aspects for cell-based therapy
17 medicinal products will be described in this paper in more detail.

36 **Food and Drug Administration (FDA)**

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40 FDA is the agency responsible for authorizing the marketing of new medicines in the
41 United States of America^{20,21}. The FDA's Center for Biologics Evaluation and Research
42 is responsible for ensuring the safety, purity, potency and effectiveness of many
43 biological products (cells, genes, tissues, blood components and derivatives, vaccines,
44 etc) for the prevention, diagnosis and treatment of human diseases. Because of their
45 biological origin cell therapy medicinal products are regulated in the Code of Federal
46 Regulations under Title 21 PART 1271, Human Cells, Tissues, and Cellular And
47 Tissue-Based Products^{22,23}. In order to promote the development of cell therapy

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3 medicinal products, the FDA has formed a working group with the pharmaceutical
4 industry called Critical Path Initiative to act in a pro-active fashion regarding the
5 development of new medicinal products.
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9 10 11 **Ministry of Health, Labour and Welfare (MHLW)** 12

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16 MHLW is the Japanese consumer protection agency. The Pharmaceutical and Medical
17 Devices Agency (PMDA) is responsible for the scientific evaluation of applications for
18 marketing authorization for new medicines in Japan. The development of a cell therapy
19 medicinal product for human use in Japan is governed by the Guideline on Clinical
20 Research Using Human Stem Cells (July 3, 2006 amended in full, November 1, 2010).
21
22 PMDA has a committee of experts in medicine and bioethics to review all human stem
23 cell clinical research. This committee is based in this guideline and the latest scientific
24 findings²⁴. On the other hand there is a specific regulation for clinical trials (Phases I to
25 III, and postregulatory), regulated by the Pharmaceutical Affairs Law (1960 Law 145).
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39 **ADVANCED THERAPIES IN EUROPE** 40 41

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43 In order to harmonize the technical aspects of new medicines, in terms of quality, safety
44 and efficacy, the EU proposed a plan of action for the development of new biotech
45 medicines. This plan included genes and cells products as a biological medicinal
46 product. ATMP have to fulfill the same scientific and regulatory standards as all other
47 medicinal products. Directive 2001/83/EC¹² (Annex I, part IV) consolidated all the
48 regulation of biotechnological products for human use, and defines for first time the
49 terms: gene therapy medicinal products and somatic cell therapy medicinal products. In
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3 2003, Directive 2003/63/EC¹³ amended Directive 2001/83/EC on medicinal products
4 for human use. Later, in 2008 the regulation of biological medicines was updated, and
5 included tissue engineering to the area of advanced therapies, Regulation (EC) No
6 1394/2007¹⁵. This regulation lays down specific rules concerning the authorization,
7 supervision and pharmacovigilance of ATMP. A transitional period was defined to
8 comply with these requirements. In the case of cell and gene therapy the period ended
9 December 30, 2011. However, for tissue engineering products a four-year period was
10 defined that will end on December 30, 2012.

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20 In 2009, Commission Directive 2009/120/EC¹⁴ was indeed the legal document that was
21 established after the Regulation (EC) No 1394/2007 to implement the changes into
22 2001/83/EC. Any organization (pharmaceutical industry, hospitals, public or private
23 research) should comply with the requirements of this regulation from January 1, 2013,
24 for the development of any ATMP of use in humans. According to the European
25 regulation^{12,13,14,15} ATMPs include sCTMP, GTMP, TEP, and Combined Advanced
26 Therapy Products (CATP).

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38 In addition, Directive 2004/23/EC²⁵, Directive 2006/17/EC²⁶ and Directive
39 2006/86/EC²⁷ describe the quality and safety standards for the donation, procurement,
40 testing, processing, preservation, storage, and distribution of human tissues and cells.
41 These directives apply to products classified as no ATMP (when cells have the same
42 essential function in the donor as in the recipient and when they do not subject to a
43 substantial manipulation)¹⁵ and therefore no medicines. For ATMP, these directives
44 only apply in relation to donation, procurement and testing of biological samples which
45 will be obtained from the cells, genes and/or tissues. With regard to ATMP with blood
46 components or blood cells, Directive 2002/98/EC²⁸ will also apply.

Somatic Cell Therapy Medicinal Products (sCTMP)

sCTMP are defined as biological medicinal products which 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 in the recipient and the donor or/and they are 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^{12,14}.

On term of regulation the following manipulations are considered “ no substantial ”: cutting, crushing, shaping, centrifuging, soaking in antibiotic or antimicrobial solutions, sterilizations, irradiation, cell separation, cell concentration, etc... all of them are described in the Annex 1, Regulation No 1394/2007¹⁵. In contrast processes that modify biological characteristics, physiological functions or structural properties of the cells or tissues are considered “ substantial”²⁹.

Active substances for a sCTMP may be manipulated cells, cellular components, lysate cells, proliferating cells and genetically modified cells. The materials in combination with cells should be considered as starting materials and thus form part of the active substance¹⁴. Cells may be of autologous, allogeneic or xenogeneic origin. Autologous products are those in which donor and recipient of cells is the same person. Allogeneic products are derived from cells or tissues removed from a donor and applied to another

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3 person. A xenogeneic cellular product includes animal viable somatic cell adapted for
4 application into a human recipient.
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9 10 **Gene Therapy Medicinal Products (GTMP)**

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14 GTMP is defined as biological medicinal product containing an active substance which
15 contains or consists of a recombinant nucleic acid used in, or administered to human
16 beings with a view to regulating, repairing, replacing, adding or deleting a genetic
17 sequence^{12,14}. Its therapeutic, prophylactic or diagnostic effect relates directly to the
18 recombinant nucleic acid sequence it contains, or to the product of genetic expression of
19 this sequence. GTMP shall not include vaccines against infectious diseases.
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29 30 **Tissue-engineered Products (TEP)**

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34 TEP are defined as a product that contains or consists of engineered cells or tissues used
35 for regenerating, repairing or replacing a human tissue (Chapter 1 - Article 2,
36 Regulation No 1394/2007)¹⁵. The biological origin of the cells and tissues may be
37 human or animal. These products contain viable or non-viable cells or tissues and
38 additional substances, such as cellular products, bio-molecules, biomaterials, chemical
39 substances, scaffolds or matrices.
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47 **As mentioned above, as for sCTMP,** cells or tissues are considered engineered if they
48 fulfil at least one of the following conditions: cells or tissues have been subject to
49 substantial manipulation, so that biological characteristics, physiological functions or
50 structural properties relevant for the intended regeneration, repair or replacement are
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3 achieved; or the cells or tissues are not intended to be used for the same essential
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5 function or functions in the recipient as in the donor¹⁵.
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9 10 **Combined Advanced Therapy Products (CATP)**

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14 **CATP are products that incorporating as an integral part of the product, one or more**
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16 **medical devices or one or more active implantable medical devices. These products**
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18 **must contain viable cells or tissues, or its cellular or tissue part containing non-viable**
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20 **cells or tissues must be liable to act upon the human body with action that can be**
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22 **considered as primary to that of the devices referred to¹⁵.**
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27 A medical device or an active implantable medical device should meet the essential
28 requirements described in Directive 93/42/EEC³⁰ concerning medical devices and
29 Directive 90/385/EEC³¹ relating to active implantable medical devices, in order to
30 ensure an appropriate level of quality and safety. Both directives were amended by
31 Directive 2007/47/EC³². **EN/ISO 10993-18³³ and EN/ISO 10993-19³⁴** describe some
32 guidelines about additional substance, which should be identified and characterized in
33 chemical and physical terms (porosity, density, microscopic structure and particular
34 size). Safety, suitability and biocompatibility of all structural components and additional
35 substances are a must in developing these products. **CATP may also incorporate**
36 **structural components, which are not identical or used in the same way as in a medical**
37 **device. All structural components should be fully characterized and evaluated for their**
38 **suitability for the intended use. Any medical device used in addition or combined to the**
39 **cells should be described and their function underpinned by means of chemical,**
40 **biological, physical and mechanical properties³⁵.**
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STAGES OF RESEARCH ON THE DEVELOPMENT OF A sCTMP IN EUROPE

In contrast with the conventional innovation model in the pharmaceutical industry, advanced therapies are usually developed by small and medium enterprises and academia (hospitals, universities, etc). In any case their development includes several phases: experimental observations, preclinical phase (animal testing under Good Laboratory Practice³⁶ conditions) (GLP) and clinical trials (Phases I to IV under Good Clinical Practice³⁷ (GCP), Good Manufacturing Practice³⁸ (GMP) and Good Pharmacovigilance Practice³⁹ (GVP), prior to an application for registration and marketing). All these phases must address the critical points in the development of cellular therapy. Clinical development should be approved by national medicines agencies, marketing authorization applications should go through the EMA with the exception of national hospital exemption, also in compliance with national requirements. The Regulation (EC) 1394/2007 describes that it is possible to prepare a sCTMP in a hospital under the exclusive professional responsibility of a medical practitioner for an individual patient. sCTMP will be manufacture on a non-routine basis according to specific quality standards. The competent authority of the member state of Union Europe should authorize the manufacturing of these products and each member state should authorize a hospital exemption clause, ensuring the compliance of traceability and pharmacovigilance with European requirements¹⁵. National agencies are currently developing rules for hospital exemption with quality requirements similar to those applied by EMA.

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3 The main critical points in the development of a new sCTMP are: selection of cellular
4 biological sample, cell type and its production process including biopsy; active
5 substance formulation (qualitative and quantitative composition), selection of
6 pharmaceutical form (cell concentration of the medicinal product; route of
7 administration; dose (single-dose, multi-dose); detailed instructions for use, application,
8 implantation or administration; dose-response relationship; shelf-life and stability;
9 pharmacological properties; quality properties of product; assessment of adverse
10 reactions and evaluation of the risk-benefit balance that must always be positive^{12,13,14,}
11 ^{15,35,40}. Both national agencies and CAT can provide regulatory advice during the
12 development of a sCTMP⁴¹.

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25 On the other hand the EMA has published several guides that describe regulatory
26 aspects for the development of a sCTMP, CHMP/410896/06³⁵,
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29 CHMP/CPWP/708420/09⁴⁰ and CHMP/CPWP/83508/09⁴² among others.

30 31 32 33 34 **Experimental Observations**

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38 At this stage of development, experimental observations focused in basic laboratory
39 research should determine the active (either differentiated progenitor or stem cells) and
40 establish a tentative mechanism of action of the sCTMP to be developed.

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The active ingredients (cells) are classified in consonance with the tissue localization from which they are obtained and their function (embryonic stem cells may be obtained from the first stages of embryo development; adult stem cells are found in the bone marrow, adipose tissue, etc; mononuclear cells from the bone marrow, etc), by their potentiality (pluripotential, etc). Currently there is much diversity in the name of these cell derived products. There is no unified naming convention, which would facilitate

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3 research in this area giving common information sources in the development of a
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5 product. Nomenclature for these active substances should be standardized at the
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7 European level, with a consensus for all sCTMP.
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10 11 **Pre-clinical Research**

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16 Preclinical development of a sCTMP refers to the set of studies on efficacy and safety
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18 of the active substance (cells) to be performed in biological systems distinct to the
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20 human that may give substantial information to address a Phase I-IIa pilot study. These
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22 may include in-vitro work with cellular models, preclinical experiments using animal
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24 cells in animal models and preclinical work using human cells in immunocompromised
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26 mice⁴³. Although there are no perfect models that mimic the human disease, these
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28 approaches may provide enough information for ethical committees and regulatory
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30 agencies to decide for further development on the basis of the proper balance between
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32 risk and benefit for a specific situation.
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36 **The selection of animal models and species should be scientifically justified. The phase**
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38 **of preclinical research is focused on toxicity and assessment of the biological activity of**
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40 **the cells⁴⁴, through pharmacodynamic, pharmacological, pharmacokinetic,**
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42 **biodistribution, tumourigenicity and interactions with other cellular or not components**
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44 **studies.**

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47 Non-clinical studies performed in animals and physiological models in the laboratory
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49 aim to analyze the physic-chemical properties and behavior of the compound both *in*
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51 *vivo* and *in vitro*. **When relevant animal models cannot be developed, *ex vivo* and/or *in***
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53 ***vitro* studies may replace animal studies. Data from preclinical studies must be**
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55 **interpreted in terms of the animal species used, since human stem cells are very**
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3 different from an animal model. Usually, two or more species (a rodent and non-rodent)
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5 are used in these experiments because the medicine application could affect differently.
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10 Non-clinical studies should be carried out in conformity with the provisions related to
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12 GLP laid down in Directive 2004/10/EC³⁶ and Directive 2004/9/EC⁴⁵ on the inspection
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14 and verification of GLP. Animal tests are designed not only to show the safety and
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16 proof of concept for efficacy of the new medicinal product, but also to assess its
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18 biodistribution, pharmacodynamics and toxicity. In contrast with small molecules and
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20 biological, the control of the amount of drug absorbed into the blood, its chemical
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22 breakdown in the body, the short-, mid- and long-term toxicity, its breakdown products
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24 (metabolites) and the rate of excretion usually measured in preclinical studies⁴⁶ are
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26 difficult to evaluate with cellular medicines. Non-clinical aspects are described in
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28 guideline 35 of the ICH S6 and should be considered. The number of animals, their
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30 genders, the frequency and duration of monitoring should be appropriate to detect
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32 possible adverse effects³⁵. An effort should be made to introduce new tests that respond
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34 to these questions when using cells as medicines.
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41 GLP are a set of principles that provides a framework within which laboratory studies
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43 are planned, performed, monitored, recorded, reported, and archived to ensure the
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45 reliability of data generated within a compliant laboratory⁴⁷. A key feature of GLP is the
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47 generation of quality-control methods and data management within the cell culture
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49 laboratory⁴⁸. GLP principles were set by the Organization for Economic Co-operation
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51 and Development (OECD). This organization has established the Mutual Acceptance of
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53 Data system in OECD member countries for the mutual acceptance of non-clinical
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55 safety study data⁴⁹. For purposes of assessment and other uses related to the protection
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3 of human being and his environment other member countries should accept GLP
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5 principles.

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7 The OECD has issued a series of recommendations for compliance with the GLP.
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9 These guidelines focus on the assessment of chemicals for very different applications,
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11 and also apply to medicines.
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14 15 16 **Clinical Research (and follow-up)** 17

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20 Clinical trials can be classified according to their purpose, phase I, phase II, phase III
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22 and Phase IV.
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27 Clinical trials in Phase I are the first step in investigating a substance or new drug in
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29 humans. They are based to evaluate its safety, determine a safe dosage range, and
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31 identify side effects. This phase provides the approximate profile of safety and tolerance
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33 of the product. In advanced therapies would be a safety and feasibility study on patients.
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36 For instance, it would not be ethical to conduct a gene therapy trial on healthy human
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38 volunteers. Whilst Phase one primary end-points must respond safety and efficacy,
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40 surrogate endpoints may check for the efficacy. Phase II studies include initial clinical
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42 research treatment effect. Clinical trials of this phase are carried out on patients with the
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44 clinical entity of interest. Its main objective is getting to know the dose with the best
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46 risk/benefit profile. Phase III studies or pivotal trials are designed to evaluate the safety
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48 and efficacy of the experimental drug trying to reproduce the conditions of common use
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50 and considering the therapeutic alternatives available for the disease studied. Phase IV
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52 convenes pharmacovigilance and additional efficacy studies and correspond to post
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54 marketing/post authorization studies with marketed medicines. The objective at this
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3 stage is to study the detection of long-term side effects, and possible effects of drug on
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5 the disease itself or studies of morbidity and mortality (Fig 1).
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14 Clinical application of sCTMP should be subject to the same regulatory principles as for
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16 any other biotechnological medicinal product for human use⁵⁰, although their technical
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18 requirements for quality, safety and efficacy must be more specific⁵¹.
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23 Requirements to conduct clinical trials in the EU are provided by Directive
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25 2001/20/EC³⁷. Clinical trials have to be designed and performed according to the
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27 overarching principles and ethical requirements laid down in GCP as laid down in
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29 Directive 2005/28/EC⁵² where principles and detailed guidelines for good clinical
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31 practice as regards investigational medicinal products for human use are described.
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36 GCP are a set of ethical and scientific requirements of internationally recognized quality
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38 that must be met in planning, conducting, recording and reporting of clinical trials
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40 involving humans. Their compliance ensures the protection of human rights, safety and
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42 welfare will of trial subjects and the reliability of clinical trial results. These studies
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44 have to be made respecting the principles of the Helsinki Declaration prepared by the
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46 Assembly of World Medical Congress, Helsinki, Finland in 1964 and revisited
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48 periodically with the main goal of protecting patient rights. GCP stipulates the clinical
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50 trial process, including protocol and Case Report Form design, analyses planning, as
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52 well as analyzing and preparing interim and final clinical trial/study reports. In contrast
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54 with small molecule clinical trials, sCTMP cannot be given to volunteers in order to
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3 demonstrate safety and feasibility. Therefore, “proof-of-concept” pilot studies consist in
4 testing the cellular medicine in a small group of patients with an untreatable disease or
5 condition and demonstrate safety and feasibility whilst observing efficacy. Phase II and
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10 III may be randomized double-blinded with placebo group. **These clinical trials focus** on
11 the study of the cellular function, their distribution, dose, effect and above all safety. A
12 recent position paper by the European Science Foundation has made a proposal for a
13 revision of the “Clinical Trial Directive (2001/20/EC)” and other recommendations to
14 facilitate clinical trials (Dec 2011).
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23 Clinical trials on the use of **sCTMP** are underway for a wide variety of diseases,
24 **however different cell types are used, most of them badly defined.** Bone marrow
25 mononuclear cells are a heterogeneous mixture of **cells⁵³**, umbilical cord blood⁵⁴ are
26 mostly but not only hematopoietic, mesenchymal⁵⁵ stromal cells from different origins
27 are selected by their capacity to adhere to the culture plastic dish, etc. **Most clinical**
28 **trials in cell therapy currently ongoing are phase I/II studies, and about 15562 studies**
29 **are registered in www.ClinicalTrials.gov.**
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43 **Manufacturing cell-based medicinal products**

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47 **Technical requirements for sCTMP are based primarily on quality, safety and efficacy**
48 **aspects. In contrast to traditional medicines, sCTMP have different and more specific**
49 **characteristics. The risks analysis of the whole manufacturing process, the quality of**
50 **manufacturing aspects and non-clinical and clinical development are aspects that should**
51 **be taken into account when manufacturing a sCTMP³⁵.**
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3 It is also necessary to conduct a risk analysis covering the entire process. Risks
4 associated with a sCTMP are highly dependent on the biological characteristics of the
5 product. Risk factors that may include, among others could be: origin of cells, level of
6 manipulation, combination of cells with bioactive molecules or materials structural,
7 management or use mode^{12,14}, etc. Recommendations of the risk analysis is part of the
8 dossier for a marketing authorization application, described in
9 EMA/CHMP/CPWP/708420/2009⁴⁰, guideline on the risk-based approach according to
10 annex I, part IV of Dir. 2001/83/EC applied to advanced therapy medicinal products.
11 Regarding safety and efficacy follow-up - risk management, was published a
12 guideline, EMEA/149995/2008⁵⁶.

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27 All batches of a sCTMP manufactured for the clinical phase should be carried out under
28 GMP standards. sCTMP in clinical phase is considered to be an investigational
29 medicinal product, then it should be in compliance with the principles of GMP
30 (Directive 2003/94/EC)³⁸. Therefore requirements for installations, staff, equipment,
31 documentation, production, quality control, batch release, labeling, etc should be
32 manufactured and checked in compliance with the requirements of GMP guidelines.

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41 In practical terms these standards are described in EudraLex-Volume 4 GMP guidelines,
42 and consists of: Part I - Basic Requirements for Medicinal Products (9 chapter), Part II -
43 Basic Requirements for Active Substances used as Starting Materials, Part III - GMP
44 related documents and 20 Annexes⁵⁷. The manufacture of sCTMP must be carried out
45 as described in the 9 chapters of Part I, in addition to that referred in Annexes: 1-
46 Manufactured of sterile medicinal products; 2- Manufacture of biological medicinal
47 products for Human use; 8- Sampling of starting and packaging materials, 13-
48 Manufactured of Investigational Medicinal Products; 14- Manufactured of Products
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3 Derived from Human Blood or Human Plasma; 15- Qualification and validation; 16-
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5 Certification by a Qualified Person and Batch Release, 17-Parametric Release, 19-
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7 Reference and Retention Samples. Likewise, detailed clinical guidelines for GCP have
8
9 been described in EudraLex-Volume 10 which contains six guidance documents
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11 applying to clinical trials⁵⁸.
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15
16 The manufacturing process of a sCTMP for clinical use must be consistent and
17
18 reproducible providing sufficient quality to the final product for patient safety. GMP
19
20 applies to both production and quality control of the medicinal product. These
21
22 guidelines ensure that medicinal products are consistently produced and controlled to
23
24 the quality standards appropriate to their intended use and according to the requirements
25
26 of the product specification⁵⁹.
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30 Concerning quality control requirements it is important to check that the active
31
32 substance of sCTMP is viable, so at the end of the process the final product for the
33
34 patient, should not include terminal sterilization, purification steps and/or viral removal.
35
36 Therefore, the quality of the starting materials derived from animal or human origin
37
38 should be analyzed. These materials comprise excipients and the donor of biological
39
40 sample for the active substance. The quality criteria required by the European regulation
41
42 for the characterization of the final product requires considerations such as, the identity
43
44 of the cellular and non-cellular components; cell purity; impurities of product or related
45
46 process; impurities as adventitious agents; potency and tumourigenicity³⁵.
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48

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50 The manufacturing process of sCTMP should be carefully designed and validated to
51
52 ensure product consistency and repeatability of the cell culture process. These products
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54 are highly heterogeneous due to their origin, starting material, degree of in vitro
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56 manipulation and manufacturing process⁶⁰.
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3 During the manufacture of a sCTMP considered an aseptic procedure, all manufacturing
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5 processes should be validated including: validation of sterility, validation of aseptic
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7 process, validation of microbiological environmental monitoring and validation of
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9 cleaning process⁶¹. Thorough study of each process involved in the manufacture of a
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11 sCTMP should be made to ensure their safety in terms of quality.
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14 15 16 **Authorization, Registration and Marketing** 17

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20 The evaluation of the medicines for their authorization and commercialization is
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22 regulated by Directive 2001/83/EC and Regulation (EC) No 726/2004⁶², amended by
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24 Regulation (EU) No 1235/2010⁶³, as regards pharmacovigilance of medicinal products
25
26 for human use. This regulation develops and improves European procedures for the
27
28 authorization, supervision and pharmacovigilance of medicinal products for human and
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30 veterinary use.
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36 There are three procedures to approve new medicinal products: the centralized procedure,
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38 generating a single marketing authorization valid throughout the EU, the decentralized
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40 procedure, in which the application is submitted to member states selected by the
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42 applicant and mutual recognition procedure, when the reference member state has
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44 already issued a marketing authorization. However, the centralized authorization
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46 procedure is compulsory for medicinal products **manufactured** by biotechnological
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48 methods and for advanced therapy medicinal products such as **sCTMP**.
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54 The CAT is involved in all scientific advice on ATMPs and in the regulatory procedures
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56 of the classification and the certification procedures. CAT is responsible for the
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3 evaluation of the marketing authorization applications for sCTMP¹⁹. Following the
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5 CHMP scientific assessment the European Commission issues a decision that is
6
7 published in the Official Journal of the European Community, which is valid for all EU
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9 countries.

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12 The marketing authorization is valid for five years and may be renewed. Once it has
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14 been renewed, it is valid indefinitely, unless the Commission chooses not to validate
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16 again for another five years. The approval decision will be taken based on the scientific
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18 criteria of quality, safety and efficacy in evaluation. These three criteria allow
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20 evaluating the risk-benefit balance of all medicines.
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25 On the other hand, in order to give micro, small and medium-sized enterprises, EMA
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27 published the Regulation (EC) No 668/2009⁶⁴, with regard to the evaluation and
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29 certification of quality and non-clinical data relating to ATMP developed (describes in
30
31 two guidelines, EMA/CAT/486831/2008/corr⁶⁵ and EMA/CAT/418458/2008/corr.⁶⁶),
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33 implementing Regulation (EC) No 1394/2007.
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36 37 38 **Post-authorization** 39

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43 Once the marketing authorization is requested and approved, EMA may request post-
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45 authorization studies, the authorization may be conditionally granted. Post authorization
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47 studies focus on pharmacovigilance; it is the science for the assessment, awareness and
48
49 prevention of any side effects or possible adverse reactions associated with medicines.
50
51 This phase is regulated by Directive 2010/84/EU⁶⁷, which define el new concept of a
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53 post authorization safety studies (PASS). PASS have the aim at collecting data to study
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55 for the assessment of the safety and efficacy of the sCTMP with the purpose of generate
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3 additional information on the effects of medicines in with usual conditions of clinical
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5 practice and to complete the information obtained during phases I, II and III.
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7 PASS can be non-interventional trial or observational and clinical trial (phase IV). With
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9 sCTMP are carried out a PASS with the aim of identifying, characterizing or
10
11 quantifying a safety hazard of cell medicine, confirming the safety profile of these
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13 products or of measuring the effectiveness of risk management measures⁶⁷.
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18 Post authorization phase shall be carried out in conformity with the provisions related to
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20 GVP. GVP are a set of measures drawn up to facilitate the performance of
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22 pharmacovigilance in the EU. The guidelines on GVP are divided into 16 modules, each
23
24 of which covers one major process in pharmacovigilance³⁹. It released modules III and
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26 X for consultation in June 2012. Each of the seven modules released covers one major
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28 process in the safety monitoring of medicines. The full set of 16 final modules is
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30 scheduled to be available by early 2013. After marketing authorisation has been
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32 granted, any change to the data in the dossier shall be submitted to the competent
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34 authorities in accordance with the requirements of Commission Regulations (EC) No
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36 1084/2003⁶⁸ and (EC) No 1085/2003⁶⁹.
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43 DISCUSSION

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47 Application, administration or implantation of human cells is opening new avenues in
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49 the search for the treatment of critical diseases, some of which are as yet incurable⁷⁰. In
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51 the last years, encouraging observations at the preclinical level have promoted the
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53 development of cell therapies that are in distinct clinical phases. Several if not all
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55 clinical trials use cells from adult origin, most of them mesenchymal-like cells. As
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3 compared with hundreds of clinical trials with other medicines only a limited number of
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5 sCTMP are translated into products for clinical development and marketing
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7 authorization (Table 2).
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10 The development and manufacture of conventional medicines is performed by physical
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12 and chemical techniques with consistency and robustness. However, sCTMP
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14 development is a technique that still far to reach such strength. sCTMP should take into
15
16 account the variability of the production process, the risk of exogenous contamination
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18 (microbiological, viral...) and variability of quality control techniques. Since active
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20 principals are active substances and not chemical compounds.
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25 The European framework for the development of sCTMP aims to provide an increased
26
27 international competitiveness of these products, the European regulation in the field of
28
29 advanced therapies ensure that all patients receive drug treatment quality.
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31 We anticipate that a deeper knowledge of regulatory issues among clinical investigators
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33 and small biotech enterprise will expand this field that holds the promise for so far
34
35 untreatable diseases.
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38 -- Table 2 near here-----
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40 Since 2003, the cells and/or cellular component are considered as medicines, so since
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42 then, public institutions such as hospitals and universities, and private companies have
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44 been forced to change their methods of clinical and non-clinical research and their
45
46 development. All this change has been accompanied by the update on the EU regulatory
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48 field. The legal and technical requirements necessary for the development of new
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50 medicines as sCTMP, are framed by common guidelines for the entire EU.
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TABLES

Table 1. Categories and topic codes to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

CATEGORY	CODE	APPLICATIONS
QUALITY	Q	Concerning the stability studies, the definition of relevant limits for impurities testing and a focus on product quality
SECURITY	S	Guidelines for potential hazards such as carcinogenicity, genotoxicity and reproductive toxicity.
EFICACY	E	For the design, development, safety and reporting of clinical trials. There are also guidelines for medicinal products derived from biotechnology processes, use of pharmacogenetics and genomic techniques for the production of more specific drugs.
MULTIDISCIPLINARY	M	For cross-cutting themes that do not conform to only one of the above categories (quality, safety and efficacy).

Table 2. Examples of Advanced Therapy Medical Product marketed in the European Union, United States of America, Japan and Canada.

COUNTRY	PRODUCT (Company)	CELLS TYPE	DESCRIPTION
European Union	ChondoCelect [®] (TiGenix NV)	Autologous cultured chondrocytes	Indicated for the repair of cartilage lesions of the cartilage of the knee in adults. Used only in case of injury of the femoral condyle cartilage of the knee (end of the femur).
USA	Carticel [®] (Genzyme Corporation)	Autologous cultured chondrocytes	A cell therapy medicine product indicated for the repair of symptomatic cartilage defects of the femoral condyle, caused by acute or repetitive traumatic the knee of adults who have not responded to a prior arthroscopic or other surgical repair procedure.
	Epicel [®] (Genzyme Corporation)	Cultured keratinocytes	A sheet of autologous keratinocytes used to replace the epidermal or top layer of skin on severely burned patients. Human keratinocytes are grown on a layer of irradiated mouse cells (xenogenic),
	Provenge [®] (Dendreon)	Autologous CD54+ cells activated with PAPGM-CSF	An autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.
	Apligraf [®] (Organogenesis)	A collagen matrix and living keratinocytes and fibroblast cells	Used to heal ulcers such as diabetic foot and venous leg ulcers
Japan	Laviv [®] (Fibrocell Science)	Autologous cultured fibroblasts	Anti-aging treatment; Fibroblasts are then re-injected into wrinkles.
Canada	Prochymal [®] (Osiris)	Mesenchymal stromal cells	A cellular suspension for the treatment of acute graft-vs-host disease (GvHD) in children. Prochymal is made up of bone marrow stem cells derived from an adult donor and is designed to control inflammation, promote tissue regeneration and prevent scar formation.

Accessed here for detailed information: <http://www.tigenix.com>; <http://www.genzyme.com>; <http://www.dendreon.com>; <http://www.organogenesis.com>; <http://www.fibrocellscience.com>; <http://www.osiris.com>.

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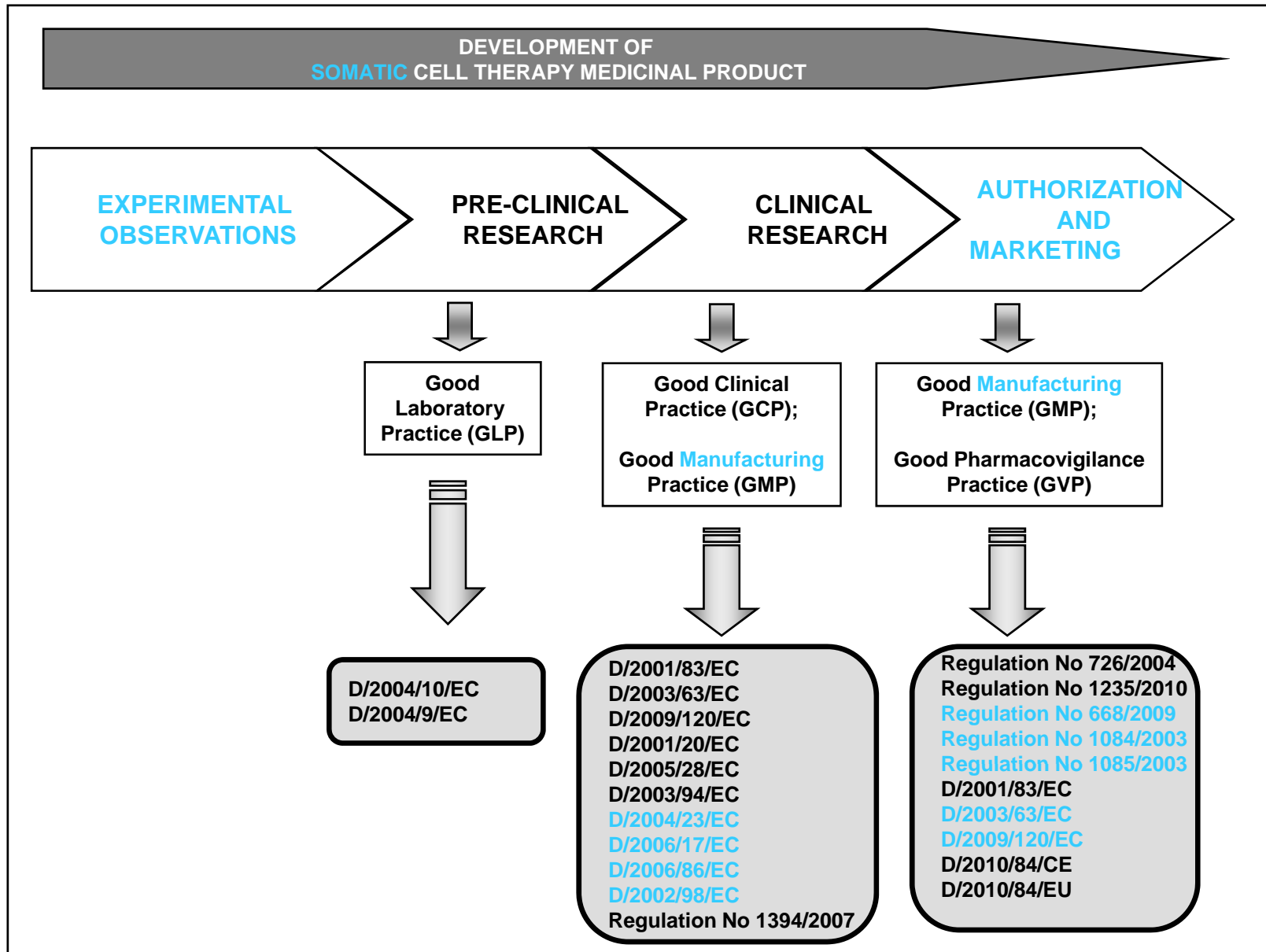


Figure 1. Regulatory issues in the development of a cellular medicine in European Union.