Commercialisation of Advanced Therapies

A Study of the EU Regulation on Advanced Therapy Medical Products

Juli Mansnérus

ACADEMIC DISSERTATION

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Helsinki 2016
Dedicated to Ben and Hilma.
Abstract

Advanced therapy medicinal products (ATMPs), is a heterogeneous class of modern biotechnology medicines encompassing products based on genes (gene therapy medical products, GTMPs), cells (somatic cell therapy medical products, CTMPs) and tissues (tissue engineering medical products, TEPs). ATMPs provide new therapeutic opportunities for many diseases and debilitating injuries to the human body, particularly in such disease areas where conventional treatments have proved insufficient. Since adoption of Advanced Therapy Medical Product Regulation (EC) No. 1394/2007 (the ATMP Regulation) in late December 2008, only six ATMPs have been granted marketing authorisations and four of them are still on the market. To foster research on ATMPs, regulators must take measures to create a facilitative regulatory environment that encourages innovation, protects public health and, finally, enables timely patient access to innovative therapies.

The primary objective of this study is to analyse the benefits and limitations of the ATMP Regulation from the perspective of SMEs, academia and non-profit organisations (such as public tissue establishments) that develop ATMPs. Secondly, this study discusses the kind of amendment to the ATMP Regulation and related regulatory instruments and processes required to accelerate translation of research into advanced therapies and to facilitate commercialisation of ATMPs whilst ensuring the safety of patients. In addition, this study analyses implications of the EU’s limited mandate in the field of public health for developers of ATMPs. As an example of potential ATMPs undergoing development, it also considers some specific, regulatory and moral patenting obstacles that impede the market entry of human embryonic stem cell (hESC) based products.

The fragmented EU-wide regulatory landscape for ATMPs appears significantly influenced and framed by the EU internal market objectives. The ATMP Regulation was set up as a *lex specialis* to ensure the free movement of ATMPs within the EU in order to facilitate their access to the internal market, and therefore to foster the competitiveness of European pharmaceutical companies while guaranteeing the highest level of protection of public health. As the number of ATMPs authorised via the mandatory centralised procedure is still very low, there is a need to determine whether the ATMP Regulation fulfils its objectives, especially from the perspective of SMEs, academia, and public tissue establishments developing ATMPs. One of these authorised products is a stem cell-based ATMP (yet no ATMPs of human embryonic origin have been authorised).

This study also investigates whether barriers to commercialisation relate to ATMPs as such or whether something else in the innovation system is impeding their market entry. In particular, following roadblocks are addressed: availability of research funding and capital investments; the complex interfaces of pharmaceutical regulatory system and IP system; data protection and ethical aspects affecting access to primary materials; disharmonised classification of ATMPs; difficulties with accommodation of personalised, niche production with industry-scale standards on GMP; difficulties with getting pre-clinical and clinical research authorisations; burdensome marketing authorisation procedure; as well as the high cost of ATMPs and difficulties with getting reimbursement. Biomedical or organisational considerations affecting market entry of ATMPs are outside the scope of this regulatory study.
Risk-proportionate approaches to clinical trials and GMP manufacture along with the European Medicine Agency’s early access incentives and initiatives are presented as potential facilitators of market entry. The main regulatory measures suggested to foster innovation, improve safety and access to advanced therapies include: facilitating R&D by adaptive, risk-proportionate approaches to clinical trials and GMP manufacture, streamlining the ATMP Regulation (classifications, in particular), simplifying regulatory processes for ATMPs, shifting from hospital exemption to marketing authorisation to avoid negative incentives, improving conditions for non-profit organisations and access to primary materials. Also optimising the division of competences between the regulatory and patent authorities in overlapping moral questions would to improve certainty in biotechnology patenting and facilitate commercialisation. It also essential to foster greater interdisciplinary collaboration, promotion of transparency, and facilitated cooperation between academia, industry, regulatory authorities as well as health technology assessment bodies and payers alike.

**Keywords:** personalised medicine, advanced therapy medical products, commercialisation, risk-proportionate approach
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Juli Mansnérus
Kauniainen, 29 August 2016
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<th>Description</th>
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<td>Amsterdam Treaty</td>
<td>The Treaty of Amsterdam amending the Treaty on European Union,</td>
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<td></td>
<td>the Treaties establishing the European Communities and Certain Related Acts,</td>
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<td></td>
<td>2 October 1997</td>
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<tr>
<td>ANT</td>
<td>altered nuclear transfer</td>
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<tr>
<td>ANTity</td>
<td>a non-viable embryo-like entity created by means of altered nuclear</td>
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<td></td>
<td>transfer</td>
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<td>ATMP(s)</td>
<td>Advanced Therapy Medical Product(s)</td>
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<td>Biomedicine</td>
<td>The Convention of Human Rights and Biomedicine of the Council of Europe</td>
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<td>Biomedicine</td>
<td>Convention</td>
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<td></td>
<td>The Directive of 98/44/EC of the European Parliament and of the Council of</td>
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<td></td>
<td>6 July 1998 on the legal protection of biotechnological inventions</td>
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<td></td>
<td>of the Court (Grand Chamber) of 18th of October 2011</td>
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<td>CAT</td>
<td>The Committee for Advanced Therapies</td>
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<td>CHMP</td>
<td>The Committee for Medicinal Products for Human Use</td>
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<td>COMP</td>
<td>The Committee on Orphan Medicinal Products</td>
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<td>Cross Border</td>
<td>The Directive 2011/24/EU of the European Parliament and the Council of 9</td>
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<td>Healthcare</td>
<td>March 2011 on the application of patients’ rights in cross-border healthcare</td>
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<td>March 2011 on the application of patients’ rights in cross-border healthcare</td>
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<tr>
<td>CTMP(s)</td>
<td>somatic cell therapy medical product(s)</td>
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<tr>
<td>DG Enterprise</td>
<td>The Directorate General for Enterprise and Industry</td>
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<tr>
<td>DG JRC-IPTS</td>
<td>The Directorate General Joint Research Centre’s Institute for Prospective</td>
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<td></td>
<td>Technological Studies</td>
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<td>DG Sanco</td>
<td>The Directorate General for Health and Consumer Affairs</td>
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<td>DG Sante</td>
<td>The Directorate General for Health and Food Safety</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>EC</td>
<td>The European Commission</td>
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<td>ECJ</td>
<td>The Court of Justice of the European Union</td>
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<td>ECHR</td>
<td>The European Convention on Human Rights</td>
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<td>ECtHR</td>
<td>The European Court of Human Rights</td>
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<td>EGE</td>
<td>The European Group of Ethics in Science and New Technologies</td>
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<td>EMA</td>
<td>The European Medicines Agency</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<td>EPC</td>
<td>The European Patent Convention</td>
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<td>EPO</td>
<td>The European Patent Office</td>
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<td>EU</td>
<td>The European Union</td>
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<td>EUCTDs</td>
<td>The EU Cell and Tissue Directives comprising of three Directives: the</td>
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<td></td>
<td>and 2006/86/EC</td>
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<tr>
<td>EudraCT</td>
<td>Database of all clinical trials that have started in the EU after 1 May 2004. (It was established in accordance with Directive 2001/20/EC to improve the supervision of clinical trials across Europe and the protection of individuals participating in these trials.)</td>
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<tr>
<td>EuropaBio</td>
<td>The European Association for Bioindustries</td>
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<td>FDA</td>
<td>The U.S. Food and Drug Administration</td>
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<td>FP7</td>
<td>the European Union's seventh framework research and innovation funding</td>
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<td></td>
<td>programme for 2007-2013</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>CLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>genetically manipulated organism</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>GTMP(s)</td>
<td>gene therapy medicinal product(s)</td>
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<td>hospital exemption</td>
<td>The hospital exemption rule (Article 28(2) of the ATMP Regulation amending Article 3(7) of Directive 2001/83)</td>
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<tr>
<td>hESC</td>
<td>human embryonic stem cells</td>
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<tr>
<td>Horizon 2020</td>
<td>Horizon 2020, the EUs Research and Innovation Programme for the years of 2014-2020</td>
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<tr>
<td>hpSCs</td>
<td>human parthenogenetic stem cells</td>
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<tr>
<td>hPSCreg</td>
<td>human pluripotent stem cell registry</td>
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<tr>
<td>IA</td>
<td>impact assessment</td>
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<tr>
<td>IMP ATMP</td>
<td>investigational advanced therapy medical product</td>
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<td>IP</td>
<td>intellectual property</td>
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<tr>
<td>iPSCs</td>
<td>induced pluripotent stem cells</td>
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<td>IVF</td>
<td><em>in vitro</em> fertilization</td>
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<td>JPO</td>
<td>Japanese Patent Office</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>Member States</td>
<td>The Member State(s) of the European Union</td>
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<td>MHRA</td>
<td>The UK Medicines and Healthcare Product Regulatory Agency</td>
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<td>NK cells</td>
<td>natural killer cells</td>
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<td>PDCO</td>
<td>The Paediatric Committee</td>
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<td>PRAC</td>
<td>The Pharmacovigilance Risk Assessment Committee</td>
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<tr>
<td>PRIME</td>
<td>priority access medicine</td>
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<td>QALY</td>
<td>quality adjusted life year</td>
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<td>R&amp;D</td>
<td>research and development</td>
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<td>SME(s)</td>
<td>micro-, small- and medium-sized enterprise(s)</td>
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<td>SCNT</td>
<td>somatic cell nuclear transfer</td>
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<td>Technion</td>
<td>Technion Research and Development Foundation</td>
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<td>TEP(s)</td>
<td>tissue engineered product(s)</td>
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<tr>
<td>TEU</td>
<td>The Treaty on the European Union</td>
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<tr>
<td>TFEU</td>
<td>Treaty of the Functioning of the European Union</td>
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<tr>
<td>Trade Secrets Directive</td>
<td>Directive of the European Parliament and of the Council on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure</td>
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<tr>
<td>TRIPS</td>
<td>The Agreement on Trade-Related Aspects of Intellectual Property Rights</td>
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<tr>
<td>UPC</td>
<td>The Unified Patent Court</td>
</tr>
<tr>
<td>UPSTO</td>
<td>United States Patent and Trademark Office</td>
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<tr>
<td>U.S.</td>
<td>The United Stated of America</td>
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<tr>
<td>WARF</td>
<td>Wisconsin Alumni Research Foundation</td>
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<tr>
<td>WHO</td>
<td>The World Health Organization</td>
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<td>WIPO</td>
<td>The World Intellectual Property Organization</td>
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List of original publications

This dissertation is based on the following publications:


This study consists of four peer-reviewed articles (Research Articles) and a summarising part comprising of Chapters 1-9. The Research Articles are referred to in the text by their roman numerals. Research Article I is in peer-review and being considered for publication by Sage Publishing. This draft is pre-published in a limited printed edition of this study. Research Articles II-IV have been re-published in the printed edition of this study with a permission of the copyright holder Koninklijke Brill NV. Whilst all Research Articles have been incorporated by reference to the electronic copy of this study.
Advanced therapy medicinal products (ATMPs), is a heterogeneous class of modern biotechnology medicines encompassing products based on genes (gene therapy medical products, GTMPs), cells (somatic cell therapy medical products, CTMPs) and tissues (tissue engineering medical products, TEPs). ATMPs provide new therapeutic opportunities for many diseases and debilitating injuries to the human body, particularly in areas of unmet medical need. The current pipeline of potential ATMP treatments include severe, untreatable or chronic diseases, and many clinical trials are currently ongoing in a number of conditions such as cancers, cardiovascular diseases, musculoskeletal and neurological conditions, as well as immune system and inflammatory disorders. The number of ATMPs authorised via the mandatory centralised procedure is still very low. To foster research on ATMPs, regulators must take measures to create a facilitative regulatory environment that encourages innovation, protects public health and, finally, enables timely patient access to innovative therapies, especially in the disease areas where conventional treatments are insufficient.

The translation of medical research activities ‘from bench to bedside’ is extremely challenging. Only a very small fraction of the therapeutic opportunities investigated is successfully commercialised and finally manages to enter the internal market as authorised medicines. In this study ‘commercialisation’ refers to the regulatory process of introducing a new ATMP into the EU market. They are usually developed by micro-, small-, and medium-sized enterprises (SMEs), research units in academia or public tissue establishments. The Advanced Therapy Medical Product Regulation (EC) No.1394/2007 (the ATMP Regulation) supplements the EU Cell and Tissue Directives (the EUCTDs) vis-à-vis ATMPs with further requirements on Good Manufacturing Practices (GMP), as well as compliance with marketing authorisation and post-marketing pharmacovigilance requirements.

The commercialisation process has three key elements. It can be seen as 1) a funnel; 2) a stagewise process; and 3) a process involving different stakeholders. Some elements of the commercialisation process have been given more emphasis than others in this study. In particular, this study investigates the benefits and limitations of the ATMP Regulation from the perspective of SMEs and academia as well as non-profit organisations (such public tissue establishments), because they are the main actors developing ATMPs. Secondly, this study discusses what kinds of amendment to the ATMP Regulation and related regulatory processes are needed to accelerate the translation of research into advanced therapies whilst ensuring safety of the patients and facilitating commercialisation of ATMPs.

It would be wrong however to attribute the currently very low number of ATMPs solely and exclusively to the ATMP Regulation, as the ATMP landscape is influenced

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1 The EUCTDs comprise of three Directives: the so-called parent Directive 2004/23/EC, which sets out for the framework legislation and two technical Directives, 2006/17/EC and 2006/86/EC, which consist of more detailed requirements of the parent Directive.

2 Yet, for avoidance of doubt, in this study commercialisation does not refer to the marketing or sales endeavours of any particular medicine or a category of medicines.
by a number of factors and other legislative instruments affecting the commercialisation prospects of these innovative products. Firstly, biomedical considerations preventing basic research findings from being tested in a clinical setting have been left outside the scope of this study. Also particularities of clinical trial design, human behaviour-, organisational-, or research infrastructure-, related factors have been left beyond the primary scope of this study. However, to provide a more balanced overview of the factors affecting the market entry of the ATMPs, some of these issues will be very briefly discussed in the epilogue (Chapter 9). Secondly, despite the primary objective of this study being to examine reasons for the low number of ATMPs pertaining to the ATMP Regulation, it is necessary to provide a general overview of the legislative landscape in which developers of ATMPs operate and discuss some aspects influencing commercialisation. The ATMP Regulation is closely linked with cell and tissue-, clinical trials-, and data protection legislation. Therefore, this study also concisely outlines the role of the EUCDTs and applicable clinical trials legislation (especially Clinical Trials Directive 2001/20/EC and Clinical Trials Regulation No. 536/2014 repealing Clinical Trials Directive 2001/20/EC) and the General Data Protection Regulation 2016/679 replacing the 20-year-old Data Protection Directive 45/95/EC.

Intellectual property (IP) aspects, protection of industrial property rights, in particular also essentially affect commercialisation prospects of ATMPs. Yet, clinical trials, data protection and IP related considerations have been discussed only in a limited sense – only as far as they overlap with the regulatory commercialisation process. For instance, further considerations regarding IP licensing have been left outside the scope of this regulatory study, despite licensing strategy may constitute an important part of commercialisation strategy of a SME developing pharmaceuticals. Reimbursement of advanced therapies along with patent protection is portrayed as an incentive to commercialise ATMPs and to refund significant development costs. Disharmonised reimbursement practices and limited reimbursability of ATMPs impose challenges for any ATMP entering the EU market, whilst moral patentability restrictions together with moral restrictions imposed on the EU funding may be used as a filter against undesirable inventions entering the EU market. The moral restrictions on research funding, patents and the EU’s limited mandate in field of reimbursement affect commercialisation of ATMPs only indirectly, however.

As an example of potential ATMPs undergoing development, some specific biomedical, as well as regulatory and patenting obstacles that impede market-entry of human embryonic stem cell (hESC) based products will be studied (see especially Research Articles I-III). Beyond some significant patient safety and efficacy related

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3 Generally speaking, intellectual property refers to the exclusive rights granted for creations of the human mind, e.g., inventions, literary and artistic works, distinctive signs and designs used in trade. Intellectual property is divided into two main groups: industrial property rights, covering patents, utility models, trademarks, industrial designs, trade secrets, new varieties of plants and geographical indications; and copyright and related rights, which relate to literary and artistic works. Patents and trade secrets are especially important for the pharmaceutical sector as a means of protecting intellectual assets. For a general overview see for instance, World Intellectual Property Organization, WIPO Intellectual Property Handbook: Policy, Law and Use. Available at: http://www.wipo.int/about-ip/en/iprm/. Accessed 21 June 2016.
biomedical roadblocks, incentive to commercialise such research is hampered by the restrictions imposed in the applicable EU research funding policies and the moral exclusion clause 6.2.c. of the Directive 98/44/EC of the European Parliament and of the Council (the Biotech Patent Directive). The ATMP Regulation does not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these cells. Hence, any such national restrictions may affect commercialisation prospects of an ATMP and patients’ access to these novel treatments directly. A marketing authorisation via the centralised procedure is not a promise that the product can be commercialised in all Member States.

The significance of these regulatory instruments notwithstanding, the main scope of this study is limited to analysis of the implications of the ATMP Regulation and the perspective of this study is limited to that of SMEs and academia, as well as non-profit organisations (such as public tissue establishments). Also the impact of the above mentioned legislation will be discussed in a limited sense, from the perspective of commercialisation of ATMPs. Furthermore, this study does not purport to cover all perspectives and fundamental rights and freedoms of each and every stakeholder involved in the regulatory process of ATMP commercialisation. Hence, for instance lesser attention will be given to other stakeholders, such as patients in this innovative process. For the sake of clarity, pursuant to this study the term ‘innovative’ does not mean no more than ‘new’ and it is meant to be neutral with respect to whether an ‘innovative’ ATMP is more (or less) effective and/or safe than existing medicines. Hence, ‘innovative’ does not in this study refer to a medicine that is actually better than another existing medicine. Such product is only assumed to be potentially better, as often positive risk-benefit-balance (i.e., the likely benefit over existing treatment options) must precede a decision to grant a marketing authorisation. Evidence generation after launch of an ATMP may become unavoidable to deal uncertainties and to address payers’ expectations. It should be also noted that not all products classified as ATMPs are new.

**Commercialisation process as a ‘funnel’**. First of all, commercialisation process can be described as a ‘funnel’. The great majority of the molecules investigated as potential medicinal products do not even progress to clinical trials in human research subjects for a number of reasons that are usually related to safety or efficacy of the product under development. It has been reported by the European Commission that less than a quarter of the molecules that are tested in clinical trials manage to obtain a marketing authorisation. In addition, usually the pathway from identification of an active substance

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4 In particular, the impact of the new Clinical Trials Regulation would be an interesting topic for a further study. Also perspectives and rights of patients needing ATMPs could be given more profound attention in further research. The perspectives and rights of tissue donors have been also studied in a limited sense. See for further details. e.g. Walin, L. Kun suostumus ei riitä kudosnäytteen ja alkion huvuttajan oikeusaseman tarkastelua. Lakimies 2008(5):773-798.

to the market entry of the medicinal product requires more than ten years of intense research.\(^6\)

**Commercialisation process as a stagewise process.** Secondly, it can be seen a stagewise process, in which each stage involves different objectives, milestones and challenges.

**Figure 1. ATMP commercialisation process from a regulatory perspective**

Clinical trials involving new medicines are usually classified into four phases.\(^7\) Prior to clinical trials, extensive pre-clinical studies are conducted. Such studies involve *in vitro* and *in vivo* (non-human) experiments that use different doses of the substance to get preliminary data on efficacy, toxicity and pharmacokinetics\(^8\). These studies help the developers to decide whether a potential substance possesses desired qualities for further development as an investigational medical product. Preceding Phase I-III clinical trials, early, exploratory, Phase 0 first-in-human trials may be conducted (however, often these are skipped for Phase I). Such studies are also often referred to as “human microdosing experiments”. They are conducted to accelerate the development of promising medicines (or biomarkers\(^9\)) to gather information on whether the medicine behaves in human subjects as predicted from preclinical studies. Usually such Phase 0 trials involve the administration of single (subtherapeutic) doses of the medicine to a very small number of research subjects to acquire pharmacokinetic information for purposes of ranking

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\(^9\) According U.K. National Institute of Health’s definition “biomarker” is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”. Downing, G.J. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clinical Pharmacology & Therapeutics* 2001;69 (3): 89-95.
potential drug candidates. Phase I trials are the first stage of testing in human subjects (unless Phase 0 trials have been conducted). Phase I trials aim at assessing the safety, tolerability, pharmacokinetics, and pharmacodynamics of a medicine in a small group of healthy volunteers. In addition, usually Phase I trials include dose escalation studies that aim at establishing the best and the safest dose. Subsequent to determination of the dosage, the next objective is to test whether the medicine has any biological effect or other activity.

Phase II trials are conducted on larger groups and they designed to assess whether the medicine has any efficacy (studying whether the medicine administered in the particular manner described in the study is able to influence the druggable target in the chosen population). Sometimes Phase II trials are divided into Phase IIA (assessing dosing requirements) and Phase IIB (studying efficacy). Whilst some trial designs combine Phase I and Phase II to test both efficacy and toxicity.

Phase III trials are designed to assess the effectiveness of the new medicine (determining whether a treatment will influence the actual disease). Hence, they investigate, its value in clinical practice. Phase III studies are usually randomised controlled trials involving a large patient population. They aim at assessing of how effective the medicine is, benchmarked against the current “gold standard” treatment.

Phase IV trials are conducted for purposes of postmarketing surveillance (involving pharmacovigilance and technical support). It should be noted that this study does not purport to cover challenges that the ATMPs face after the market entry, such as challenges with Phase IV clinical trials and post marketing surveillance. As it is discussed in Section 8.3 evidence generation after market entry of is becoming more and more important when a number of participants tested in clinical trials is very small.

It should be also noted that the above described traditional Phase I-III clinical trials paradigm may not be optimally suitable for development of ATMPs. Such sequential approach may in some cases appear inherently inefficient in development of niche and tailor-made products. As trials on ATMPs are often small-scale, a small sample size may lead to misleading signs of efficacy. Sequential trial paradigm gives major importance to Phase II studies, because they typically provide information for “go” or “no go” decisions to further trials. Hence, a risk of false negative or false positive outcome of a Phase II constitutes a relevant scientific concern. Clinical Trials on investigational advanced therapy medical product (IMP ATMPs) are covered by Clinical Trials Regulation. In context of clinical trials and production of ATMPs for such trials, developers of ATMPs encounter some particular difficulties due to the unique characteristics of these innovative therapies. Among other things, the variability of the

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10 A Phase 0 study does not provide information on safety or efficacy, as its dosing is too low to cause any therapeutic effect.
11 ‘Pharmacodynamics’ refer to reactions between medicines and living systems. See for instance Meibohm et al., supra note 8.
12 Yet, in some specific circumstances real patients are used, (for instance in case of patients who have terminal cancer and the treatment is likely to cause substantial harm to healthy volunteers).
14 See for instance DeMets, et al., supra note 4, 3-7.
primary materials renders it very challenging to prove the homogeneity of the ATMP.\textsuperscript{15} Niche and tailor-made ATMPs, the extremely small batch sizes and short shelf-lives can render extensive testing of the product under development impossible. Likewise, the conduct of randomised controlled clinical trials in humans may not always be possible or would be ethically contentious, if the administration of the product necessitates a surgical procedure as the majority of TEPs do, or where no alternative treatments are available. Hence, the unique nature of ATMPs calls for more flexible risk-proportionate approaches to GMP manufacture and clinical trials.

Furthermore, the European Commission has expressed a concern that the development of ATMPs is impeded by the fact that researchers usually do not have enough funding and regulatory expertise to successfully traverse through the marketing authorisation procedures.\textsuperscript{16} Also non-harmonised pricing and reimbursement practices of ATMPs applied by the national authorities of the Member States of the EU constitute some significant challenges for those who wish to commercialise these novel therapies (as the EU lacks competence to regulate health care as a public service). In addition, the significant uncertainties relating to IP rights affecting commercialisation prospects of the ATMPs, as well as to the expected returns of investments may constitute substantial deal-stoppers for those investing in these novel therapies. New IP, including but not limited to know-how and patentable inventions as well as so called regulatory IP may arise in connection with any of the above described stages of the commercialisation process. Especially, patents are needed to attract capital for investments to fund very remarkable development costs associated with development of novel therapies. Regulatory IP may be almost as valuable as patent protection in some specific circumstances (for instance when patent protection does not exist).\textsuperscript{17} Figure 2. below describes different roadblocks ATMPs under development may encounter on their way to market and their presence may also overlap depending on the very unique characteristics of each ATMP. For the sake of clarity, these roadblocks may also appear in different chronological order in the commercialisation process. (For instance IP may

\textsuperscript{15} European Commission, supra note 6. 3.

\textsuperscript{16} Ibid.

\textsuperscript{17} When it comes to data exclusivity, according to Article 10.1.iii of Directive 2001/83/EY the applicant is not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if it can demonstrate or that the medicinal product is essentially similar to a medicinal product which has been authorised within the EU, in accordance with EU provisions in force, for not less than six years and is marketed in the Member State for which the application is made. Yet, this period shall be extended to 10 years in the case of high-technology medicinal products (such as ATMPs) having been authorised via the centralised marketing authorisation procedure. Furthermore, a Member State may also extend this period to 10 years by a single decision covering all the medicinal products marketed on its territory where it considers this necessary in the interest of public health. Member States are free not to apply the six-year period beyond the date of expiry of a patent protecting the original medicinal product. Whilst market exclusivity for orphan medicines is specified in Article 8.1 of the Orphan Regulation (EC) No 141/1200. If a new medical product qualifies for orphan drug designation (it must be intended for the diagnosis, prevention, or treatment of a life threatening or debilitating condition affecting no more than five in 10 000 persons), European regulatory authorities cannot accept another marketing authorisation application for the same therapeutic indication regarding a similar medical product for 10 years after the orphan designation.
arise for a novel indication of an existing licensed medicine.) Each one of these aspects will be discussed in further detail in Chapter 7. As these obstacles are interconnected, any of these roadblocks may constitute an impediment for market entry of an ATMP.

**Figure 2. ATMP commercialisation roadblocks**

<table>
<thead>
<tr>
<th>Funding</th>
<th>IP</th>
<th>Materials</th>
<th>Class</th>
<th>GMP</th>
<th>Trials</th>
<th>MA</th>
<th>Cost</th>
</tr>
</thead>
</table>

Abbreviations: IP=intellectual property, Materials=primary materials of ATMPs, Class= classification of ATMPs, GMP=good manufacturing practice, Trials= preclinical and clinical trials on ATMPs, MA=marketing authorisation, Cost= cost, pricing and reimbursement of ATMPs.

**Commercialisation process involving different stakeholders.** Thirdly, it is vital to involve key stakeholders as early as possible in a commercialisation process. The interdependent relations between different stakeholders in Figure 3. below can be described as follows:

1. Academic clinician wants to innovate novel advanced therapies and needs patients to translate the research “from bench to bedside”;
2. Academia needs high impact publications to get research funding and IP to attract investors for university spin-offs;
3. Industry needs clinicians to innovate and academia to support proof-of-concept and reverse translation\(^{18}\) of research;
4. Academia needs industry to acquire its IP and commercialise it subsequent to clinical trials;
5. The EU Commission and the European Medicines Agency (EMA) along with the national competent authorities of the Member States (NCAs) need to ensure patient safety and quality of the ATMPs, whilst facilitating commercialisation to foster maximum availability of novel therapies in the internal market;
6. Patients need access to new, effective and safe therapies in areas of unmet medical need or when the existing treatments have proved inadequate;
7. Donors of cell and tissue samples (that are same as patients in case of autologous products) have self-determination rights (e.g. regarding primary and secondary uses of samples) and right to privacy; and
8. Health technology assessment bodies and payers (HTAs) need to ensure fairness of health technology assessment for purposes of defining reimbursement criteria of medicines.\(^ {19}\)

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\(^{18}\) Reverse translation from “bench to bedside and back”.

\(^{19}\) Figure 3. has been adapted (and amended) from a presentation by Mark Lowdell describing the relationship between different stakeholders involved in commercialisation of ATMPs as a “virtuous circle”. Please note that this figure has been complemented with author’s further observations regarding the role of
Yet, the stakeholders described in Figure 3. above are not limited thereto. For instance, when it comes to development of hESC based ATMPs, such research has raised some significant debate among wider interest groups. These stakeholders include among others European courts, legislators, policymakers, academia, stem cell scientists, pharmaceutical industry, patient organisations, religious groups and the general public.

There is a distinct lack of consistent, shared normative basis for ethical assessment of the use and commercialisation of stem cell technologies in Europe. When reflecting the scope of issues in field of stem cell science requiring governance at the EU level, some reasons for this this deficiency become quickly evident. First of all, it appears that even within each and every Member State of the EU there seems to be no definitive consensus over permissibility or legitimacy or utility of application of hESC technologies and commercialisation of such technologies. However, in some European jurisdictions a weaker or stronger consensus may have developed either about the permissibility of hESC technologies and its applications per se, or about the regulatory governance and applicable legislative (hard law and/or soft law) frameworks regulating some specific uses of hESC technologies and its applications. Yet, such consensus may differ from jurisdiction to jurisdiction across the region due to religious, political, social, cultural and professional values or reasons. Hence, the European view

Abbreviations: EC= The European Commission, EMA= The European Medicines Agency; NCAs= national competent authorities, HTAs= health technology assessment bodies and payers, donors= donors of cell or tissue samples.
on regulatory governance of stem cell technologies may even appear as less evident than a national one. As an unavoidable consequence of this disharmony, the legitimacy of a European governance framework for novel health technologies (such as hESC research) may appear less or more fragile that of any specific national framework.21

Despite the ATMP Regulation as such is a very technical, ethically neutral piece of legislation, the regulatory landscape of advanced therapies appears especially influenced and complicated by following principles of biolaw: respect for human dignity; protection of life; prohibition of commercial exploitation of human body; precautionary principle and principle of respect for private life that will be discussed as a part of this study. The structure of the study is following:

**Chapters**

- Chapter 1 describes the main elements of the commercialisation process. It is described as 1) a *funnel*; 2) a *stagewise process*; and 3) a *process involving different stakeholders*. Also the structure of the study will be presented.
- Chapter 2 introduces the main regulatory and legislative instruments that influence the commercialisation prospects of ATMPs in the EU.
- Chapter 3 presents the positioning, role of bioethics in medical and biolaw and patent law, objectives, research questions, scope, methodology and references of the study.
- Chapter 4 provides further background information for the study by portraying the multidimensional and fragmented regulatory landscape. It discusses the scope of the EU’s limited mandate in public health and safety. It also discusses the multilayered, flexible and variable approach of the Council of Europe and the emergence of the human rights framework as a normative framework for the EU. In addition, it addresses the incoherence between patent and pharmaceutical regulatory systems and the emerging human rights framework as an impediment to functioning internal markets.
- Chapter 5 of the study discusses the dimensions of human dignity as empowerment and as a constraint in light of the Convention of Human Rights and Biomedicine of the Council of Europe (the Biomedicine Convention). The complex notion of human dignity and its relation to other principles including protection of life and prohibition of commercial exploitation of human body are

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21 Richard Ashcroft has presented a number of reasons for this. First of all, he points out that if “the legitimacy of the European framework can be expected to be as weak, if not weaker, than the weakest legitimacy framework of the European framework of all contributing states.” Secondly, he argues that there may be some independent reasons why the legitimacy of the European is weaker than the national ones. According to his view these reasons may include (but are not limited to) the perceived ‘democratic deficit’ of the EU, or the Structure of the Council of Europe as a council of states, not citizens, or the perception of the European Court of Human Rights and the European Court of Justice as being remote from democratic control and oversight. Ashcroft, R. “Novel Rights Based Approaches to Health Technologies” in Flea, M., Farrell A-M., Hervey, T.A. and Murphy, T. (eds.), *European Law and New Health Technologies*. (Oxford: Oxford University), 2013, 307-322. See also Dzehtsiarou, K., Greene, A. Legitimacy and the Future of the European Court of Human Rights: Critical Perspectives from Academia and Practitioners. *German Law Journal* 2011;12:1707.
discussed in context of translational research. Finally, the boundaries of the freedom of science in the age of personalised medicine are analysed.

- Chapter 6 discusses how stakeholder participation has shaped the legislative framework affecting the commercialisation prospects of advanced therapies in the pluralistic and legally fragmented Europe. Firstly, Chapter 6 presents and complements some of the observations of Research Article IV regarding the genesis of the EUCTDs and the ATMP Regulation and it also provides some further clarifications. Secondly, it discusses briefly the emergence the legislative framework for clinical trials. Thirdly, it also concisely discusses the genesis of the Biotech Patent Directive.

- Chapter 7 presents and discusses the main findings of the study. It incorporates and updates some of the main findings regarding practical implications of the ATMP Regulation as in Research Article IV. It also addresses some further perspectives such as commercialisation obstacles pertaining to clinical trials, privacy protection, research funding, IP and reimbursement related considerations.

- Chapter 8 draws conclusions on the outcome of the ATMP Regulation and other factors influencing ATMP market entry. First, some observations regarding the benefits and shortcomings of the ATMP regulation presented in Research Article IV are discussed in further detail. Second, some of the possible amendment proposals to the ATMP Regulation and other measures to foster innovation will be presented. Third, the role of the precautionary principle in context of the emerging risk-proportionate approaches in GMP and clinical trials will be discussed. Finally, the evidence v. access balance will be analysed in light of the EMA’s early access schemes.

- Chapter 9 outlines some further impediments to commercialisation of ATMPs that have been left beyond the primary scope of this study. These include among other things trial design-, human behaviour-, and organisational- and research infrastructure related factors affecting market entry of ATMPs.

**Research Articles**

- Research Article I “Bioethical and Legal Perspectives on Cell Reprogramming Technologies” introduces some key biological and biotechnological concepts of stem cell research. The central question raised is whether there can be technological solutions to the hESC dilemma. Research Article I is a background article that presents and analyses biomedical, bioethical and legal perspectives of different cell reprogramming technologies. It notes that induced pluripotent stem cells (iPSCs) have been presented and often perceived as a more ethical alternative to hESCs, which are embroiled in a significant ethical controversy. It discusses some potential promises and perils of iPSCs for regenerative medicine and also offers some ethical perspectives regarding the hypothetical use of iPSCs in reproductive applications. In particular, it considers whether or not iPSCs are ethically speaking a less problematic alternative to hESCs. Therefore, the
prospects of iPSCs for regenerative medicine are discussed in the light of the current scientific knowledge. Paradoxical linkages between iPSC and hESC technologies are also analysed from a bioethical perspective. In addition it discusses some other technological alternatives to SCNT. Legal and ethical patentability considerations affecting the commercialisation of various pluripotent stem cell based products are also discussed. Finally, it considers how novel cell reprogramming technologies complicate our understanding of human dignity.

➢ Research Article II “Brüstle v. Greenpeace: Implications for Commercialisation of Translational Stem Cell Research” is a legal dogmatic case commentary that discusses how the lack of consensus on a definition of the term embryo has resulted in legal uncertainty affecting the permissibility of hESC research and the commercialisation prospects and patenting of inventions of hESC origin in the EU. In particular, it discusses the Court of Justice of the European Union’s (the ECJ) ruling in Brüstle v. Greenpeace case which, by providing a very broad definition of a human embryo, restricts the patentability of hESC-based inventions, and is intended to harmonise the patenting practices regarding interpretation of Article 6.2.c of the Biotech Patent Directive. This case fills the gaps in national laws by providing binding interpretation guidelines for national courts. Implications of this judgment for translational hESC research together with other barriers to commercialisation of such research have been analysed.

➢ Research Article III “Patentability of Parthenogenic Stem Cells: International Stem Cell Corporation v. Comptroller General of Patents” is a brief update commentary on Research Article II which seeks to clarify some inaccuracies that followed from the Brüstle judgment. The ECJ’s ruling in Case C-364/13 International Stem Cell Corporation v. Comptroller General of Patents Designs and Trademarks aims at harmonising the patenting practices regarding interpretation of Article 6.2.c of the Biotech Patent Directive in respect of the patentability of human parthenogenic stem cells. Since it alters the patenting regime for hESC applications by stating that moral restrictions against hESC patents are only applicable to cells derived from embryos that had the potential to develop into a human being, human parthenogenetic stem cells-based (hpSC) inventions may be patentable in Europe. This represents a leap forward to striking a balance between protecting human dignity and integrity whilst granting patent incentives for biomedical research.

➢ Research Article IV “Encountering Challenges with the EU Regulation on Advanced Therapy Medical Products” is the most important Research Article of this study. By using the problem-based approach it analyses how well the ATMP Regulation meets the needs of SMEs, academia, and public tissue establishments developing ATMPs. Benefits and shortcomings of the ATMP Regulation are identified, and possible amendments are proposed to accelerate the translation of research into advanced therapies and to facilitate the commercialisation of ATMPs whilst ensuring safety.
2 Introduction

The ATMP Regulation stems initially from EU-wide internal market objectives. It was set up as special legislation to ensure the free movement of ATMPs within the EU in order to facilitate their access to the internal market. Its primary objective was to “foster the competitiveness of European pharmaceutical companies, while guaranteeing the highest level protection of public health.”

Subsequent to the adoption of the ATMP Regulation in December 2008, only six ATMPs have been granted marketing authorisations via the mandatory centralised procedure as of August 2016: one cell therapy, Sipuleucel-T for metastatic castrate-resistant prostate cancer (Provenge, 2013); two GTMPs, alipogene tiparvovec for lipoprotein lipase deficiency (Glybera, 2012) and an oncologic immunotherapy talimogene laherparepvec for treating adults with melanoma (Imlygic, 2016); and three TEPs autologous cartilage cells expanded ex vivo expressing specific marker proteins (ChondroCelect, 2009), matrix applied characterised autologous cultured chondrocytes for cartilage defects (MACI, 2013); and ex vivo expanded autologous human corneal epithelial cells containing stem cells for severe limbal stem cell deficiency caused by burns to the eyes (Holoclar, 2015). For Provenge, marketing authorisation has been withdrawn due to the bankruptcy of the marketing authorisation holder and for MACI it has been suspended due to the closure of the manufacturing site. In addition to the above mentioned products, an ATMP sitimagene ceradenovec (Cerepro, 2002) was granted an orphan designation to treat operable high grade glioma with ganciclovir sodium. Yet, later its marketing authorisation application under the ATMP Regulation was withdrawn, because clear evidence of a clinically meaningful benefit in relation to risk could not be confirmed in later clinical trials.

Only one of these four currently authorised products (Holoclar) is a stem cell-based ATMP. No ATMPs of human embryonic origin have been authorised. Clinical trials on...
hESCs are still in their early phases.\textsuperscript{26} Currently, the main uses of hESCs relate to toxicology screenings and the study of models of disease in the laboratory setting. Such research activities play an important role as analytical tools for developing ATMPs and in pursuit of further understanding of the pathogenesis of particular diseases. Limitations on such preclinical uses of hESCs may adversely affect the drug development process because of a loss of viable analytical tools.

The small number of ATMPs in the internal market has meant a need to determine whether the ATMP Regulation fulfils its objectives, especially in terms of SMEs\textsuperscript{27}, academia, and public tissue establishments\textsuperscript{28} developing ATMPs. According to the EMA, the ATMP Regulation intends to “provide incentives to help them continue their research on and development of advanced therapies.”\textsuperscript{29} However, it appears that developers of ATMPs have encountered a number of challenges with implementation of the requirements mandated by this relatively new legislation.\textsuperscript{30} As there is very little research on how the ATMP Regulation affects SMEs and academia, as well as non-profit organisations (such as public tissue establishments), this study assesses how well the ATMP Regulation fulfils its objectives, especially from the perspective of these stakeholders. It also proposes amendments to the ATMP Regulation and related marketing authorisation processes to accelerate the translation of research into advanced therapies and to facilitate commercialisation of ATMPs whilst ensuring the safety of the patients.

Despite the primary objective of this study being to analyse the implications of the ATMP Regulation, it would not be accurate to assume that the currently very small number of ATMPs results exclusively from the requirements imposed by ATMP Regulation. The ATMP landscape is much more complicated than that, being influenced by a number of factors and other legislative instruments affecting the commercialisation prospects of these innovative products. There is thus a need to provide a general overview of the legislative landscape in which developers of ATMPs

\textsuperscript{26} See Table 2. in Appendix 2 for further details.
\textsuperscript{27} According to the EU definition, SMEs employ less than 250 persons and have an annual turnover not exceeding EUR 50 million, and/or an annual balance sheet total not exceeding EUR 43 million. Within the SME category, a small enterprise is defined as one which employs less than 50 persons and whose annual turnover and/or annual balance sheet total does not exceed EUR 10 million. Please refer to Article 2 of the Commission Recommendation 2003/361/EC of 6 May 2003 concerning the definition of micro-, small-, and medium-sized enterprises, OJ L 124, 20.5.2003, 36.
\textsuperscript{28} Tissue establishment is defined in the glossary of terms of the European Association of Tissue Banks (EATB) as “a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells (2004/23/EC).” European Association of Tissue Banks. Glossary of Terms. Available at: http://www.eatb.org/tissue/glossary.html. Accessed 21 June 2016.
\textsuperscript{30} Mansnérus, supra note 22, 427.
operate.\textsuperscript{31} In addition to an introduction to the ATMP Regulation, this Chapter introduces the EUCTDs and applicable clinical trials legislation (especially Clinical Trials Directive 2001/20/EC and Clinical Trials Regulation No. 536/2014 repealing Clinical Trials Directive 2001/20/EC). It also briefly outlines the impact of EU research funding policies and the Biotech Patent Directive. Whilst the EU’s mandate in public health will be discussed in Chapter 4, which describes this multilayered and fragmented research area.

The hESC-based products are a subset of ATMPs whose embryonic origin involves further ethical challenges on their way “from bench to bedside” in the EU. As shown in Research Article I, research on human embryos has been perceived to be of paramount importance for regenerative medicine for a number of reasons. Firstly, the hESCs may renew themselves in cell cultures almost endlessly. Secondly, they possess a pluripotent capability to develop into the different cell types of the human body. Thirdly, hESC not only provide an endless supply of human cells, but also provide the possibility of \textit{in vitro} embryo diagnoses, which in turn enable unique investigational opportunities for some disease mechanisms that cannot be examined by means of \textit{in vivo} clinical trials involving humans or animals.\textsuperscript{32} However, the hESC-based ATMPs being developed face a number of biomedical, legal and ethical challenges. Generally speaking, the many risks usually associated with ATMPs are applicable to emerging hESC-based therapies, In addition to these legal and ethical challenges there some additional biomedical obstacles that hESC and iPSC technologies still need to overcome on their route to the clinic. However, when it comes to the “translational roadblocks” of stem cell therapies, the main focus will be ethical and legal patenting issues indirectly affecting their commercialisation prospects.\textsuperscript{33}

The moral patenting restrictions affecting the commercialisation prospects of hESC-based inventions in the EU has been addressed in Research Articles I, II and III. As Research Article II presents, for ethical reasons the national stem cell policies in Europe range from highly restrictive policies banning all research on hESCs to liberal ones permitting creation of human embryos for research purposes by somatic cell nuclear transfer (SCNT), applied by a few Member States. It has been reported that the majority of Member States have adopted an intermediate position which permits

\begin{itemize}
  \item The applicable legislation and other relevant guidance and documentation issued by authorities have been taken into consideration as of 30 July 2016.
  \item All pluripotent cells are known to be associated with some substantial risks and there are some roadblocks ahead that need to be overcome on their route to the clinic. To be suitable for therapeutic purposes, these cells must be first differentiated into the required cell type and the grafts should, to the greatest degree possible, contain only differentiated cells because pluripotent cells may give rise to teratomas. See e.g., Power, C., Rasko, J. Will Cell Reprogramming Resolve the Embryonic Stem Cell Controversy? A Narrative Review. \textit{Ann Intern Med}. 2011;155:114-21.
\end{itemize}
research on surplus in vitro fertilization (IVF) embryos with the ultimate objective of alleviating human suffering and improving collective or individual human health and well-being. As discussed in Research Articles II and III, in addition to these ethical issues and a number of regulatory challenges SMEs developing different types of ATMPs are encountering, developers of hESC-based products face some significant additional barriers to commercialisation that arise out of the disharmonised implementation of the Biotech Patent Directive in the EU.

The legislative landscape governing commercialisation of ATMPs has been found quite complex. The intricacy of regulation appears at all levels of the development processes of new pharmaceutical products; research funding is subject to scientific, ethical and political consideration at local, national and EU levels, and clinical trials are subjected to scientific scrutiny through a marketing authorisation system, as well as the review of ethical committees, and principles of Good Clinical Practise (GCP) during ongoing trials. Chapter 7 of this study addresses roadblocks arising at all of these levels. This complexity is increased by the form of regulation varying vis-à-vis the type of the health technology; e.g., pharmaceutical products are subject to different forms of regulatory control than medical devices, and ATMPs are subject to somewhat different forms of regulatory control from conventional pharmaceutical products. Furthermore, it has been claimed that regulation often seems to precede the development of technology (e.g., research funding priorities may direct the general focus of scientific research even prior to medical innovations taking place) and the regulatory oversight may continue for as long as the medical product or procedure is being used (e.g., pharmacovigilance, post-market evidence generation for marketing authorisation and/or reimbursement of a medicine, risk management schemes and product liability regulating the safety of the product in the market). With the prospect of creating novel therapeutic opportunities whilst safeguarding public health, many stakeholders are involved in ensuring that the applicable regulation is effective and negotiated by all affected parties: policy-makers, regulators, industry, scientists, academics, patient organisations and the general public.


37 See e.g. op. cit., 70-71. See also Section 8.3 of this study for further details regarding the role of post-market evidence generation.

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alike. This approach does not necessitate fully shared common values, but it does require at least a mutual agreement on terminology to understand what exactly is being regulated, according to Amanda Warren-Jones.\(^ {38}\)

As a starting point of my study, it is acknowledged that not all EU legislation should and can be harmonised in ethical sense. In contrast, the European regulators have an obligation to respect the plurality of values in the EU pursuant to Article 4.2 of the Treaty on the European Union (TEU) — the equality of Member States before the Treaties as well as their national identities, inherent in their fundamental structures, political and constitutional shall be respected. This means that as the EU’s mandate is based on internal market objectives, the EU lacks competence to harmonise ethical norms applicable in its Member States. My study argues that regulators should rather ensure that legislation on ATMPs and biomedical research is flexible enough to adjust in course of scientific advancements and rapidly changing present-day conditions. Therefore, non-coercive, flexible measures should be promoted as far as possible in case of ethically sensitive areas of biomedical research where no consensus exists and plurality of values prevails. Whilst, beyond ethical considerations, certain technical aspects, such as classifications of ATMPs should be harmonised to improve functionality of internal markets.

Indeed, the search for common definitions constitutes an essential first step before further considering how exactly a certain technology should be regulated. As noted in Research Article IV, in the case of ATMPs the fragmented use of terminology — the distinct lack of common, EU-wide harmonised classifications — has resulted in a significant barrier to commercialisation in the internal market. However, the lack of harmonised ATMP classifications represents just one of the indications of the fragmented development of regulation on advanced therapies. Regulation of ATMPs has been spread across many regulatory instruments. The plethora of regulatory instruments for advanced therapies has made it increasingly difficult for the developers of ATMPs to traverse the complex sets of rules, regulations, ethical codes, and other soft law. Firstly, the general marketing authorisation procedure that allows new medical products to enter the internal market is regulated in Directive 2001/83/EC (the Medical Products Directive), which is drafted sufficiently ambiguously to accommodate the cell and tissues used in tissue engineering:

“[a] substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medical product.”\(^ {39}\)

In addition, the scope of the Medical Products Directive was subsequently amended by Directive 2003/63/EC, and the distinction in Recital 9 between GTMPs and CTMPs was incorporated into the new Annex 1 of the Medical Products Directive. These

\(^{38}\) Warren-Jones, supra note 36, 71.

\(^{39}\) Article 1.2. of the Directive 2001/83/EC.
amendments notwithstanding, the ATMP Regulation was introduced to cover TEPs, whereas EUCTDs cover donation, procurement and testing of tissues and cells purported to be used for industrially manufactured products and medical devices outside the mandatory centralised marketing authorisations. Hence, from the perspective of developers of ATMPs this means that there are currently many separate legislative instruments that may apply depending on the type of activity, instead of a single efficient body of legislation with accessible definitions that could cover all such activities. This may constitute a confusing array of regulatory instruments facing those who actually develop ATMPs.40

In addition to fragmented practice caused by the lack of common terminology and the fact that rules mandating quality, safety, procurement, testing, processing, preservation, storage, authorisation, supervision and pharmacovigilance of ATMPs are spread across so many regulatory instruments, some significant ethical controversies hamper development and commercialisation of some specific types of ATMP. Indeed, significant fragmentation of national research policies and the patenting practices applying to ATMPs, especially in case of hESC-based inventions prevails. The division of competences between the EPO and the regulatory authorities also raises particular concerns about impaired predictability and increasingly incoherent practices in the biotechnological patenting sector.

2.1 The EU funding and patentability affecting commercialisation prospects

Since 1984, the European Commission has provided funding for scientific research via framework programmes for research and innovation covering funding periods that span many years. When it comes to research funding for novel health technologies (such as hESC research), the Seventh Framework Programme (FP7) focused significantly on translational research, which pursues translating basic research into usable and marketable health technologies.41 Within FP7, the role of basic research was perceived as a driver of growth.42 Funding under FP7 has been confined by the principle of “European added value”, which required discourse between researchers in the Member States to foster competitiveness in the health technology sector.43 Although research has

40 Warren-Jones, supra note 36, 85.
43 Ibid. More specifically, the European Commission claims that: “one key aspect of the European added value is the transnationality of many actions: research projects are carried out by consortia which include participants from different European (and other) countries; fellowships in FP7 require mobility over national borders. Indeed, many research challenges (e.g. fusion research, etc), are so complex that they
been framed by the Lisbon Strategy that seeks to make Europe the most dynamic, competitive, knowledge-based economy in the world, which is capable of sustaining economic growth, employment and social consistency, it should be noted that the European Commission has issued a Lisbon Strategy evaluation document in which it is reported that some of the endorsed ambitions, those related to fostering innovations, have not resulted in faster decision-making. Despite the importance of fostering innovations being highlighted by the European Council, including the case of "the need for a strong, affordable Community Patent", the delivery of a solution has been rather slow. Subsequent to the FP7, Horizon 2020 has been the Research and Innovation Programme of the EU for 2014-2020. Horizon 2020 also emphasises the vital role of research and innovation for European Union economic growth and for attracting private investment, yet the European Commission does not finance research projects that involve destruction of embryos under its current Framework Programme for Research and Innovation Horizon 2020, which may adversely affect the commercialisation prospects of some hESC-based ATMPs, including downstream products.

Beyond issues of research funding, the Biotech Patent Directive constitutes another viable example of the importance of the internal market objectives as key drivers of regulation in the European health technology field. The Biotech Patent Directive in particular is justified by the idea that differences in the legal protection of biotechnology inventions in various Member States are conducive to imposing barriers on trade in the internal market. In Recital 7 of the Biotech Patent Directive, harmonisation of biotechnology patenting practices is justified by the need to foster the competitiveness of the internal market as "uncoordinated development of national laws on the legal protection of biotechnological inventions" in the EU risks causing additional "disincentives to trade, to the detriment of the industrial development of such inventions and impediments to the smooth operation of the internal market". However, it has been noted in Research Article II that the implementation of the moral exclusions provision of the Biotech Patent Directive has been greatly disharmonised in the EU. The ethical controversies hampering the patentability prospects of hESC research are very complicated, multifaceted legal issues. Some commentators, such as...
Hellstadius, along with Van Overwalle, have even described the role of ethics as a “distraction” in patent law.\textsuperscript{50}

The current European legislative framework for patents involves a very fragmented, but co-operative relationship between many institutions, expressed in numerous regulatory instruments and practices. It also yields an indirect regulatory effect on hESC-based inventions, partly via the basic requirements for patentability of inventions (e.g., novelty, the inventive step, and industrial application) and in part via moral exclusions from patentability.\textsuperscript{51} Generally speaking, there are two types of motives for excluding hESC inventions from patentability; economic and political.\textsuperscript{52} The main economic reason is the perception of patents for unethical inventions as a waste of social resources,\textsuperscript{53} whereas the political reasons relate to the public perception of the nature of a hESC patent. As patents constitute incentives for innovation, the refutation of patent protection simultaneously constitutes the removal of the incentive, and hence discourages R&D on certain types of technology. Patents are needed to attract private investment and accelerate the growth of university spin-offs (as described in Section 7.2). The significant difficulty in accommodating the moral aspects of hESCs into the traditional patentable subject matter scope has been addressed.\textsuperscript{54} The difficulty of aligning the ethical notion of human dignity with patent protection of inventions of embryonic origin has been recognised by the EPO\textsuperscript{55} and the ECJ\textsuperscript{56} alike in their stem cell decisions. Patent proceedings have become a forum for other stakeholders (such as prolife activists) for participation via opposition proceedings.\textsuperscript{57} In the late 1980s, the introduction of the first draft of the Biotech Patent Directive had already provoked public opposition by various stakeholders, discussions which have intensified in the course of advancements in stem cell science.


\textsuperscript{52} Hellstadius, supra note 50, 29.

\textsuperscript{53} To illustrate the social dimension, Hellstadius refers to the Minutes of the Round Table organised by the European Group on Ethics in Science and New Technologies on 20 November 2001 in Brussels, World Intellectual Property Organization (WIPO) Secretariat at the Roundtable on the ethical aspects of patenting inventions involving human stem cells.


\textsuperscript{55} See Enlarged Board of Appeal, WARF, G02/06 and Decision of the Opposition Division of 21 July 2003 on European patent no. EP0695351 (University of Edinburgh).


\textsuperscript{57} Hellstadius, supra note 50, 90.
When it comes to the current forum for the expression of values in patent law ethics, the EPO has been seen to operate in its own domain in the absence of guidance from regulatory law integrating ethical concerns, since the existing regulatory legislation is currently not used by the patent offices and courts in the application of the morality exclusion. According to Hellstadius however, ethical considerations appear to have a superseding role in the sense that the application of the morality clause cannot be undermined by any technical criteria being fulfilled. Plomer has advocated that as a starting-point the scope of moral exemptions in patent law should be in line with the constitutional limits set out by the background legal framework of the European Union and Treaties, which suggest “respect for the diversity of national cultural moral traditions in a pluralistic and democratic Europe”. Consequently, a wide margin of appreciation must by granted to the Member States in respecting the differing moral traditions in ethically sensitive questions in Plomer’s view of the interpretation of the moral provisions in the EU law. It seems however very problematic that the margin of appreciation exercised by the ECJ and the European Court of human rights (ECtHR) apparently differs in the case of the legal status granted to an embryo.

In addition, the division of competences between the European patent system and the pharmaceutical regulatory system and its impact on the application of the patent morality clause has raised some significant debate. It has been also noted that despite the EPO having to some extent sought common European values and ethical standards, the impact of existing pharmaceutical regulatory legislation on the interpretation of the morality clause appears very infrequently in the case law of the EPO. As mentioned in Research Article II, the ECJ established in the Brüstle case, that certain types of

58 Hellstadius, op. cit., 91. It has been pointed out that such a tie is reinforced in some of the contracting states of the EPC, where the morality clause related to existing research regulation is substantiated by direct references in the legislation. Please refer to Hellstadius, Å. “A Comparative Analysis of the National Implementation of the Directive’s Morality Clause”, in Plomer, A., Torremans, P. (eds.), Embryonic Stem Cell Patents European Law and Ethics. (Oxford: Oxford University Press), 2009, 117-141.
59 Plomer, supra note 54, 489.
61 Hellstadius, supra note 50, 408-410. Hellstadius argues that the EPO should take the existing values and norms expressed in the national (non-patent) regulatory legislation in force into account to a greater extent in interpreting the morality clause. According to Hellstadius, the actual mandate of patent authorities is more fitted to questions relating to other patentability criteria such as novelty, the inventive step, and commercial exploitation of inventions. She further asks: if risk assessment is not the primary function of the EPO or even its duty, for what purpose is the EPO as a patent office trying to evaluate risks involved with a specific technology? Secondly, does the EPO have the required expertise for conducting such a risk assessment in connection with its standard patent examination process? (p.286). Whilst Amanda Warren-Jones has suggested that by means of the moral provision in patent law, the patent system should merely act as a filter against undesirable inventions. Hence, it complements the sanctioning function of other regulatory organs. Warren-Jones, A. Vital parameters for patent morality – a question of form’, Journal of Intellectual Property Law & Practice, 2007; (2)12; 832-846. Hence, the division of competences appears to be problematic if the purpose of the morality provision is to identify inventions contrary to public order or morality, and patent authorities end up conducting risk assessments, which is already ultimately a duty of the regulatory authorities.
hESC-based inventions (i.e., those necessitating destruction of human embryos) are ineligible for patent protection, despite the fact that the subject matter of the invention could be commercialised in a number of the EU Member States. It should also be noted that the EUCTDs and the ATMP Regulation have both implemented a permissive default approach to commercialisation of stem cell research.63

From the perspective of coherence of the legal system, it is undesirable that this kind of obvious discrepancy arises in a situation in which patentability is denied on moral grounds despite the permissive regulatory approach. It has been reasonably argued that the EPO’s competence in risk assessment seems questionable as it is not its primary function or even its duty. However, despite concerns about the scope of the EPO’s mandate, the Boards and Divisions of the EPO are currently conducting risk assessments that could be more aptly done by the pharmaceutical regulatory authorities.64 Therefore, it seems reasonable to argue that the scope of assessment of the patent morality clause should be kept strictly within the limits of the patent system, namely, commercial exploitation.65 Given the complex nature of ATMPs and possible risk-adjusted approaches to be used in GMP manufacture and trials, it is evident that risk assessments pertaining to the ATMPs require much specialised expertise. As shown in Section 7.6.3 of this study, the risk-proportionate approach to clinical trials and GMP are indeed subject to comprehensive stakeholder consultations that aim at establishing common acceptable standards and principles to deal with risks associated with advanced therapies.

Since patent authorities are by no means vested with adequate competence and resources to assess whether a product may constitute a public health risk, it is reasonable to argue that to improve the regulatory coherence of the EPO they should take the decisions of competent regulatory authorities into consideration as supplementary (regulatory) material in the assessment of the morality exclusion. Pursuant to the idea of reflexive law (that will be further clarified in Section 3.4.2 of this study) this approach could improve coherence between the pharmaceutical regulatory system and the patent system, and allow significant adaptation and flexibility in present-day conditions over time and place.

63 Plomer, supra note 60, 127.
64 Hellstadius, supra note 50, 408-410. Hellstadius finds it especially problematic that the Boards of Appeal of the EPO have addressed the question of risk assessment as part of their mandate under Article 53(a) EPC, despite it is not their duty. See for instance, PSG, T 356/93. See also Hellstadius, op. cit., 286.
2.2 The EU Cell and Tissue Directives setting high quality and safety standards

The EUCTDs were issued by the European Commission in 2004 to ensure harmonised and high standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human cells and tissues for human applications, to facilitate their cross-border movements and to ensure availability in the EU. However, subsequent to the adoption of the ATMP Regulation the EUCTDs were reduced to cover donation, procurement and testing of tissues and cells purported to be used for industrially manufactured products and medical devices. The EUCTDs comprise of three Directives: the so-called parent Directive 2004/23/EC, which sets out for the framework legislation and two technical Directives, 2006/17/EC and 2006/86/EC, which consist of more detailed requirements of the parent Directive. The EUCTDs introduced requirements for biobanks, which required substantial investments and reorganisations. However, such requirements are now generally perceived positive.

2.3 The ATMP Regulation aiming at ensuring safety and effectiveness of ATMPs

All modern biotechnology medicinal products currently regulated at EU level are subject to a centralised marketing authorisation procedure, involving a single scientific evaluation of the quality, safety and efficacy of the product, which is carried out to the highest possible standard by the EMA. The ATMP Regulation that came into force in the EU on 30 December 2008 was set up as a lex specialis introducing particular...
provisions to the existing pharmaceutical legislation in respect of authorisation, supervision and pharmacovigilance of ATMPs to ensure that they are safe and effective.\textsuperscript{69} The ATMP Regulation encompasses the following categories of medicinal products for human use: GTMPs, CTMPs and TEPs. They have been described as a “complex, heterogeneous class of innovative therapies that combine features of medicine, cell biology, science and engineering to regenerate, repair or replace damaged tissues or cells”.\textsuperscript{70}

Table 3. Definitions of the ATMP subcategories\textsuperscript{71}

<table>
<thead>
<tr>
<th>ATMP subcategory</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTMP</td>
<td>GTMP means a biological medicinal product which has the following characteristics: it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.</td>
</tr>
<tr>
<td>CTMP</td>
<td>CTMP means a biological medicinal product which has the following characteristics: 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. It 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.</td>
</tr>
<tr>
<td>TEP</td>
<td>TEP means a biological medicinal product containing or consisting of engineered cells or tissues. It 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.</td>
</tr>
<tr>
<td>Combined ATMPs</td>
<td>These are medicines that contain one or more medical devices as an integral part of the medicine. An example of this is cells embedded in a biodegradable matrix or scaffold.</td>
</tr>
</tbody>
</table>


\textsuperscript{71} These definitions are adapted from the European Medicines Agency. \textit{Reflection paper on classification of advanced therapy medicinal products, op.cit.} Please note that official legal definitions are provided for a GTMP in Part IV of Annex I to Directive 2001/83/EC; for a CTMP in Part IV of Annex I to Directive 2001/83/EC and for TEP in Article 2.1.b. of the ATMP Regulation.
The investigation whether a product under development falls within any of these categories may require profound scientific analysis. Especially, the aspect whether a manipulation of a living material should be considered as “substantial” may be very challenging to answer. Article 2 l.c. of the ATMP Regulation defines ATMPs as ‘engineered’ products that contain or consist of cells or tissues that have been subject to substantial manipulation, so that “biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved” or “the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.”

Before adoption of the ATMP Regulation, Directive 2003/63/EC amending Directive 2001/83/EC had introduced the definition of ATMPs in 2003, characterising them as products GTMPs and CTMPs. TEPs were previously considered as an unregulated class of medicinal products and the absence of an unambiguous legal and regulatory framework at the EU level had resulted in divergent national approaches for the authorisation of TEPs. Some Member States authorised them as medicinal products, others as medical devices or as tissue products, whereas some had issued particular national guidelines to regulate ATMPs. As reported, this remarkable discrepancy in national regulatory approaches not only established real obstacles to the free movement of TEPs but it could also limit availability these new therapies. It was noted that the unclear legal status of TEPs that had resulted in the fragmentation of the market within the EU, constituting a disadvantage for European companies and academia developing these innovative products.

The current ATMP Regulation provides tailored regulatory principles for evaluation, for the mandatory centralised marketing authorisation procedure for ATMPs, for post-authorisation follow-up and for traceability. As noted, the new

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72 European Union Regulation (EC) No. 1394/2007 of the European Parliament and Council of 13 November 2007 on Advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union L324:121–137. It should be noted that this study does not aim at providing any specific guidance regarding scientific classification of any particular pharmaceutical product. For further details, please refer to “Reflection paper on classification of advanced therapy medicinal products” issued by the EMA. It provides further guidance regarding classification of ATMPs. It also provides “decision trees” that may facilitate classification of ATMPs.


75 Bock, et al., op. cit., 13. See also Mansnéurus, supra note 22, 429.

76 Pirnay, et al., supra note 22, 539. See also Mansnéurus, ibid. The drafting history of the ATMP Regulation, will be discussed in further detail in Section 6.2. of this study.

scientific committee at the EMA, the Committee for Advanced Therapies (CAT) was founded pursuant to the ATMP Regulation as a multidisciplinary body, with primary responsibility to assess the quality, safety and efficacy of ATMPs, and to follow scientific developments in the field. The CAT also provides an advisory service to innovators developing ATMPs. Since June 2009 the CAT has issued scientific recommendations on ATMPs classification.\textsuperscript{78} The legislation also provides incentives tailored to SMEs that develop ATMPs.\textsuperscript{79} Recently, some of these incentives have been extended to cover academia and non profit actors.\textsuperscript{80} 

Since adoption of the ATMP Regulation, as presented in Table 1 of Appendix 1, only six marketing authorisations have been granted to ATMPs thus far and currently four of them are still on the market.\textsuperscript{81} The low number of marketing authorisations granted is despite the increasing amount of companies and investment in the field.\textsuperscript{82} A recent study by Hanna et al. reveals significant increases in clinical trials on ATMPs reported in the EudraCT, ClinicalTrials.gov, and ICTRP (International Clinical Trials Registry Platform of the World Health Organization) during the recent years (number of ATMPs in development increased from 12 trials in 2004 to 150 in 2014). A study by Hanna et al. identified 939 clinical trials on ATMPs (85% ongoing, 15% completed) from 1999 to June 2015. The great majority of trials were in the early stages (Phase I, I/II: 64.3%, Phase II, II/III: 27.9%, Phase III: 6.9%). Per category of ATMP, 53.6% of trials involved CTMPs, 22.8% TEPs, 22.4% GTMPs, and 1.2% combined ATMPs. Disease areas included cancer (24.8%), cardiovascular diseases (19.4%), musculoskeletal (10.5%), immune system and inflammation (11.5%), and others. Of the trials, 47.2% enrolled less than 25 patients. To address particularities of ATMPs new clinical trial approaches are being considered (e.g., small sample size, non-randomised trials, single-arm trials, surrogate endpoints, integrated protocols, and adaptive designs). Therefore, Hanna et al. conclude that “evidence generation post-launch will become unavoidable to address payers’ expectations.”\textsuperscript{83}


\textsuperscript{78} European Medicines Agency, op.cit. 


\textsuperscript{80} These aspects of ATMP regulation has been discussed in Research Article IV and Section 7.7.2 of this study. Possible amendments improving the potential impact of to these incentives will be discussed in Section 8.1.1. of this study. 

\textsuperscript{81} See Table 1. in Appendix 1. for further details. 


Furthermore, it has been reported by Barfoot et al. that the field of stem cell research has grown globally very rapidly over the past decade. According to Barfoot et al., the volume of research output and the number of publications as well as citation frequency has increased significantly in hESCs and iPSCs related topics. There is an evident need for a re-assessment of how the ATMP Regulation is being implemented, as commercialisation of these medicines appears to be very slow. Research Article IV and the Chapter 7 of this study analyse possible reasons for this by investigating why so few ATMPs have progressed through the clinical trials to commercialisation of these products. It is particularly investigated whether obstacles to a fully-fledged market entry of these medicines relate to ATMPs as such or whether something else in the innovation system is hindering their progress. The harmonisation attempts, notwithstanding some obstacles remain as the ATMP Regulation has been so divergently implemented across the Member States, which is against the initial purpose of the EU regulation that was supposed to guarantee regulatory uniformity. Therefore, there is a need to further streamline and clarify of the ATMP Regulation. However, more harmonisation should not result in making regulatory compliance an excessively resource-consuming activity for the developers and manufacturers of ATMPs and it should not divert resources from their innovative activities.

Moreover, the ATMP Regulation allows hospitals to treat patients with ATMPs on a “non-routine basis” according to specific quality standards, and used within the same Member States in a hospital under the exclusive professional responsibility of a physician, under an individual medical prescription for a custom-made product for an individual patient. Hospital exemption necessitates the application of national requirements on quality, traceability, and pharmacovigilance similar to those required for authorised medicinal products. Some Member States have implemented this so-called “hospital exemption”, whereas others have utilised different definitions for the use of “non-routine”, and some have not defined it at all. Consequently, lack of a uniform definition has resulted in significant discrepancies in the national implementation of hospital exemption (as it has been reported in Research Article IV and further specified in Section 7.7.1 of this study). These findings suggest that there is a need for the European Commission to further clarify and streamline this definition.


85 More specifically, it was reported that in terms of the number of the publications, there were 4402 publications in 1996, which represented 0.4% of global publications. Whilst the number increased to 21193 publications in 2012, representing 1% of global publications. Furthermore it was reported that during 2008-2012 stem cell publications demonstrated annual growth rate of 7.0% in comparison to the world average growth rate of 2.9% across all field of research. According to the report the hESC publications showed a growth rate of 5.1%. Whilst, the emerging field of iPSC research grew more rapidly representing an annual growth rate of 77%. According to the report stem cell publications, on average, were cited 50% more than the global average for all related disciplines.

86 Mansnérus, supra note 22, 460.
2.4 The Clinical Trials Regulation simplifying the submission of an application dossier for authorisation and harmonising the procedures for conducting clinical trials

Initially, the objective of the Clinical Trials Directive 2001/20/EC (Clinical Trials Directive) was to simplify and harmonise the administrative rules governing clinical trials in the EU. However, this aim was achieved only partly, rendering it difficult to conduct a clinical trial in many Member States. The implementation of the Clinical Trials Directive had resulted in a significant increase in the time and costs of conducting a clinical trial in the EU. These problems coupled with the lack of cooperation between the Member States and inefficient pooling of expertise caused a 25 percent decline in the number of clinical trial applications in the EU from 2007 to 2011.

In the era of personalised medicine, developers of ATMPs are targeting more and more very specific groups of patients identified by means of genomic data. To recruit an adequate number of patients for such trials, it may be essential to involve cross-border trial sites. Therefore, there is a need cover clinical trials conducted in many Member States by the same rules. The Clinical Trials Regulation was created by the European Commission to facilitate cross-border clinical trials within the EU. It was adopted by the European Parliament in 2 April 2014 and is expected to become effective by October 2018 at the latest. It applies to all individuals in the EU. The new Clinical Trials Regulation repealing the Clinical Trials Directive aims at reversing the decrease in number of investigations of medicines conducted by making the EU more attractive for clinical trial research whilst maintaining high standards of patient safety. To achieve these goals it aims at harmonising procedures for conducting clinical trials and simplifying the submission of an application dossier for clinical trials authorisation. The Clinical Trial Regulation also covers clinical trials on IMP ATMPs.

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87 More specifically, it has been reported in the Explanatory Memorandum to the Proposal for a Regulation of the European Parliament and the Council (dated July 2012) that staffing requirements for the clinical trial authorisation process for sponsors doubled. Also insurance fees were increased by 800 percent for industry sponsors and there was a 98 percent increase in administrative costs for non-commercial sponsors. In addition, delays for launching a clinical trial increased by 90 percent to 152 days. Available at: http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf. Accessed 21 June 2016.

88 Op. cit., 2. The decrease was 12% from 2007 to 2010.

89 It was adopted by the by the Council of Ministers (14 April 2014) and signed off on 16 April 2014. It was published in the Official Journal on 27 May 2014. Article 82(1) of the Regulation requires the EMA to draw up the functional specifications together with the time frame for their implementation, in collaboration with the Member States and European Commission. The European Medicines Agency. Delivery time frame for the EU portal and EU database Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500199078.pdf. Accessed 21 June 2016. According to the EMA, it is predicted that the clinical trials portal and database are planned to be available for an independent audit by August 2017. If the system receives a green light from the audit, the Clinical Trial Regulation will come into effect by October 2018 at the latest.
Some aspects of the drafting history of the Clinical Trials Regulation will be briefly discussed in Section 6.3 of this study.

It should be noted that certain aspects of clinical trial will not be covered by the Clinical Trials Regulation and they remain country-specific. These aspects include ethics, legal representation of participant not able to consent, substantial rules of liability in case of damages, requirements for investigators and site qualification, as well as country specific documentation requirements (e.g. notarisation of documents, language etc). Further analysis of these country-specific rules is left outside the scope of this study.
3 Methodology

3.1 Positioning the study in the emerging field of European medical and biolaw

Traditionally, our legal system has been categorised into a number of legal disciplines.90 The reasons for the emergence for a new discipline relate to societal change, juridification of society, internationalisation of the sources of law, as well as the fact that legal problems are often located at the interfaces between several disciplines.91 This study is primarily positioned in the developing field of European medical and biolaw, an emergent discipline that shares interfaces with several other disciplines. The field of medical and biolaw is also a multilayered one and is still establishing its position as a legal discipline in Europe. It shares many interfaces with medical and bioethics and is strongly influenced by the fundamental human rights principles, treaties and conventions (such as the ECHR and the Biomedicine Convention) that incorporate ethical perspectives into black letter law. As a discipline, it is also influenced by miscellaneous soft law instruments such as ethical codes issued by interest organisations or groups pursuing further accommodation of ethical interests in healthcare. This multidimensional field of study will be briefly discussed in Chapter 4 to provide a general overview of recent developments underpinning medical and biolaw.

In addition, some limited aspects of this study partly overlap with intellectual property law, patent law in particular. Within the scope of this study patent law is depicted as an indirect form of regulation of stem cell technologies in Europe. This study does not purport to provide a comprehensive or systematic general review of moral patentability exclusions, a topic that has been already widely analysed.92 The scope of the study in terms of patent law is limited to the indirect implications of Article 6.2.c. of the Biotech Patent Directive for commercialisation potential of hESC-based ATMPs.

Furthermore, the research questions are significantly influenced by the most recent scientific developments in translational stem cell research. Notwithstanding this interdisciplinary field of study, the main perspective adopted in the present study is that of medical and biolaw. Before further introducing the scope, research questions and objectives of this study, as well as its methodology and main sources, it is therefore necessary to briefly discuss some of the special characteristics of the emerging legal discipline of European medical and biolaw as influencing the methodological approach chosen here. Among legal scholars there is still no definitive consensus on whether

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92 For a more comprehensive and systematic review of the subject matter, see Hellstadius, supra note 50.
medical and biolaw should be perceived as a distinct, independent field of law separating it from other legal domains. Whether medical and biolaw should be understood as a range of legal disciplines dealing with the same object or as a special branch or sub-discipline of more established legal disciplines (e.g., administrative law, criminal law, environmental law or human rights law) has been discussed. Some scholars refer to this legal area as “health law”\(^{93}\) or “welfare law”\(^{94}\), whereas as others call it “medical and biolaw”\(^{95}\) and some have even asked whether it would be appropriate to distinguish “medical law” and “biolaw” as two separate disciplines.\(^{96}\)

When it comes to the Finnish doctrine, Raimo Lahti has claimed that “medical law and the closely linked field of biolaw, addressing biomedicine and its technical applications, represent new and evolving disciplines and sectors of law.”\(^{97}\) Lahti perceives “medical and biolaw” as a larger discipline than “health law”. His view is that the discipline of medical law conventionally covers legal issues that relate to the patient-doctor relationship (or the patient’s relationship with some other healthcare professional); i.e., relating to healthcare personnel, medicine and healthcare. He also sees “health law” as complementary to medical law, addressing legal issues relating to the healthcare system as a part of public law. According to Lahti, “health law is integrally linked with social welfare law, which conventionally comprises sets of legal norms concerning social security.”\(^{98}\) Laura Walin, along with Raimo Lahti, perceives “biolaw” as the most recent of these legal areas.\(^{99}\) Emergence of this area of law, which relates to advances in biology and medicine,\(^{100}\) has been influenced by the novel applications of biomedicine and biotechnology in particular, coupled with a greater understanding of the role of bioethics.

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100 Lahti, *ibid*. See also Lehtonen, L., Lohiniva-Kerkelä, M., and Pahlman, I. *Terveysoikeus* (in English: “Health law”). (Helsinki: Talentum), 2015. 15. Whilst Lehtonen et al. have described “health law” as more comprehensive than “medial law” or “patients’ law”. They note that term “health law” has been used in the European context. (For instance the conferences of the European Association of Health Law and the Journal of European Health Law issues by the association cover a wide range of health related topics.)
Sjef Gevers has maintained that the scope of the regulation is too broad to perceive *health law* as all laws relating to health care and health protection, claiming that the scope of health law should rather be restricted to *organisation, financing and delivery of health care*, issues particularly related to health care services.\(^{101}\) By contrast, Asbørn Kønstad has provided a slightly broader definition specifying five areas of interest of health law: *organising and financing of health care services, special diseases and intervention* (encompassing things such as compulsory care, organ donation, and medical research), *pharmaceutical regulation, health care professionals’ rights and duties* and *patient rights*.\(^{102}\) While my study seems to fit the best into the wider definition provided by Lahti, attention will also be paid to some of the aspects Kønstad mentions (pharmaceutical regulation and medical research, in particular). Notwithstanding these limitations, medical and biolaw as legal disciplines appear as quite complex fields that deal with a great array of topics across the legal landscape. In any case, in the European and Nordic literature the basic understanding seems to be that medical and biolaw is a legal category deserving its own place within the legal academia.\(^{103}\)

It has been noted that the boundaries of this new area of law are fluid.\(^{104}\) There are many different perceptions of the origins of medical and biolaw and its relation to other disciplines. In Mette Hartlev’s view, notwithstanding its multifaceted origins, health law must be considered a legal discipline in its own right, one which is not only based on other disciplines but has developed its own methodologies and principles.\(^{105}\) These principles, largely inspired by human rights law, exceed the boundaries between traditional legal disciplines (e.g., public law and private law). Many of these principles inspired by human rights law can be derived from the Biomedicine Convention, which provides a common framework for the protection of social and individual human rights in biomedicine. The Biomedicine Convention’s broad scope together with its human rights orientation has been deemed to have provided an opportunity for the development of medical and biolaw as a legal discipline.\(^{106}\) The right to the protection of human dignity and identity, the right of respect of one’s integrity, the right to (equal access to) health care and prohibition of discrimination especially constitute the cornerstones of the Biomedicine Convention. However, most of the provisions of the Biomedicine Convention still require further clarification. In particular, its founding principle, protection of human dignity, is quite an imprecise concept as it does not seem to offer clear guidance for a number of issues arising from present-day provision of health care.

\[^{101}\] Gevers, *supra* note 93, 261-272.  
\[^{103}\] Hartlev, *supra* note 93, 51.  
\[^{104}\] Lahti, *supra* note 97, 249.  
or the conduct of biomedical research in human research subjects or materials of human origin, such as translational stem cell research. However, not all principles governing medical and biolaw can simply be reduced to those mentioned in the Biomedicine Convention. For instance, the individual’s right to self-determination has not been mentioned in the Convention or in its Explanatory Report. This principle has been perceived to underpin respect for one’s integrity and to constitute an essential dimension of human dignity.

In the context of clinical trials in human research subjects, the principle of self-determination can be subordinated to the principle of avoiding harm. There are also several other principles that have been perceived to influence the discipline of medical and biolaw. The freedom of science has been mentioned as a principle that may in the context of translational stem cell research challenge the principle of human dignity.

In conceptualising “European medical and biolaw” as a legal discipline, it is also important to reflect on whether or not that area of law is being studied as a collection of legal sources (e.g., legislation and case law), or as the legal activities that investigate such sources, either from an academic or more practical perspective. Gevers has referred to health law as both a body of law and activities concerned with this body. In addition, he has emphasised the importance of detecting and framing the identity of health law in respect of the both the body of law it is concerned with and the way it deals with the subject. In Section 3.4.1 of this study, some important objectives of European medical and biolaw framing the regulatory landscape for ATMPs in the EU have been identified.

### 3.2 The role of bioethics as dynamic and elastic human rights principles

The interplay between medical and biolaw and bioethics presents methodological challenges for this study. First of all, there are limits to legal regulation. Lahti has argued that shortcomings will follow if we involve legal regulation in the fulfilment of contentious moral principles. Doing so would risk objectives set by law not being attained. Secondly, in such circumstances morality cannot retain its function of being critical of law and legal practice. Hence, Lahti emphasises the need for the legislator in a pluralistic society to limit himself to setting borderline conditions that are as flexible as possible and within which individuals and groups of individuals can exercise their

108 Walin, supra note 96, 109.
109 Hartlev, supra note 93, 51.
110 Gevers, supra note 93, 261-272.
moral autonomy. Especially when it comes to the subjects of legal regulation where no universal consensus exists, such as the legal status of a human embryo, there is an increased need for legislators to consider the ethical discourse and plurality of values embedded in the society underpinning the legal question.

More generally, laws have been perceived as particular concepts, whereas ethics have been seen as an abstract phenomenon. Whilst ethics pursue idealistic ends such as respect for human dignity or the well-being of an individual or the society at large, the pursuit of social stability and predictability constitutes idealistic legal endeavour. Previous studies in medical and biolaw have adopted different approaches to the relation between law and ethics. A fundamental methodological question is whether law can be seen as a reflection of morality or whether it can be separated from morality. Traditionally, the approaches to the relationship between law and ethics have ranged from the total emancipation of law from morality (legal positivism) to pursuing the closest possible synchronisation of both normative structures. Among others, Laura Walin adopted a legal positivistic approach that separates biolaw from bioethics in her doctoral dissertation. In Walin’s approach, biolaw is perceived as being based on the rules of logic and reason. Walin has in light of Kaarlo Tuori’s Critical Legal Positivism also argued that medical and biolaw may be regarded as a stratified phenomenon whose core identity of that discipline cannot be jeopardised rapid and necessary but superficial changes. In contrast, Riitta Burrell adopted a more naturalistic approach in her doctoral dissertation in which biolaw was seen to stem from bioethics. Her approach resembles that of the school of natural law, which finds that since the law necessarily illustrates the morality of society, it cannot be based simply on reason and logic.

A point of departure is that bioethics precedes law and is finally becoming a part of law in the form of dynamic and elastic human rights principles. Ethical considerations may also form so-called soft law or influence the wording of “hard law” as well as the interpretations of legal provisions. For this study, “soft law” means quasi-legal instruments with no formally or legally binding effect, or whose binding force is weaker than the binding effect of traditional “hard law”. Roberto Andormo has pointed out that soft law instruments are vital role to the development of universal norms in bioethics. His view is that such instruments should not be underestimated since they do not constitute binding legislation as such, because soft law may operate indirectly by means

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113 Hellstadius, supra note 50, 41.
115 Hellstadius, supra note 50, 87.
116 Walin, supra note 96, 107.
118 Burrell, supra note 96, 35-36.
of persuasion instead of coercion. In the long term, soft law may become a binding norm, either by resulting in a treaty or by being recognised as customary law.\textsuperscript{120}

Bioethics, being the ethics of biomedical research, addresses the challenges posed by modern health technologies. From the perspective of the legislator, regulating novel health technologies is especially challenging, as such technology merges multiple disciplines ranging from medicine and bioethics to biotechnology. Bioethics analyses a range of ethical issues arising in connection with medical practice as a result of the advances in biomedical sciences and technologies.\textsuperscript{121} The early origins of bioethics date back to antiquity, where \textit{bios} relates to the earthly life and its requirements, a cycle of which humanity is inevitably part.\textsuperscript{122} However, the emergence of modern bioethics stems from the Nuremberg trials in which medical researchers were found guilty of “crimes against humanity”.\textsuperscript{123} Bioethics have since been formalised and codified in the form of a number human rights instruments in biomedical research (e.g., the Biomedicine Convention and the World Medical Association Helsinki Declaration on Ethical Principles for Medical Research Involving Human Subjects). Lahti has concluded that “\textit{bioethics has become the established umbrella term covering the ethical dimensions of medical treatment and care, healthcare, biological and medical research, and of environmental issues}.”\textsuperscript{124} In the course of advancements in biotechnology, a range of related proprietary issues has also arisen, such as those concerning commercialising material of human origin. These discussions often inevitably touch upon fundamental issues such as the scope of the concept of human dignity and the question of whether the concept of property is applicable to human embryos or other biological materials of embryonic origin such as hESCs.

Ethical philosophy aims at universally applicable content and transcendent viewpoints, whereas the nature of the legal system is concrete and specific.\textsuperscript{125} This causes an unavoidable dilemma since the main ethical principles involved in bioethics are not universally recognised or subject to universal consent. It appears that in the age of modern biomedicine, \textit{human dignity} as a universal right provides national legislators with a wide margin of appreciation in some important value-choice questions, whereas some codified ethical principles remain just principles and their impact on law and the decision-making process is treated by institutional means such as ethics committees.


\textsuperscript{121} See e.g. Plomer, A. \textit{The Law and Ethics of Medical Research: International Bioethics and Human Rights}. (London: Cavendish Publishing), 2005.


\textsuperscript{123} Yale Law School. The Avalon Project. \textit{The International Military Tribunal for Germany. Contents of The Nuremberg Trials Collection}. Available at: http://avalon.law.yale.edu/subject_menus/imt.asp. Accessed 18 August 2016. See also Hellstadius, supra note 50, 89 that refers to Nuremberg trials’ role in context of emergence of modern bioethics. See also e.g., Kemp, et al. supra note 122.

\textsuperscript{124} Lahti, supra note 97, 250.

\textsuperscript{125} Hellstadius, supra note 50, 87.
supervising research governance.\textsuperscript{126} In addition, national competent authorities and agencies tend to interpret general and imprecise legislation based on case-by-case examination, international declarations without legal status, and codes of conduct by professional organisations beyond the law. Hence, the use of the \textit{soft law} instrument can be significant as it influences the legislation and the decision-making processes in parliaments.\textsuperscript{127} For instance in case of ATMPs, the GMP Guidelines are not as such legally binding. Yet, in practise they will get a binding effect when GMP compliance is required by the authorities as a condition for a clinical trial authorisation or a marketing authorisation.

Beyond the legal philosophical discussions, when the relation between bioethics and medical and biolaw is analysed at a more practical level, it appears that this relation differs from country to country in the EU (e.g., Member States have adopted very different approaches to bioethical and legal aspects of the governance of hESC research). Ethical values and human rights are dynamic.\textsuperscript{128} Despite medical and biolaw being an area where law and bioethics overlap significantly, not everything can or should be regulated by law. Yet, the overlapping area between bioethics and medical and biolaw should not be too small, according to Göran Hermerén.\textsuperscript{129} This relation has been initially described by Rainer Moufang as two intersecting circles, which only leaves out the overlapping area of legal rules of a morally neutral, purely technical nature.\textsuperscript{130}

Interestingly, the ATMP Regulation can be seen as a rather technical piece of legislation. It has been described being “ethically neutral”.\textsuperscript{131} However, as described in Section 6.2 some significant ethical considerations regarding the use of materials of human origin were raised in course of its drafting process. Currently, the human rights perspective appears from its Recital 8 stating that as a starting point the ATMP Regulation respect the fundamental rights and observes the principles reflected in the Charter of Fundamental Rights of the EU and also takes into account Biomedicine Convention. The approach adopted in the ATMP Regulation allows for some significant flexibility and a wide margin of appreciation in ethical issues. For example, in Recital 7 it is stated the ATMP Regulation does not interfere with the decisions by Member States (for instance, positions adopted by ethical committees of Member

\textsuperscript{126} Hellstadius \textit{op. cit.}, 93.

\textsuperscript{127} Hellstadius, \textit{op.cit.}, 87.


\textsuperscript{129} Hermerén, \textit{op. cit.}, 5-40.


States) on whether to allow the use of any specific type of human cells, such as those of human embryonic origin. Hence, the ATMP Regulation does not seek to affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of or derived from these cells. Yet, it seeks to facilitate market access of any types of ATMPs, including hESC based products providing that sale, supply or use of such products is not prohibited by national laws of a particular Member State.

3.3 Objective, research questions and scope

Translational medicine is a rapidly growing discipline within biomedical and public health research intended to improve the health of individuals and the community by ‘translating’ its research findings into novel diagnostic tools, medicines, procedures and policies governing research, as well as education. It seeks especially to accelerate the discovery of new diagnostic tools and treatments by using an interdisciplinary, very collaborative ‘bench-to-bedside’ approach.\(^\text{132}\) Initially, translational medicine was described as "the marriage between new discoveries in basic science and clinical practice".\(^\text{133}\) The translational process can also be seen, as initially described by Marincola, as a two-way road; ‘from bench to bedside and back’. Discoveries from the bench may be translated into clinical application and/or the translation of clinical findings into the understanding of molecular mechanisms.\(^\text{134}\)

From a regulatory perspective, the translational approach could be characterised as a hybrid between basic research and clinical treatment.\(^\text{135}\) Regulating ‘hybrids’ has usually been seen to constitute a great challenge for legislators.\(^\text{136}\) The regulation of translational research is a hybrid sector that seemingly involves particular characteristics which research based on a traditional division of disciplines is powerless to address adequately.\(^\text{137}\) For regulation of translational hESC research especially, these

\(^{137}\) See also Lahti, supra note 97,250. Lahti discusses the emergence of biolaw as a new discipline and he also raises the question of whether the object or context of regulation in this hybrid sector involves particular characteristics that research based on a traditional division of subjects is incapable of adequately addressing. He has expressed the view that medical law and biolaw “focuses on the legal issues of healthcare and those involving medical technology and other applications in an integrative way.” He perceives medical and biolaw as a new legal discipline which allows for structuring and
regulatory challenges are numerous and multifaceted. The regulatory uncertainty in this area of translational research risks constituting a significant impediment for development and commercialisation of hESC-based advanced therapies, especially as ethical aspects of some types of hESC-research activity may compromise the legitimacy of such research. Hence, better regulatory clarity in this area is urgently needed. This not only requires analysis of the multilayered, variable and complex set of rules and regulations governing ATMPs in general (and hESC research in particular), but also necessitates a critical review of multiple ethical considerations underpinning the legislative framework. The scope and content of the undefined concept of human dignity and rights arising therefrom in particular constitute a core element for this ethical debate.

The Institute of Medicine's Clinical Research Roundtable has identified two major bottlenecks (i.e., specific areas in need of improvement) for efficient translation; the first translational block (T1) prevents basic research findings from being tested in a clinical setting, whereas the second translational block (T2) prevents proven interventions from becoming standard practice.\textsuperscript{138} It has been noted that blocks T1 and T2 face different challenges. T1 predominantly deals more with biological and biotechnological issues, clinical trial recruitment, and some regulatory concerns, whereas as T2 struggles more with human behaviour and organisational indolence, as well as research infrastructure and resource limitations. As a starting-point, the translational approach is strongly interdisciplinary. According to Woolf:

\begin{quote}
\textit{\"{}successful health interventions in hospitals, homes, and statehouses require the translation of other \textquoteleft{}basic sciences\textquoteright{}—such as epidemiology, behavioural science, psychology, communication, cognition, social marketing, economics, political science—\textquoteleft{}not only the translation of biotechnological insights and novel therapies.\textquoteright{}\"{}\}
\end{quote}

In my view, legal science should be also added to Woolf’s list of “basic sciences” above. In addition, I would like to suggest legal and bioethical constraints preventing the efficient translation of research, access to therapies and commercialisation of novel therapeutics as a third significant translational block (T3). This study investigates the legal and ethical crossing points of translational research in terms of the development of ATMPs.

\begin{flushright}
\textsuperscript{138} Woolf, supra note 132. According to Woolf, the first roadblock (T1) has been perceived as “the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans,” whereas the second roadblock (T2) has been described as “the translation of results from clinical studies into everyday clinical practice and health decision making.” See also American Medical Association. Clinical Research Initiatives. Available at: http://www.ama-assn.org/ama/pub/about-ama/our-people/ama-councils/council-science-public-health/clinical-research.page? Accessed 21 June 2016.
\end{flushright}
The main research questions of this regulatory study are:

1. What are the benefits and limitations of the ATMP Regulation for SMEs and academia developing ATMPs?

2. What kinds of amendment to the ATMP Regulation and related regulatory processes are needed to:
   
   (i) accelerate translation of research into advanced therapies whilst ensuring the safety of the patients; and

   (ii) facilitate commercialisation of ATMPs?

Despite the primary objective of this study is to analyse regulatory aspects affecting commercialisation of ATMPs, it would be wrong however to attribute the currently very low number of ATMPs solely and exclusively to the ATMP Regulation, as the ATMP landscape is influenced by a number of factors and other legislative instruments affecting the commercialisation prospects of these new products. Therefore, in addition to the above mentioned primary research questions there is a need to study what other roadblocks to commercialisation will developers of ATMPs encounter on their way from ‘bench to bedside’ and how will they meet these challenges. Yet, analysis of these aspects is limited to legal and ethical considerations pertaining to regulatory commercialisation process. In addition, hESC-based inventions will be discussed as example of products facing obstacles to market entry.

The objective of primary research questions this study is to evaluate the benefits and limitations of the ATMP Regulation for SMEs, research units in academia, and public tissue establishments developing ATMPs. This pragmatic study proposes practical amendments to the ATMP Regulation and related marketing authorisation processes to accelerate translation of research into advanced therapies and to facilitate commercialisation of ATMPs whilst ensuring patient safety. This study analyses the reasons for the low number of authorised ATMPs on the market, in particular by investigating why so few ATMPs have been granted marketing authorisations. Hence, the scope of research questions 1 and 2 is limited to aspects pertaining to the ATMP Regulation impeding market-entry of ATMPs undergoing development prior to a grant of marketing authorisation by the EMA via the mandatory centralised procedure. As only a small number of ATMPs have been granted marketing authorisations thus far (and currently only one is a stem cell product), this study will not only discuss regulatory challenges faced by developers of stem cell based products, but will more generally analyse commercialisation and the challenges SMEs and academia developing ATMPs usually face. Further aspects beyond commercialisation of ATMPs, such as pharmaceutical marketing of ATMPs to health care professionals, are beyond the scope of this study.

To provide a balanced overview of the multiple aspects influencing commercialisation of ATMPs, there is a need to investigate whether barriers to
commercialisation relate to ATMPs as such or whether something else in the innovation system is impeding their market entry. These aspects investigated include among other things difficulties with the availability of primary materials, difficulties in obtaining authorisations for preclinical or clinical trials, as well as research funding, IP and reimbursement related issues. Yet, it should be noted that despite the relevance of these aspects, the primary scope of this study covers regulatory commercialisation obstacles directly associated with the ATMP Regulation. Hence, only some limited aspects of clinical trials pertaining to the developing quality management framework for ATMP manufacture and clinical trials are covered in this study. Further analysis of biomedical obstacles preventing basic research findings from being tested in a clinical setting, as well as human behaviour, organisational or research infrastructure related factors affecting ATMP market entry will be left outside the primary scope of this study. Biomedical considerations and the particularities of clinical trial design have been discussed in a very limited sense only.

In addition, as an example of ATMPs under development, this study investigates what kinds of obstacles to market-entry developers of hESC-based products encounter in particular. The impact of EU funding policies moral patentability restrictions stemming from the Biotech Patent Directive will be discussed in this context. Relevant case law that aims at harmonising the European stem cell patenting practices has been discussed in Research Articles II and III. Study of patenting aspects is limited to assessing the implications of the moral patentability restrictions on hESC-based applications, as well as ethical assessment of some related emerging technologies such as iPSC-based inventions in regenerative medicine in the EU. Further analysis regarding the general patentability criteria (i.e., novelty\textsuperscript{139}, the inventive step\textsuperscript{140} and industrial application\textsuperscript{141}) are left out. The \textit{invention v. discovery} dichotomy will not be studied either, despite being an important aspect affecting biotechnology patenting in general. Further ethical considerations beyond patenting and commercialisation of stem cell research will also be left out. There is also a need to discuss the European regulatory approaches to hESC research governance, as well as the European perception of the ambiguous notion of human dignity that influences the ethical landscape for stem cell patents in Europe. Yet, it should be noted that national law is not the object of this study. However, some references to national laws will be made to illustrate the fragmentation of the regulatory landscape for hESC research governance and commercialisation of hESC research. The role of the morality clause in the European unitary patent system and the forthcoming Unified Patent Court will not be discussed in detail. The new Trade Secrets Directive will not be discussed in detail. Neither licensing of biotechnological inventions nor further analysis of patenting aspects regarding commercialisation of university inventions are within the detailed scope of this study.

\begin{itemize}
\item \textsuperscript{139} Article 54 of the EPC.
\item \textsuperscript{140} Article 56 of the EPC.
\item \textsuperscript{141} Article 57 of the EPC.
\end{itemize}
3.4 Research methods

One of the major challenges the discipline of medical and biolaw is facing today in the pluralistic and legally fragmented Europe is how to keep abreast of the latest scientific advancements in translational medicine. Lahti has pointed out that the objective of

“[c]reating coherence in legal science is challenging at the present time, when the fragmentation and pluralism of legal orders and the ‘polycentricity’ of legal sources are characteristic features of the legal development.”142

Consequently, the novelty of this constantly evolving discipline, and its multiple sources of information poses additional methodological challenges. Thus some unconventional methods and references have been required. Lahti has emphasised the importance of not only considering the interaction between law and ethics regarding healthcare and medicine, but also seeing the relevance of health economics, health sociology and health policy when dealing with cross-disciplinarity or multi-disciplinarity.143

Bache et al.’s framing approach has been used to organise the hard law and soft law instruments that regulate hESC research by means of the dominant market frame, (human) rights and ethics frame, as well as risk frame. This approach can be used to challenge the rigorous traditional distinctions often made in legal theory between legal and ethical perspectives in science. It can extend the analysis beyond the traditional dichotomy between what is ‘right’ (positivistic approach) and what is ‘good’ (naturalistic approach). This approach is especially useful in investigating the active role of both the legislator and all stakeholders in the legislative process. Therefore, it is complemented by the problem-based legisprudential approach. The more traditional legal dogmatic approach has been used in the systematisation of legal norms and the interpretation of legal rules. However, as will be described below, this study is by no means rigorously dogmatic.

This combination of three approaches allows for some flexibility. This study comprises four Research Articles: the main methodology of Research Articles I and IV is the problem-based approach, whereas Research Articles II and III are more traditionally legal-dogmatic case commentaries. This summarising part of the dissertation has mainly used Bache et al.’s framing approach and the problem-based approach as the main methodologies. The use of the problem-based approach can be justified as medical and biolaw is evolving so rapidly and new problems emerge in the course of medical development and innovation. Legal and ethical aspects of commercialisation of advanced therapies is a very little investigated field. This dissertation is intended to initiate the discussion of this topic, but it does not purport to

142 Lahti, supra note 97, 251.
143 Op. cit., 3-4. More specifically, according to Lahti “[t]he interplay among the various sectors of law and disciplines, as well as the experts representing these branches, is vital to the resolution of these issues”.

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analyse each and every problem that crops up in the commercialisation process, as it mainly focuses on regulatory problems arising from the ATMP Regulation. It also seeks to stimulate discussion and propose further research into other legal questions relating to the commercialisation of advanced therapies that still remain to be explored in greater detail.

3.4.1 The framing approach challenging the distinctions between legal and ethical perspectives

The framing approach can be used to organise and delineate the highly fragmented regulatory landscape for novel health technologies in the EU. Framing tools include the market, risk and human rights/ethics. My objective is to use these concepts to analyse factors affecting the current European regulatory landscape for ATMPs. Initially, Bache et al. have argued that this framing approach can also be used methodologically to frustrate the rigorous traditional distinctions often made in legal theory between legal and ethical perspectives in science. Pursuant to this approach, new health technologies are perceived as having both norms and values built into them. Framing tools, as described by Bache et al., both reflect and reproduce those values and norms. This approach challenges the potentially harmful idea that law is not able to keep abreast of the rapidly-evolving technology as well as contesting the perception of law as an inefficient means of regulating behaviour and social outcomes (the problem of pace as mentioned by Roger Brownsword).

Recital 13 the ATMP Regulation also addresses the need for a commercialisation process that provides for sufficient flexibility to accommodate the rapid evolution of science and technology. Hence, this approach is especially useful in investigating the active role of both the legislator and other stakeholders in the legislative process. The scope and limitations of the EU’s competence in the field of public health will be discussed in light of market, risk and human rights/ethics frames in Section 4.1.

3.4.2 The problem-based legisprudential approach

Many doctoral dissertations in medical and biolaw have adopted a pragmatic, problem-based approach as their main research methodology. In the problem-based approach, research questions stem from real-life situations, the objective being to systematically analyse legal rules and regulations that influence real-life situations. The research question in the more traditional legal dogmatic (and jurisprudential) approach stems

144 Bache, et al., supra note 41, 7-45.
146 See, e.g., Walin, supra note 96.
from the legal system or more specifically from a legal discipline. The point of departure for the latter is the legal rule as such, whilst the problem-based approach deals with the prevailing political and/or sociocultural reality. In contrast to the traditional legal dogmatic approach, research in the problem-based approach typically overlaps various legal disciplines. Medical and biolaw research is also typically interdisciplinary in nature, which may result in the use of unconventional reference material, such as sources of a medical or ethical nature. The more traditional legal dogmatic approach may often confine research more strictly within a particular legal discipline, which may (if successful) foster very profound legal analysis of a specific legal rule. The problem-based approach has sometimes been criticised for generating less profound analysis. It is evident that when the research question is dispersed around different legal disciplines it may be very hard to conduct very profound analysis within one discipline and some compromises must be made. Yet the merits of this approach are elsewhere in that the problem-based approach contributes to resolving practical legal issues that arise in real-life situations. It may also serve to reveal incoherence between different legal regimes, such as the pharmaceutical regulatory system and the patent system.

As this study constitutes a regulatory review of the challenges of the ATMP Regulation from the perspective of the actual developers of ATMPs, a problem-based, legisprudential approach is used as the primary methodology. Yet, it is complemented in by the legal dogmatic one. In systematising the legal references, guidance has been sought from the legal dogmatic approach with certain reservations regarding the use of some untypical reference material as indicated in Section 3.4.4 of the study.

The study is largely concerned with the legislators’ (and stakeholders’) role in the law-making process, in contrast to the traditional jurisprudential approach in which these questions are considered from the perspective of the judge. The legisprudential approach argues that practical reason in legislation comes into practice throughout the process of law-making. In this context, a range of questions and problems is investigated, including the validity and legitimacy of human rights norms and principles, their meaning, the structure of the legal framework of the European medical and biolaw, and so on. As in the legisprudential approach, attention is shifted from the judge to the legislator, the following questions arising: in what sense must the legislator take the systematicity of the legal order into consideration? What counts as a valid norm? For instance, does human dignity count as a valid norm? Legisprudence also builds upon the contextual interpretation of rationality, subject, and freedom in order to focus on practical reason in legislation. The legisprudential model relies on the idea of a ‘social contract’ in which the subjects trade off conceptions of freedom for conceptions

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148 Walin, supra note 96, 24.
about freedom. In this model, this trade-off must be justified by the norm-giver. No rule can be considered legitimate if this justification or legitimation is lacking. Freedom as a principle constitutes the basis for principles of rational legislation that can finally be realised in the duties of the legislator. Luc Wintgens has categorised the principles of legisprudence as follows:

1. *The principle of coherence* requiring that those norms make sense as a whole;

2. *The principle of alternativity* assuming that social subjects are initially free and capable of rationally organising their freedom in a context with others. Hence they are primarily to act on conceptions of freedom. According to Wintgens, the replacement of a conception about freedom for conceptions of freedom can only be legitimate if it is legitimated or justified as an alternative for failing social interaction;

3. *The principle of temporality* requiring that limitation of freedom on a conception about freedom must be justified as “on time”. According to Wintgens, any justification is embedded in a context, because rationality as reasonableness is context related, and therefore historically situated. Hence, if the justification of a norm is successful it will only be temporarily so, as norms can become obsolete. Wintgens thus argues that principle of temporality then requires an ongoing justification over time, and not simply at the moment that a norm is issued; and

4. *The principle of the necessity of normative density*, in accordance with which rules should not automatically contain sanctions as the strongest form of normative density. Wintgens’s view is that if sanctions are included, this requires a specific and supplementary justification of why weaker alternatives (information campaign, incentives, labelling, covenants and so on) are not used.

This legisprudential approach to the rationality of legislation provides an interesting alternative perspective on the problematic exponential increase in legal systems and the decreasing quality of legislation in most European democracies. It has been argued by Wintgens that

“upon the requisite that a norm-giver considers more seriously his way of creating norms and the requirement to show how he did by justifying his norms legisprudence has the potential to contribute to an improvement of the quality of legislation.”

According to Wintgens, such an improvement of the quality of legislation as the main purpose of legisprudence may be expected to result in a decrease in legislative norms, since better norms need less correction, adaptation and change. Legisprudence also

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151 Vlad Perju has pointed out that in Wintgens’ model there is an inherent difficulty in distinguishing between will and reasoning about will. Its central difficulty is how far reflection on pure will qua will can take us, according to Perju. In his view “[r]eliance on pure will may just be, as social theory has discovered since the nineteenth century, a form of surrender to the normatively blind social processes that shape that will.” Perju, V. A comment on “legisprudence”. *BUL Rev.* 2009;(89):427.

152 Wintgens, *supra* note 149, 231-282.

allows for stepping away from paternalistic criminalisations, as it significantly relies on non-coercive, flexible, self-regulatory measures that can adjust smoothly to varying conditions over time and place. Yet, it has been argued Vlad Perju that despite Wintgens’s inviting approach to judicial review opens interesting avenues for legisprudence, “it would be unfortunate for scholars to turn a blind eye on the work of courts now that legislation begins to receive the attention it deserves”. By contrast, Perju finds that “[a]s such articulating principles of legislation for use within the proportionality framework is an area where legisprudence can make an important contribution.”\textsuperscript{154} In this study, Wintgens approach will be applied when assessing proportionality of limitations imposed to freedom of science.

As described in Chapter 4 of this study, the current European regulatory framework for novel health technologies is legally fragmentary, multilayered and lacking internal coherence. Consequently, the complexity of the regulatory framework risks constitute significant impediments for the market entry of ATMPs, and there is an obvious need for the European legislator to get involved in novel and innovative legislative approaches to create facilitating, proactive and more flexible legislative solutions in collaboration with all stakeholders. This brings us to another important aspect; stakeholder participation influencing legislative processes. It appears that various stakeholders participate today because of their failure to influence the legislative process on the content of the existing regulatory framework.\textsuperscript{155} The opportunity to participate in the legislative process by expressing values is an essential characteristic of a democratic society. As described by Shawn Harmon, stakeholder participation may take place either upstream or downstream. Upstream participation may influence priority settings such as research funding policies and hence indirectly influence the commercialisation prospects of ATMPs, whereas downstream participation may involve measures once the regulatory framework exists, such as biotechnology patent invalidation proceedings.

As an information tool, the impact assessment (IA) has a significant role in how law and policy are being developed and decided in the EU.\textsuperscript{156} Sections 6.1 and 6.2 of this study analyse the impact of various stakeholders affecting the scope and content of the EUCTDs and the ATMP Regulation, as well as emphasising the legislators’ duty to collaborate with different interest groups to create a balanced normative framework in this field. Stakeholders being involved in the legislative process involves interest groups ranging from the industry representatives (both SMEs and big pharma) to tissue establishments, academia and patient organisations. Section 6.3 discusses upstream stakeholder participation affecting the creation of the Clinical Trials Regulation, and Section 6.4 discusses the impact of stakeholders in drafting the Biotech Patent

\textsuperscript{154}Perju, supra note 151, 434.


Directive, whilst the Brüstle case discussed in Research Article II and the ISCO case in Research Article III represent examples of downstream stakeholder participation.

Furthermore, there are certain principles such as “the principle of protection of human dignity” that require further clarification and justification, especially when that principle is used as a constraint in contexts limiting other constitutional rights, such as the freedom of science in translational research. Lahti has also argued that in a moral (ethical) discussion we should pursue rationality, i.e., we should among other things at least seek to achieve consensus on the concepts used in discussing bioethical questions and we should utilise research findings on biology and medicine as far as possible. 157 The objective of Research Article I of this study is to introduce the biomedical context that constitutes the basis for further ethical discussion and legal analysis of the concept of human dignity. This approach does not exclude the possibility of differences in the value judgments of those participating in this discourse.158 Instead, Lahti refers to Jabbari’s notion of “reflexive law”159, in accordance with which he thinks that there is reason to believe that the regulation on human embryos should be “continually reflexive” to changes in medical technology and in the enlightened public discourse.160 Hence, in line with Jabbari’s view, Lahti concludes that “in the context of embryo research we cannot appeal to substantive moral values, for agreement is denied by the conflict of ethical theories”.161 This observation also boils down to the need to create institutions (such as ethical committees) which serve as a forum for informed discussion and procedures that can promote compromise.162 Darryl Marcer has also pointed out that pursuant to the idea of the flexible reflexive law, in regulating science ethical committees that can issue resolutions after having consulted experts just as issues relating to embryo research allow for justification of a certain action pro tem.163 This not only calls for the legislator having an active role in who should actively cooperate with interest groups, but it also requires that the legisprudential principle of temporality must be taken into account.

Any limitation of freedom on a conception about freedom must be justified as “on time” and any such justification must be adequately embedded in its context. To better understand how using the principle of protection of human dignity could be justified in the age of personalised medicine, Research Article I addresses the issue of how recent developments in cell reprogramming complicate our perception of human dignity, whilst Chapter 5 discusses how the notion of human dignity manifests itself in the existing legislative instruments. Section 4.3 discusses the difficulties that arise in trying

157 Lahti, supra note 111, 439, 466-452.
160 Lahti, supra note 111, 468.
161 Ibid.
162 Ibid.
to accommodate the human rights approach in the European regulatory framework for novel health technologies.

3.4.3 The legal dogmatic approach

In this study, the legal dogmatic approach has been used as the main method of systematising and interpreting legal rules. This approach involves systematisation of legal concepts and provisions and as well as interpretation and qualification of the legislation. This study aims at critically evaluating the legislation and its objectives and practical function. It should be noted that the study is by no means rigorously dogmatic, because it requires perception of interdisciplinary elements (such as ethical, economic or medical ones). For that reason, some non-traditional sources of information are used (predominantly, bioindustry association reports and commentaries) in addition to traditional legal references.

Dogmatics consists of two levels: the first the general level, where dogmatics is understood as scientific processing of all legal material. 164 In a more specific sense, dogmatics is perceived as sentences that form a system which enables one to conceptually and systematically value the application of law. 165 The best doctrinal study of law can offer is to be a source of practical arguments used in legal reasoning to support the conclusion. 166 Hence, this study ultimately seeks practical conclusions and amendment proposals to the existing ATMP Regulation by using the dogmatic methodology together with the legisprudential approach. Furthermore, the study seeks to provide an overview of other possible factors affecting ATMP commercialisation prospects in the EU and propose approaches to deal with these obstacles. As legal science is based on the substance of the legal sources, we should analyse the applicable material law. Ultimately, the legal sources are used to pursue coherence in the argumentation.

3.4.4 References

The legal dogmatic methodology sets out to treat the legal sources of law, practice, doctrine and customary law, with the objective of describing “the law in force”. Such legal sources are applied in accordance with the doctrine on the hierarchy of the legal

sources, in which the main concern is their legitimacy and treatment.\textsuperscript{167} The interpretation of the legal rules and other norms is based on law (TEU ranking the highest, followed by other EU legislation and national interpretations thereof, international treaties and conventions), preparatory works (travaux préparatoires) and applicable case law (the case law of the ECJ and ECtHR ranking highest in the hierarchy, followed by the rulings of the Supreme Courts). Pursuant to the legal dogmatic methodology, the legal norms must be interpreted in line with international treaties and conventions. For instance, the substantive provisions of the Biomedicine Convention and its Protocols are implemented in the Finnish legal order and constitute statutory law equal to those of Finnish Parliamentary Acts.\textsuperscript{168} However, despite some references to national laws, the focus of this study is mainly the EU law. Rulings of courts, (especially the ECJ and ECtHR and the Supreme Courts of the EU Members), and other case law is also of great importance.

The primary focus is relevant EU legislation (ranging from the treaties to applicable regulations and directives) and rulings of the ECJ (as the ultimate instance interpreting the EU law) and the ECtHR (as the ultimate guardian of human rights under the ECHR). National legislations of the Member States or case law will only be discussed to illustrate differences in national implementation of the EU legislation. This study is complemented by a review of secondary references of importance such as preparatory materials, guidelines, instructions or resolutions issued by regulatory authorities (such as ethical boards, as well as the Opinions from the Advocate General of the ECJ), whereas tertiary references, such as empirical data (first-hand information), peer-reviewed articles, relevant literature, bioindustry association reports, commentaries and ethical guidelines and professional guidelines (second-hand information) are used when examining more practical implications of the ATMP Regulation for developers of these innovative products. It should be noted that, despite this formal hierarchy of norms, there is an emerging trend to ethical guidelines and professional codes of conduct being given increasing attention in legal decision-making.\textsuperscript{169} The interdisciplinary nature of the study means that the use of tertiary references is not limited to legal references only, covering ethical, economic and medical ones as well. In particular, such references are necessary in identifying benefits and possible shortcomings with this relatively new ATMP Regulation and proposing possible practical amendments to it.

The preliminary hypothesis in investigating the primary research questions is that despite the European regulatory landscape for novel health technologies seeming very fragmented and not optimally efficient in many respects, the EUCRDs and the ATMP Regulation are closely interwoven and influence the ATMP playing field together.

\textsuperscript{167} See, e.g., Hellstadius, supra note 50, 42.
\textsuperscript{168} See, e.g., Lahti, supra note 97, 256.
\textsuperscript{169} See, e.g., Lahti, supra note 97, 259. As pointed out by Andorno, supra note 120 soft law instruments also have a vital role in the development of universal norms in bioethics. According to Andorno, the soft law may become a binding norm in the long term, either by resulting in a treaty or by being recognised as customary law.
Hence it is necessary to analyse the legislative processes of the EUCDTs and the ATMP Regulation jointly. A two-tier approach has thus been adopted. To understand the rationale behind the EUCDTs and the ATMP Regulation, in addition to relevant EU legislation and the national legislation of the Member States, especially opinions, proposals and reports that were issued by the European Commission and industry organisations listed in Figure 4. below were reviewed.\textsuperscript{170} The predictive views of these reports are assessed retrospectively against the current implications of the ATMP Regulation in order to (i) identify benefits and possible shortcomings with the ATMP Regulation; and (ii) to propose possible practical amendments to it to accelerate translation of research into advanced therapies and to facilitate commercialisation of ATMPs whilst ensuring a high level of safety. In addition, the influence of stakeholder engagement in the legislative process is discussed.

When contextualising the ATMP Regulation into the wider legislative landscape, it becomes evident that not only the ATMP Regulation together with the EUCDTs, but also the clinical trials and data protection legislation, funding policies, IP protection and reimbursement related considerations influence the market entry of ATMPs. It should

be also noted that beyond these considerations, there are also significant biomedical obstacles that prevent basic research findings from being tested in a clinical setting, as well as human behaviour, organisational or research infrastructure related factors affecting their market entry. Despite these aspects having been left out of this study, some will be briefly discussed at the end of this study to provide a more balanced overview of factors affecting the ATMP field.

In case of hESC-based ATMPs, it is assumed that the EU funding policies and patenting restrictions indirectly influence their commercialisation prospects. The main legal frameworks within which the Biotech Patent Directive operates (especially the EPC patent system and the EU legal order) each have unique legal characteristics which constitute the legal construction of the moral exclusion clauses of the Biotech Patent Directive. The following sources in particular are considered: the Biotech Patent Directive, the broader principles of EU law under which the Biotech Patent Directive has legal effect, the relevant national and international legal instruments on the protection of the human embryo, the implementation of the Biotech Patent Directive in national laws of the Member States, national and international patent law instruments, the policies and/or practices of national patent offices, the opinions of the EGE and the applicable case law, such as that of the ECJ, the ECtHR and the EPO. It should be noted that the European biotechnology patenting landscape is multidimensional, as sets of rules and regulations exist at various levels and in institutional settings. Both competences and corresponding rules are currently divided among the legal systems. The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) provides the general international framework for legislation on patents. However, the national patent legislation is significantly influenced by and dependent on the EU and the EPO. The Member States of the EU are required to comply with the Biotech Patent Directive, which harmonises the European biotechnology patenting practices as well as interpretations of the ECJ. Simultaneously, the EPO and the EPC have had a substantial influence on the patent legislation of its contracting states, which have voluntarily adapted their laws to conform to the EPC. In addition, the judgments of the ECJ also seem to influence the scope of the EU funding policies (e.g., the research funding programmes have refused to fund research that necessitates destruction of human embryos in line with the Brüstle case). The hierarchy of norms from the perspective of the legal basis of the national laws is that the EU legislation, i.e., the Biotech Patent Directive, has priority over the EPC and the national laws. Pursuant to Article 2 of the EPC, the European patents shall have the same legal effects and are subject to same requirements as national patents.
Figure 4. List of main references and stakeholder consultations underpinning the EUCTDs and the ATMP Regulation
4 Multilayered and fragmented field of research

The study of European medical and biolaw and commercialisation of advanced therapies in particular is a multilayered and fragmented field of research. The mandates, powers and relationships among the EU, the Council of Europe, and the EPO are very complex. The regulatory aspects of commercialisation of advanced therapies intersects the competence of the EU Member States, the EU institutions (such as the EMA and the EPO), the Council of Europe as a central policy-making forum via the jurisprudence of the ECtHR and the ECJ alike.

4.1 The scope and objectives of the EU’s mandate in public health and safety

Historically, the EU’s mandate in the field of public health and health policy has been limited – matters pertaining to public health have remained as responsibilities of the Member States. Initially, the EU did not have an own public health policy.\(^171\) Despite the EU’s limited competence, public health aspects have influenced the EU legislation. For instance, the first legislative instrument harmonising pharmaceutical legislation, Directive 65/65/EEC states the protection of public health as a primary objective of the Directive.\(^172\) The initial mandate to issue legislation in the pharmaceutical field was based on Article 100 of the Treaty Establishing the European Economic Community that allowed the Commission to issue directives that directly influence functioning of the internal market.\(^173\) Hence, formally the EU only issued legislation on such public health matters that aimed at optimising functionality of the internal market.\(^174\) The EU’s competence in the field of public health was formalised in the Maastricht Treaty in 1992.\(^175\) It focused primarily on stimulating cooperation between Member States and supporting national actions and vested the EU with only limited legislative powers on health related issues.\(^176\) Whilst subsequent to the adoption of the Amsterdam Treaty in


\(^{172}\) The Directive 65/65/EEC was issued as a response to the Thalidomide scandal, which prompted the legislators to take measures to protect public health. See e.g. Wahlroos, H. *Euroopan unionin lääkevalvonnan kehitys ja lääkeinformaatio – sisämarkkinoita vai kansanterveyttä?* Academic Dissertation, University of Eastern Finland. (Kuopio: Kuopion Yliopiston julkaisuja A. Farmaseutitset tieteet 63), 2003, 41.

\(^{173}\) Treaty establishing the European Economic Community, Rome, 25 March 1957.

\(^{174}\) Wahlroos, *supra* note 172, 192.

\(^{175}\) Treaty of Maastricht on European Union was signed in Maastricht on 7 February 1992 and it entered into force on 1 November 1993.

the late nineties, the European Commission has obtained a mandate to set high EU-wide standards for the quality and safety of organs and other substances of human.177

The EU’s mandate in the field of regulation of advanced therapies evolved in course of developments in the tissue engineering field in the late nineties. In 2000, the Lisbon Agenda recognised health protection as a prerequisite for economic growth measured with the indicator “Healthy Life Years”.178 Simultaneously, with the emergence of novel therapeutic opportunities in advanced therapies, the industry encouraged EU policymakers to create a favourable regulatory atmosphere to facilitate the development of a strong internal market for ATMPs.179 At the time of drafting the ATMP Regulation, Article 152.4.a of the Amsterdam Treaty clarified the horizontal nature of the EU’s health policy, implying an obligation to ensure protection of public health in all EU policies.180 It also established a legal foundation for the EU to interfere with the applicable ATMP practice and regulations in the Member States.181 However, proportionality and subsidiary principles pursuant to Article 5 of the TEU allow the European Commission to take actions in the public health sector only if their objectives cannot be adequately attained by the Member States and the European Commission can do so better because of the extent and impact of such objectives.182 Hence, in the case of “common safety concerns in public health”, both the EU and its Member States are authorised to act, but the Member States may take action only if the EU does not act or decides not to do so. Assessment of proportionality entails a three part test: 1) is the measure suitable to achieve a legitimate aim, 2) is the measure necessary to achieve that aim or are less restrictive means available, and 3) does the measure have an excessive effect on the party's interests.183 In light of these criteria, the proportionality and subsidiary principles mean that the “common safety concerns in public health in an area in which application of existing EU legislation and additional national measures have proven insufficient”, were in practise the only back door for the European Commission to regulate the ATMPs. The scope of the EU’s competence is also limited by Article 4.2 of the TEU that imposes an obligation to respect national identities of the Member States. This means that the European regulators have an obligation to respect the

178 Rosenkötter, et al., supra note 176, 2.
179 Pirnay, et al., supra note 22, 554. See also Mansnérus, supra note 22, 431.
plurality of values in the EU. As the EU’s mandate is based on internal market objectives, the EU lacks a formal competence to harmonise ethical norms applicable in its Member States.

The EU regulatory landscape ATMPs is still today significantly influenced and framed by the EU-wide internal market objectives.\(^\text{184}\) Common safety considerations however are an area where competence is shared between the EU and its Member States.\(^\text{185}\) Despite the EU’s initial competence was enhanced through subsequent Treaties, now Article 168 Treaty of the Functioning of the European Union (TFEU), still gives the EU relatively restricted mandate in areas of public health.\(^\text{186}\) The EU lacks the competence to regulate health care as a public service, as it is not subordinate to the internal EU market. Consequently, healthcare continues to remain a national competence; Article 168 (7) of the TFEU requires that the EU “shall respect the responsibilities of the member states for the definition of their health policy and for the organization and delivery of their health services”. The current restricted mandate for health notwithstanding, the EU has an important role to play in national public health and health systems policies and has expanded its initial remit in areas beyond the TFEU.\(^\text{187}\) Currently, the division of competences between the EU and its Member States can also be seen in the various measures that the EU may take under TFEU Article 168. First, the EU may, among other things adopt harmonisation measures setting high standards of quality and safety for substances of human origin and medicinal products and devices.\(^\text{188}\) In the case of ATMPs, the EU has a mandate to establish mandatory standards for GMP, marketing authorisations and post-marketing pharmacovigilance requirements. Secondly, it may also adopt incentive measures to protect and improve human health.\(^\text{189}\) Furthermore, the EU may encourage and support cooperation between the Member States in the area of public health via the open method of coordination.\(^\text{190}\)

Hence, the internal market perspective still remains as the major motive for harmonisation measures in the field of public health. An assumption is that the global market for health technologies affects and increases competition in this rapidly-evolving field.\(^\text{191}\) For instance, Gottweis et al. have discussed the impact of global markets on hESC research prospects and found that global markets increase competition in the stem cell field.\(^\text{192}\) Also Bache et al. suggest that the main rationale and justification for the EU legislation on new health technologies is the fostering

\(^{184}\) Bache, et al., supra note 41, 21.
\(^{185}\) Article 4 TFEU.
\(^{186}\) See Article 168 (4), TFEU.
\(^{188}\) Article 168 (4) TFEU.
\(^{189}\) Article 168 (5) TFEU.
\(^{190}\) Article 168 (2) TFEU.
\(^{191}\) Bache, et al., supra note 41, 21.
competitiveness in the internal EU market. That rationale is also included in the objectives of the ATMP Regulation that was set up as a lex specialis to ensure the free movement of ATMPs within the EU in order to facilitate their access to the internal market. Other relevant frameworks shaping the EU regulatory landscape for novel health technologies are the objective of health technology related risk management and the need to safeguard human rights and ethics. The dominant internal market objective is challenged and confined by these framing mechanisms.

Currently, Article 115 of TFEU provides for the Council, acting unanimously in accordance with a special legislative procedure and after consulting the European Parliament and the Economic and Social Committee, to issue directives for the approximation of such laws, regulations or administrative provisions of the Member States as directly affect the establishment or functioning of the internal market. Article 114 of the TFEU details the EU’s competence to create and sustain the internal market. Facilitation of trade in medical products on the internal market has been represented as a supporting rationale of the EU legislation on new health technologies:

“[t]he trade in medical products within the EU is hindered by disparities between certain national provisions, in particular between provisions relating to medical products and such disparities directly affect the functioning of the internal market.”

In addition, the importance of the internal market perspective can be seen in the EU legislation on pre-clinical and clinical research directly associated with marketing authorisation and pharmacovigilance. Under the TFEU, the definition and implementation of all EU policies must ensure a high level of human health protection. Currently, Article 168(1) the TFEU requires that EU actions in public health

“shall be directed towards improving public health, preventing physical and mental illness and diseases, and obviating sources of danger to physical and mental health. Such action shall cover the fight against the major health scourges, by promoting research into their causes, their transmission and their prevention, as well as health information and education, and monitoring, early warning of and combating serious cross-border threats to health. ”

Pursuant to the TFEU public health is a policy area where the European Union complements and supports the actions of the Member States. The TFEU complements the Member States' action in reducing drug-related health damage, including information and prevention. In the first place, the EU lacks the competence to

195 Reference is made to Directive 2001/83/EU, as amended, Recital 4.
196 Bache, et al., supra note 41, 23.
197 Article 168 (1) TFEU.
regulate health care as a public service, as it does not subordinate it to the internal EU market. Common safety considerations however are an area where competence is shared between the EU and its Member States.\textsuperscript{200} Protection of public health seems subordinate to the internal market objective as follows:

\begin{quote}{\small \textquotedblleft[\textit{w}hile the fundamental objective of the regulation on medical products is to safeguard public health; this aim should nevertheless be achieved by means that do not impede the free movement of safe medical products within the Union.\textsuperscript{201}\textquotedblright

The EU law requires that all laboratories carrying out clinical trials must comply with the OECD’s principles of Good Laboratory Practice (GLP).\textsuperscript{202} The EMA has adopted a long list of GLP-principles (Scientific Guidelines for Human Medical Products) that have been deemed a \textit{“to operate and reinforce a mutually supportive interaction between markets and risk”}.\textsuperscript{203} The market discourse is embedded in and supported by a risk discourse in that conducting a GLP-compliant study that is usually required for studies used to support applications for clinical trials or marketing authorisations is much more expensive than a non-GLP-compliant study because of the specific documentation and data management requirements.\textsuperscript{204} Studies necessary to demonstrate the quality and nonclinical safety of ATMPs are often carried out by SMEs. It has been further noted in Research Article IV and Chapter 7 of this study that such costs can constitute a substantial financial burden for them. However, this higher cost may be justified by the need to ensure safety and quality in ATMPs that may enter the internal market via the mandatory centralised marketing authorisation procedure. Simultaneously, as will be discussed in Section 7.8 of this study, higher costs affect access to medicines, which consequently raises further ethical issues; among other things, the fairness of allocation criteria for limited resources. In addition, as presented in Section 5.4 criminal law sets out the ultimate boundaries for the risk frame.

In addition, so-called soft law instruments regulating non-clinical studies has been adopted in the EU to complement risk regulation by providing guidelines on how to meet the legal GLP-requirements.\textsuperscript{205} The role of soft law has been discussed in Section 3.2. from a methodological perspective. These soft law guidelines are not legally binding, as developers of medicines may deviate from them. However, any alternative approaches must be duly justified pursuant to the proposed risk-proportionate approach. Research Article IV, Section 7.6.3. and Section 8.2 of this study in particular will address this issue in the light of the application of the precautionary principle and the possible risk-proportionate approach to assessment of manufacturing and clinical trials.

\begin{footnotesize}
\bibitem{200} Article 4 TFEU.
\bibitem{201} Directive 2010/84/EU, Recital 4. See also Bache, et al., \textit{supra} note 41, 23.
\bibitem{202} These appended to Directive 2004/10/EC in Annex 1.
\bibitem{203} Bache, et al., \textit{supra} note 41, 27.
\bibitem{204} \textit{Ibid.}
\end{footnotesize}
on ATMPs. Furthermore, additional specific guidance for ATMPs has been issued.\textsuperscript{206} Some of these specific guidelines on ATMPs encompass clinical research as well, and are construed in terms of its relationship with EU legislation on the mandatory marketing authorisation process.\textsuperscript{207} Hence, the risk discourse remains essential and is directly associated with the market discourse aiming at safe and efficacious novel ATMPs to enter the internal market. The risk discourse also influences clinical trials, where the Clinical Trials Directive refers to the protection of clinical trial subjects, in particular weighing the risks and inconveniences of the trials against their benefits.\textsuperscript{208} Likewise under Article 3, the Clinical Trials Regulation (replacing the Clinical Trials Directive):

\begin{quote}
"[a] clinical trial may be conducted only if: (a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and (b) it is designed to generate reliable and robust data."
\end{quote}

Consequently, protection of clinical trial subjects must be safeguarded via risk assessment based on the results of toxicological studies preceding any clinical trial, ethics committee assessment, and/or other applicable screening measures required by the competent national authorities, as well as data protection rules. Risks are also crucial in specifying requirements for preclinical and clinical trials, the manufacture and import of IMP ATMPs, labelling, the verification of compliance of such products with the GMP and the Good Clinical Practice (GCP) inspections and notification of any adverse events. All trials pursuant to the Clinical Trials Regulation must be designed, conducted and reported in accordance with GCP. Specific requirements of GCP are set out in Directive 2005/28/EC, which contains further requirements regarding investigational medical products used in clinical trials, further specific requirements on data collection and processing, and inspection mechanisms. The Clinical Trials Regulation illustrates how market and risk approaches are closely entwined, since

\begin{footnotesize}
\begin{itemize}
\item Bache, et al. supra note 41, 28.
\item Directive 2001/20/EC, Article 3.
\end{itemize}
\end{footnotesize}
marketing of medical products is seen as the underlying basis for the Regulation, whereas risks appear to be embedded in the markets.  

A second example of the importance of the internal market objectives can be found in ethics and the risk-based approach to markets applied to the regulation of orphan medicines. In all of these circumstances, the EU legislation is perceived to create incentives for creating new health technologies that would not be otherwise developed so rapidly under ordinary market conditions. In these contexts according to Bache at al., ethics and rights may be used to justify interference in and departure from a market frame. Some attention will be paid to orphan drugs in the context of discussing pricing and reimbursement issues in Section 7.8 and adaptive pathways in Section 8.3 that aim at enabling early and progressive patient access to a medicine.

A third example of the overall dominance of the internal market frame presented by Bache et al. is the impact of EU law affecting the pricing of novel health technologies and their coverage under national reimbursement systems. As will be further discussed in Section 7.8, despite there being no EU legislation regarding pricing and reimbursement of pharmaceuticals, it should be noted that some steps forward to assessment of potential common health technology methodologies have been taken (such as sharing national health technology assessments found in the Directive on Patients’ Rights to Cross-Border Health Care). Some other recent developments include the European Commission’s proposal on transparency, where the rationale for creating a tighter timeline for pricing and reimbursement decision-making and fostering more effective enforcement appear to be largely based on a market rationale. Another plausible example of the risk-market relation is the post-market regulation for pharmaceuticals, such as the EU-wide prohibition on consumer advertising of prescription-only medicines. Such specific aspects of marketing and advertising have been left out of this study. The EU legislation on regulation of materials of human origin also suggest a close relation between market and the risk, as its central objective is to foster confidence in different national risk regulation systems to encourage innovation.

Market and risk frames shaping the regulatory landscape for ATMPs and other novel health technologies in the EU are complemented by human rights and ethics as

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209 Bache, et al. supra note 41, 29 refer to the role of Clinical Trials Directive that is being replaced by the Clinical Trials Regulation.
216 Bache, et al. supra note 41, 40.
218 Bache et al., supra note 41, 39.
framing tools. The impact of the human rights and ethics frame is strengthening. This complicates the EU’s initial mandate under risk and market frames – fostering competitiveness of the internal market and protection of public health. Despite harmonisation of ethical considerations fall outside the EU’s mandate, human rights perspectives are emerging. Subsequent to the adaption of the Lisbon Treaty, Charter of Fundamental Rights of the EU became legally binding. Today Article 35 of the Charter requires that a high level of human health protection shall be ensured in the definition and implementation of all EU policies and activities. To ensure compliance with this Charter, the European Commission submits new legislative proposals for the EU regulations to a “human rights proof test”.  

Bache et al. have argued that human rights and ethics often seem to be used to legitimise other framing options than as a frame in themselves. The amorphous notion of human dignity has been discussed in Chapter 5 of this study. Furthermore, as mentioned above, the ethics frame can be seen in terms of EU research funding decisions under FP7, since a research proposal that contravenes fundamental ethical principles shall not be selected. The same applies to research proposals under the current Research and Innovation Programme for the EU, Horizon 2020. Article 19 of the Regulation on the Horizon 2020 Programme refers to the ethical principles to be followed for research and innovation activities it accepts by emphasising the need to comply with national, EU and international human rights legislation, the EU Charter of Fundamental Rights and the ECHRs and its protocols in particular. The role of the European Group of Ethics in Science and New Technologies (EGE) in issuing advisory opinions to the European Commission also reflects the legitimating function of human rights and ethics. The introduction of ethics to hESC research is associated with the avoidance of regulatory uncertainty and potentially harmful confused public debate. Hence, ethics can be seen to play a pivotal role in legitimation of the EU regulation. Furthermore, in practice it also seems to have another important role in production of an expert-led EU regulatory environment that supports innovation in novel health technologies.

Despite the strengthening of human rights approach, the EU’s lacks competence to set binding ethical standards and to interfere with organisation of healthcare services in

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222 The EGE, set up by the European Commission in 1991, is an independent body composed of experts whose task is to advise the European Commission on ethical questions relating to science and new technologies. The EGE has provided two opinions on the use of embryos in vitro for research purposes.
its Member States. Favale et al. have expressed a concern that despite the EU’s mandate in the field of public health does not allow for union-wide harmonisation of ethical aspects of new health technologies, the European Parliament puts pressure on the legislators to include ethical provisions leaving some novel health technologies beyond the harmonisation measures. Yet, the EU’s competence in the field of public health only allows for risk management related (precautionary) scientifically justified legislation of technical and value neutral of character. The increased pressure on the legislators to accommodate ethical considerations into “technical” pieces of legislation is consequence of the strengthening position of the European human rights norms, which adds the pressure to establish “common European ethics” and concrete contents for human rights principles.

Under the TFEU, the Member States remain responsible for the definition of their health policies and the organisation, management and delivery of their health services and medical care, including the allocation of resources assigned to them.225 As the Member States remain ultimately responsible for the delivery of health care services, the availability of advanced therapies across the Member States may vary. For instance, Recital 7 of the ATMP Regulation states that:

“The regulation of advanced therapy medicinal products at Community level should not interfere with decisions made by Member States on whether to allow the use of any specific type of human cells, such as embryonic stem cells, or animal cells. It should also not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of or derived from these cells.”

The Article 28.3 of the ATMP Regulation also amends Directive 2001/83/EC by adding following paragraph to its Article 4:

“This Directive and all Regulations referred to therein shall not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these cells, on grounds not dealt with in the aforementioned Community legislation. –“

In practice inclusion of this paragraph means that a Member State may prohibit or restrict the use of any specific types of ATMPs despite the EU-wide marketing authorisation. This means that advanced therapies may not be equally accessible to patients in all Member States.226 Despite this provision was initially purported to allow flexibility to accommodate different ethical positions of the Member States regarding the use of hESCs as a primary material, 227 it does not specify any specific cell types for which this provision may apply. Hence, this provision may allow the Member States to exclude any types of cells (even without ethical grounds), despite initially the purpose of this provision was to allow margin of appreciation in ethically contentious issues.

225 Article 168 (7) TFEU.
227 ATMP IA Report, supra note 170, see section 6.7 “Use of embryonic stem cells”.

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The increased “human rights pressure” may lead to incorporation of ethical content into ostensibly technical pieces of legislation.\(^{228}\)

Despite the EU’s competence is formally limited to actions under *market* and *risk* frames, as a consequence of the emergence of the *human rights* (and *ethics*) these frames shaping the regulatory landscape for ATMPs seem to overlap significantly. In the context of regulating ATMPs, it appears that the EU’s approach to risk, human rights and ethics stems from the need to foster the competitive spirit of the EU market. In terms of regulation of novel health technologies, Bache et al. have emphasised that there is an objective of creating an internal market that is safer, more respectful of human rights and more ethical than other global markets. They further conclude that in that sense, this approach to framing the EU market differs from the traditional idea that markets are all about free trade, whereas risks, human rights and ethics impose obstacles on free trade.\(^{229}\) Hence, the internal market objective as the dominant frame could help to create new ATMPs, especially by defining what is being researched and developed to foster internal market competitiveness and optimise economic growth. However, as will be noted in Chapter 8 of this study, the outcome does not seem optimal thus far in the case of ATMPs and the current legislative landscape for ATMPs leaves a lot to be desired. Bache et al. have described law as an active, relevant and continuously efficacious way of shaping new health technologies, such as ATMPs.\(^{230}\) Among other things, they see much potential in law, perceiving it as reaching well beyond the few formal articulations of enforceable rights via EU law on new health technologies, and involving an abundant array of regulation.\(^{231}\) They take the view that legal entitlements and responsibilities are revealed as more than formal articulations in national or supra-national legal instruments, but have social meaning when they are employed via the products and processes in practice by active stakeholders.

In conclusion, markets and risks appear to be pivotal frames for novel health technologies in the EU; the EU regulation on ATMPs is essentially focused on the risk-benefits balance, which appears to be constructed to ensure public confidence in novel products entering the internal market, and optimise their production and availability.\(^{232}\) In case of ATMPs, these two frames underpinning the ATMP Regulation in the EU do not, on the face of it, seem theoretically juxtaposed; rather they can be seen as mutually supportive. However, as will be further discussed in Chapter 7 of this study, it can be asked whether these frames enjoyed an optimal balance, as the number of ATMPs in the market is so low and access to these medicines is not equally guaranteed within the EU. As a starting-point, my hypothesis is that laws can optimally be used as means to promote and facilitate advances in science, and to improve well-being in society. On the other hand, laws are not optimally designed and, if they are too

\(^{228}\) Favale et al., *supra* note 131, 90, 97-99, 111.

\(^{229}\) Bache, et al., *supra* note 41, 41-44.


\(^{231}\) *Op. cit.*, 43.

heavily influenced by limited interests of some group of stakeholders that dominates over the interests of some other relevant stakeholders, laws may be conducive to creating so-called “translational blocks” (that will be discussed further in Chapter 7 of this study) imposing impediments to translational medical research and commercialisation of such research. From the perspective of the market frame, such a situation indicates a bias in the legislative process. This may lead to a situation in which either the risks or human rights and ethical perspectives of a law are not optimally balanced against the internal market objectives. As an example of this problem, the EU legislation on ATMPs is understood as an important site for engagement over a panoply of questions that is worthy of legal protection and what kind of interests might be privileged. Therefore, there is a need to analyse the role and importance of stakeholder engagement influencing legislative processes in the rapidly evolving ATMP field.

4.2 The multilayered, flexible and variable approach of the Council of Europe

The Council of Europe’s approach to regulating novel health technologies is a multilayered one, ranging from the fundamental human rights principles included in the ECHR to more technical rules specified in a number of rather technical documents that regulate particular health technologies. The more general rules not only appear to have a broader scope of regulation, but also seem to possess a stronger legal status as so-called “hard law” (as opposed to “soft law” comprising the recommendations and guidelines that complement mandatory legislation and often guide governance of health technologies at a more practical level). However, the fundamental rights incorporated in the ECHR seem simultaneously to regulate novel health technologies indirectly, whereas the soft law constituting of recommendations and comparable soft law instruments more directly and practically regulates development and use of such technologies. The Biomedicine Convention and its Additional Protocols seem to be positioned somewhere in between the fundamental human rights specified in the ECHR and technology-specific soft law instruments. Since the adoption of the Biomedicine Convention in 1997 and its later protocols on Cloning (1998), Transplantation (2002), Biomedical Research (2005) and Genetic Testing for Health Purposes (2008), the Council of Europe has been actively involved in developing a normative framework for human rights in biomedicine, which has evolved from the ECHR (1950).
medicine by complementing the ECHR in biomedicine and genetic science and by establishing European standards in this field. Whilst protection of human rights constitutes a core objective for the Biomedicine Convention, its scope is not restricted to that. The Biomedicine Convention not only contains provisions that are relevant for everyday health care, but some of its provisions are also applicable to very technical procedures and medical research.

In addition, the Council of Europe’s regulatory framework governing novel health technologies seems quite flexible and variable. This depends partly on the intergovernmental character of its regulatory instruments such as the Biomedicine Convention, and the margin of appreciation doctrine applied by the ECtHR. Hence the ECHR makes a dynamic interpretation in light of “present day’s circumstances or conditions”. According to the ECtHR’s view, the ECHR is not designed to guarantee theoretical rights, but effective and practical rights. In Henriette Roscam Abbing’s view, human rights instruments are “living instruments” and the codification of fundamental values in human rights does not remove the philosophical and moral concept of the norm, as the norm “floats” in the sphere of those concepts and remains a stimulant for innovative jurisprudence and fresh regulation. O’Connell et al. by contrast have pointed out that the flexibility of the system also seems qualified, as the margin of appreciation granted to the contracting states may vary over time and there is a possibility that the ECtHR may find specific factors that justify closer scrutiny. This flexibility has been deemed to be disguised as the margin of appreciation and that doctrine has been criticised every now and then as spineless and perceived merely as a pragmatic substitute for a thought-out process. This kind of criticism is quite understandable as novel health technologies such as translational hESC research and cell reprogramming research in particular raise a number of ethical issues and disagreement. While the Council of Europe’s human rights framework is not infinitely

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237 Please refer to paragraphs 8-20 and 165 of the Explanatory Report to the Biomedicine Convention.
239 O’Connell, et al., supra note 233, 53-57.
240 Roscam Abbing, supra note 128, 20.
242 Dickson v. United Kingdom, (Application no. 44362/04), 4 December 2007.
243 See Evans v. the United Kingdom ([GC], no. 6339/05, ECHR 2007-I) that concerned the fate of frozen human embryos. According to the joint dissenting opinion of Judges Türmen, Tsatsa Nikolovska, Spielmann and Ziemele, “[a] sensitive case like this cannot be decided on a simplistic, mechanical basis, namely, that there is no consensus in Europe, therefore the Government have a wide margin of appreciation; the legislation falls within the margin of appreciation ... that margin of appreciation should not prevent the Court from exercising its control, in particular in relation to the question whether a fair balance between all competing interests has been struck at the domestic level. The Court should not use the margin of appreciation principle as a merely pragmatic substitute for a thought-out approach to the problem of proper scope of review”. More recently, according to the Concurring Opinion of Judge Pinto de Albuquerque in Parrillo v. Italy (App. no. 46470/11), an identical remark could be made in Parrillo. See also O’Connell, et al. supra note 233, 69. See also Murphy T. Repetition, Revolution and Resonance: An Introduction to New Technologies and Human Rights. (Oxford: Oxford University Press), 2009; 1-18.
plastic, it does appear to play two important roles.\textsuperscript{244} According to O'Connell et al., the first is defining and safeguarding a minimum level of respect for human rights (the autonomy type of rights in particular, including the requirement of free and informed consent,\textsuperscript{245} the right to respect for private life,\textsuperscript{246} as well as the right to health,\textsuperscript{247} and equality and non-discrimination).\textsuperscript{248} Its second important role is to specify what interests must be considered, balanced and promoted in any applicable national legislative context.

Furthermore, it should be noted that the Biomedicine Convention and the ECHR have adopted different approaches to notions of human dignity. Whilst both of these regulatory instruments rely on notions of dignity, this reliance is explicit in the case of the Biomedicine Convention and associated with the ethical idea of dignity as a restriction on certain kinds of action.\textsuperscript{249} This difference notwithstanding, potential conflicts may be largely avoided by the intergovernmental character of the Biomedicine Convention and the margin of appreciation doctrine applied by the ECtHR (as well as the victim standing requirement of the ECHR).\textsuperscript{250} However, this does not imply a European consensus on human dignity. Furthermore, in light of the ECtHR’s recent ruling in Parrillo v. Italy (App. no. 46470/11) there appears to be a disagreement regarding the appropriate scope of the margin of appreciation doctrine as applied to the status of donations surplus IVF embryos to medical research.

The Council of Europe’s approach to regulating novel health technologies allows significant flexibility for the contracting states (subject to safeguarding human rights) in regulating health technologies at a national level. The ECtHR jurisprudence and the Biomedicine Convention, however, have both stimulated the need for informed public debate on these bioethical questions in a democratic society.\textsuperscript{251} Despite the Council of Europe’s position on regulating novel health technologies being multilayered, variable and flexible, the human rights framework still appears to provide some reference points that can guide our interpretation of the scope and extent of human rights in the course of rapid developments in stem cell science and therapeutic opportunities in the age of translational, personalised medicine. Some of these reference points seem more obvious than others. For instance, the notion of human dignity is very often referred to in the context of hESC research as a limitation on certain types of actions. However, there is

\textsuperscript{244} O'Connell, et al., supra note 233, 69.
\textsuperscript{245} Glass v. United Kingdom (App. no. 61827/00), 9 March 2004. VC v. Slovakia (App. no. 18968/07), 8 November 2011.
\textsuperscript{246} S. and Marper v. United Kingdom (App. nos. 30562/04 and 30566/04), 4 December 2008.
\textsuperscript{247} Oyal v. Turkey (app. no. 4864/05), 23 March 2010.
\textsuperscript{248} O’Connell, et al., supra note 233, 69.
\textsuperscript{249} In the context of hESC research, Article 18.1 of the Biomedicine Convention emphasises the need to protect embryos in research settings by stating that “where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo.” Article 18.2 of the Biomedicine Convention however bans creation of embryos for research purposes by stipulating that “no creation of human embryos for research purposes is prohibited.”
\textsuperscript{250} O’Connell, et al., supra note 233, 69.
\textsuperscript{251} Ibid.
no definitive consensus on the exact scope and extent of the use of human dignity as a constraint. As will be discussed in Chapter 5 of this study, some commentators have even argued that this concept risks becoming too amorphous to be useful.

4.3 Emergence of the human rights framework as a normative framework for the EU

Despite significant fragmentation being seen in the distinct lack of a common European normative framework for novel health technologies, some consensus seems to be emerging in the development of a normative framework of human rights (that also simultaneously underpins the regulation of novel healthcare technologies in the EU). Simultaneously, the EU’s developing legislation on human rights resulted in the Charter of Fundamental Rights of the European Union in 2000 and the EU’s current endeavours to accede to the ECHR would require the EU to adopt the ECHR as a binding legal instrument constituting part of EU law. Some commentators have been quite optimistic, arguing that these developments indicate that the human rights framework is now evolving as a normative framework for the EU. Yet, these developments appear quite ambiguous, which is not at all surprising from the historical perspective.

Already two decades ago, the ECJ ruled in its Opinion 2/94 on 28 March 1996 that the European Community could not accede to the ECHR under the provisions of the European community law. Only a Treaty amendment could reverse this judgment. In 2009, the Lisbon Treaty did that by inserting Article 6(2) in the TEU that required the EU to accede to the ECHR. Indeed, that is first one of the two particularly important changes that have emphasised the legal duty to align EU law with fundamental human rights. The Lisbon Treaty not only requires the EU to accede to the ECHR, but it also formally recognises the Charter of Fundamental Rights of the EU, assigned the same value as the Treaties. The Lisbon Treaty added a Protocol 8 to the Treaties, regulating modalities of the accession, as well as a declaration necessitating that accession to the ECHR must comply with the ‘specific characteristics’ of EU law. Yet,
these new provisions of Lisbon Treaty could not as such make the EU a contracting party to the ECHR. In order to reach that outcome, the EU was required to negotiate a specific accession agreement with the Council of Europe (the Accession Agreement). However, the Accession Agreement was rejected by the ECJ’s Opinion on 18 December 2014. From the perspective of human rights and fundamental freedoms this situation appears paradoxical; the ECJ seeks to protect the basic elements of EU law by disregarding the fundamental values upon which the EU is established. It should be noted that the Charter of Fundamental Rights of the European Union also reaffirms the rights as they result from the ECHR and the case-law of the ECJ and of the ECtHR.

Yet, some strengthening of the human rights-based approach can be seen in the strategy for the effective implementation of the Charter of Fundamental Rights by the European Union. To ensure compliance with this Charter, the European Commission will submit new legislative proposals for the EU regulations to a “human rights proof test”. Hence the implementation of current EU legislation should undoubtedly also pass the human rights proof test. Roscam Abbing has pointed out that especially “where this implementation touches upon the core human rights, regulatory diversity is not indicated”. Furthermore, she mentions the prohibition of financial gain from the human body and its parts (as stipulated in Article 3.2 of the Charter of Fundamental Rights and Article 21 of the Biomedicine Convention), as an important principle to be observed, particularly when considering the recent commodification and commercialisation debate in this domain. Some room is nevertheless left for scepticism given how little the Biomedicine Convention has been invoked in the ECtHR (and by the Supreme Courts of the contracting states), and the fact that no application submitted to the ECtHR can be based on the breach of the Biomedicine Convention


259 Roscam Abbing, supra note 128, 21.

260 Ibid.

261 Some scholars have criticised the reluctance of the national Supreme Courts to take in to consideration requirements arising out of the Biomedicine Convention in their decion-making. For instance, Raimo Lahti refers to a precedent of the Finnish Supreme Court (KKO 2008:93), which concerned infant male circumcision. The Supreme Court held that the conduct of a mother who had her four-year-old Muslim son circumcised for religious reason was not to be deemed illegal. Yet, in its argumentation, the Supreme Court did not refer to the Biomedicine Convention, which at the time had yet to be ratified. Lahti, R. Statement to Constitutional Law Committee on proposition of the Government (HE) 216/2008 regarding the ratification of the Convention for the Protection of Human rights and the Dignity of the Human Being with regard to the Application of Biology and Medicine and its two additional Protocols, as well as implementation of thereto related provisions of a legislative nature and amendments in the Penal Code’s Chapter 11 Section 11 and Chapter 47 Section 3, dated 17 February 2009.
alone (it must be founded on the alleged breach of the ECHR instead). Hence, predicting that the Biomedicine Convention is likely to have a quite small practical role in litigation or policy formation in the EU context seems reasonable.262 It should also be noted that the ratification status of the Biomedicine Convention is rather irregular, as it has currently been ratified by only 29 of 47 the contracting states of the Council of Europe.

Furthermore, after the ECJ’s rejection of the Accession Agreement draft many issues are still to be resolved and there is no certainty that consensus will be achieved. It should be noted especially that in the “final” version of the draft accession agreement, ECJ rulings will be subject to the external control of the ECtHR. The ECJ delivered its opinion on the draft agreement on the accession of the ECHR in December 2014, identifying a number of issues regarding its compatibility with EU law. In its current form, the ECJ finds that the draft agreement on the accession of the EU to the ECHR is not compatible with EU law.263

First, the ECJ made some preliminary remarks asserting for the first time that the EU is not a state under international law.264 In addition, the ECJ expresses a concern that the approach adopted in the draft Accession Agreement, which is to treat the EU as a state and to give it a role identical in every respect to that of any other contracting party, specifically disregards the intrinsic nature of the EU. It also stated that the EU system is ‘sui generis’ by arguing that “the fact that the EU has a new kind of legal order, the nature of which is peculiar to the EU, its own constitutional framework and founding principles, a particularly sophisticated institutional structure and a full set of legal rules to ensure its operation, has consequences as regards the procedure for and conditions of accession to the ECHR”.265 The ECJ also highlighted that it is important to ensure the primacy and direct effect of EU law,266 referring also to the EU’s goals of “creating an ever closer union among the peoples of Europe” (second paragraph of Article 1 TEU).267 In particular, according to the ECJ, the draft Accession Agreement does not take account of the fact that on the matters covered by the transfer of powers to the EU, the Member States have accepted that their relations are governed by EU law to the exclusion of any other law.

262 Ashcroft, supra note 21, 311.
266 Op.cit., para., 166: “[...-]EU law is characterised by the fact that it stems from an independent source of law, the Treaties, by its primacy over the laws of the Member States (see, to that effect, judgments in Costa, EU:C:1964:66, p. 594, and Internationale Handelsgesellschaft, EU:C:1970:114, paragraph 3; Opinions 1/91, EU:C:1991:490, paragraph 21, and 1/09, EU:C:2011:123, paragraph 65; and judgment in Melloni, C-399/11, EU:C:2013:107, paragraph 59), and by the direct effect of a whole series of provisions which are applicable to their nationals and to the Member States themselves (judgment in van Gend & Loos, EU:C:1963:1, p. 12, and Opinion 1/09, EU:C:2011:123, paragraph 65).”
Thereafter, the ECJ found the draft Accession Agreement incompatible with the EU law for five main reasons:

1. Firstly, it did not take account of the specific characteristics of EU law in the following respects:
   i. It did not limit the possibility of Member States applying higher human rights standards than EU law, despite the ECJ had ruled that Member States could not have higher standards than the Charter of Rights of Fundamental of the EU, where the EU has fully harmonised the law. According the ECJ the same rule applies for the ECHR and the draft Accession Agreement does not take that aspect into consideration.
   ii. Furthermore, the ECJ found that the Accession Agreement did consider the application of the premise of ‘mutual trust’, which “[... requires, particularly with regard to the area of freedom, security and justice, each of those States, save in exceptional circumstances, to consider all the other Member States to be complying with EU law and particularly with the fundamental rights recognised by EU law.”
   iii. The ECJ notes that Protocol No 16 to the ECHR allows the highest courts of the Member States to request advisory opinions from the ECtHR on questions of principle relating to the interpretation or application of the rights and freedoms guaranteed by the ECHR (or its protocols). The ECJ points out that subsequent to the accession, the ECHR forms an integral part of EU law. Hence, the preliminary ruling procedure mechanism established by that protocol may affect the autonomy and effectiveness of the preliminary ruling procedure provided for by the Article 267 FTEU, especially where rights guaranteed by the Charter of Fundamental Rights of the EU correspond to those secured by the ECHR. The ECJ finds that there is no provision in the current draft Accession Agreement to ensure this coordination.

2. Secondly, the ECJ found that draft Accession Agreement violated Article 344 TFEU, which grants the ECJ monopoly on inter-state dispute settlement regarding EU law between Member States, since it failed to exclude the possible use of the ECtHR to settle such disputes instead.

3. Thirdly, the ECJ finds the proposed co-respondent system, which creates a new type of procedure where both the EU and a Member State could be parties to an ECtHR case, incompatible with EU law, as
   i. it would give the ECtHR the power to interpret EU law when assessing the admissibility of requests to apply this process;
   ii. a ruling by the ECtHR on the joint responsibility of the EU and its Member States could interfere with Member State reservations to the ECHR; and
   iii. the ECtHR should not have the power to allocate responsibility for breach of the ECHR between the EU and Member States, since only the ECJ has the mandate to rule on EU law.

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269 The ECJ refers to Melloni, C-399/11, EU:C:2013:107, para. 60.
4. Fourth, the rules in the draft Accession Agreement on the prior involvement of ECJ before the ECtHR ruled on EU law issues were also found incompatible with EU law because
i. they did not reserve to the EU the power to rule on whether the ECJ has already dealt with a case; and
ii. they did not permit the ECJ to rule on the interpretation, not just the validity, of EU law.²⁷⁵

5. As a final point, the ECJ found rules on the common foreign and security policy incompatible with EU law, because a non-EU court cannot be given the power of judicial review over EU acts, despite the ECJ has no such jurisdiction itself regarding most issues pertaining to common foreign and security policy.²⁷⁶

It is apparent that political and historical tensions on the relative autonomy, constitutional balance and ultimate authority of the national courts and the two supranational courts were present when negotiating the draft Accession Agreement.²⁷⁷ It also obvious that EU accession to the ECHR cannot proceed on the basis of the current draft Accession Agreement. The ECJ has proposed amendments to the Accession Agreement to ensure its compliance with the EU law addressing the above mentioned issues. Yet, any such changes to the Accession Agreement must be negotiated by all 47 of the parties to the ECHR. If consensus is reached, then the Accession Agreement would need to be ratified by all of them to enter into force. In addition, it would need to be agreed unanimously by the EU Council and ratified by the European Parliament. Nevertheless, whatever form of the Accession Agreement will take, it is an important objective for the EU to ensure that EU law is compliant with the ECHR. Indeed, under Article 6(2) of the TEU, accession of the EU to the ECHR is an obligation: the EU “shall accede” to the ECHR. Yet, such legal obligation stemming from the EU Treaties cannot bind third parties (such as the ECtHR or non-EU contracting states of the ECHR).²⁷⁸

In light of the emerging human rights framework, it has been argued that despite the ECJ being the ultimate instance in EU law related disputes in the EU (also those pertaining to application of patent law), the ECJ should still consider the wide margin of appreciation doctrine applied by the ECtHR to a greater extent in important value-choice questions in field of modern biotechnology and human rights.²⁷⁹ However, no such formal legal obligation exists (although it would be desirable in terms of normative coherence). Despite pursuant to Article 344 TFEU the ECJ has monopoly in interstate dispute settlement regarding EU law, the legal framework regulating novel health technologies should be formed in a coherent way that allows the various

²⁷⁷ Plomer, supra note 60, 112.
²⁷⁸ In case the ECtHR, or one or more non-EU Member States, would refuse to continue with accession negotiations, the EU institutions and the Member States could not be held liable for that.
²⁷⁹ See e.g., Mansnérous, et al., supra note 34, 82.
legitimate interests involved to be appropriately taken into consideration in line with the obligations imposed by the ECHR.

4.4 Incoherence between patent and pharmaceutical regulatory systems and the emerging human rights framework as an impediment to functioning internal markets

Excluding unethical inventions from patentability arises as a significant issue in the relation between the patent system and the pharmaceutical regulatory one. On first observing the relation between the pharmaceutical regulatory and the patent system, Hellstadius pointed out that within the current framework, the pharmaceutical regulatory system has not disqualified itself from ethical considerations involved in patenting by giving competence to the patent system to address moral issues associated with the patentability of biotechnological innovations.²⁸⁰ In contrast, it seems to retain the authority on moral questions (especially in terms of regulatory rules relating to research ethics and authorisation of research and clinical trials). In the case of ATMPs, it sets out acceptable standards for GMP, marketing authorisations and post-marketing pharmacovigilance requirements. By means of the incentive-function of the morality exclusion, the patent system has an indirect power to influence investment in research and development. Consequently, the incentive-reducing effects may direct funding and developments away from socially objectionable technologies. This indicates that the different roles and purposes of patent and regulatory systems overlap to some extent, since patent authorities and courts influence the grant of patents and removal of economic incentives for research in terms of ethics.²⁸¹

The extent to which the regulatory system should have an impact on the interpretation of the patent morality clause is a fundamental issue. More specifically, the question is whether or not the patent system should be separate from or influenced by corresponding legislation within the regulatory system. Another fundamental issue is how far developments in the human rights framework should influenced the patent system. It is reasonable to argue that the morality exclusion in patent law should be kept within strict limits against the background of the operation of the biotechnology patenting system. In a pluralistic Europe, the use of the morality provisions in the national, regional and international patent systems should respect national approaches to morality and the ordre public.²⁸² As discussed in Research Article II, an extensive application of the morality exclusion by the ECJ in Brüstle has already resulted in an undesirable discrepancy between national regulatory legislation and the regional exclusions from patentability, as the patentability of hESC-based innovations that

²⁸⁰ Hellstadius, supra note 50, 34.
²⁸¹ Hellstadius, op.cit., 30.
²⁸² In particular, TEU 4.2 requires the EU regulators to respect “national identity” of the Member States.
necessitate destruction of human embryos is not allowed where the invention is still free to be exploited commercially in the most of the EU Member States. In particular, it raises concerns about proportionality of the patentability restrictions.\textsuperscript{283} Also it can be questioned whether the EU should within its limited mandate pursue ethical harmonisation measures.

In looking at the other fundamental question, the influence of the emerging human rights framework, the ECtHR’s approach allows a wide margin of appreciation in moral matters, where no uniform European conception in the legal and social orders of the contracting states to the ECHR exists. In principle, under the ECHR the contracting state is deemed to be best placed to provide an opinion on the precise content of moral requirements, especially concerning matters of belief regarding the nature of human life in relation to the rapid advances in science.\textsuperscript{284} The doctrine of margin of appreciation applied by the ECtHR extends both the contracting state’s decision to intervene in such areas and, once having intervened, it also covers rules that the contracting state establishes to attain a balance between competing interests.\textsuperscript{285} Interestingly, however, the ECJ has not been as eager to grant a margin of appreciation in certain important value-choice questions pertaining to European patent law.

The ECJ encounters some significant challenges with keeping its interpretations in ethically contentious matters abreast of the latest developments in science. Many commentators have questioned the approach adopted by the ECJ in \textit{Brüstle} as there is apparently no uniform European consensus on the scientific and legal definition of the beginning of life and the margin of appreciation granted to the EU Member States.\textsuperscript{286} Some significant criticism has been directed at the ECJ’s \textit{Brüstle} ruling as, according to jurisprudence under the ECHR thus far, the full protection of life begins at birth. However, some protection of life before birth exists, depending on the interpretation of other rights.\textsuperscript{287} In the absence of a European consensus on the scientific or legal definition of the beginning of human life, the question for embryo protection in hESC research should translate into a wide margin of appreciation as to how the contracting state balances competing interests. As discussed, the compliance with the ECHR does not automatically mean that the ECJ must grant the EU Member States as wide margin of appreciation in value choice questions as the ECtHR just because the ECtHR has been inclined to grant a wide margin of appreciation to the contracting states of the ECHR. In contrast, a more relevant argument is that the ECJ should under the EU law respect differences in views of the EU Member States in sensitive matters in the application of biomedicine where fundamental values are involved. Currently nearly 60

\textsuperscript{283} In light of the proportionality principle it is questionable whether this restriction is suitable to achieve a legitimate aim, and whether it is necessary to achieve that aim (especially, as there are less restrictive means available). It can be also argued that the measure has an excessive effect on the patent applicant’s interests. See e.g. Plomer, \textit{supra} note 60.

\textsuperscript{284} \textit{Op.cit.}, 25

\textsuperscript{285} \textit{Ibid.}

\textsuperscript{286} See e.g. Plomer, \textit{supra} note 60. See also e.g. Mansnérus, et al., \textit{supra} note 34.

\textsuperscript{287} Roscam Abbing, \textit{supra} note 128, 25 e.g., protection of life and health of a pregnant woman.
percent of signatories to the ECHR are also Member States of the EU and among these states a great diversity of values prevails. The EU may still pursue a higher level of harmonisation and the ECJ may choose to apply a narrower margin of appreciation, but it should present convincing arguments when doing so. Especially, limitations affecting freedom of science and access to therapies should be duly justified in terms of present day circumstances and conditions. Hence, in a case of a collision between competing constitutional rights representing different human dignity positions (for instance, rights of a research embryo v. rights of a patient in need of therapies), a careful balance must be pursued in light of current scientific understanding.

If the purpose of the moral assessment in patent law is to protect values which are already expressed in the pharmaceutical regulatory legislation of the EU Member States (e.g., human dignity) there is indeed a need to assess whether or not the patent legislation and decision-making processes should be adjusted to the regulatory systems to protect such values. A basic assumption is that the European Commission respects differences in views in sensitive matters in the application of biomedicine where fundamental values are involved.\textsuperscript{288} Hence, it is also very difficult to justify the ECJ’s highly restrictive \textit{Brüstle} ruling in light of the EUTCDs and the ATMP Regulation that both have implemented a permissive approach, granting the EU Member States a margin of appreciation on the moral and legal limitations of research and commercial uses of human embryos and embryonic tissues and cells.\textsuperscript{289} Likewise, the ATMP Regulation respects the Member State legislation prohibiting or restricting sale, supply or use of medical products containing, consisting of, or derived from any specific type of human cells (e.g. hESCs).\textsuperscript{290} It is difficult to find consistent legal support for the ECJ’s ruling claiming that the specific prohibition under Article 6.2.c of the Biotech Patent Directive truly reflects a common European view of human dignity in the context of patenting hESC applications. Indeed, the ECJ’s ruling seems to ignore the fact that research and commercial uses of hESCs are permissible under EU law, and respect for the plurality of moral and religious cultures should be reflected in the margin of appreciation granted to the EU Member States.\textsuperscript{291} Furthermore, the ECJ’s interpretation based on the human dignity argument appears to lack a solid legal foundation in the EU or the Council of Europe’s legal orders, and is at odds with the legal and political reality on the level of protection granted to the human embryo across the EU Member States. In contrast to the ECJ’s judgment, the use of surplus IVF embryos and destruction of such embryos is legally permissible in many EU Member States. Three EU Member States (Belgium, Sweden and the United Kingdom) even allow creation of embryos by SCNT for research purposes.

\textsuperscript{288} Roscam Abbing, \textit{op. cit.}, 24.  
\textsuperscript{289} See Plomer, \textit{supra} note 60, 127. See also Mansnérus, et al., \textit{supra} note 34, 22.  
\textsuperscript{290} Roscam Abbing, \textit{supra} note 128, 24.  
\textsuperscript{291} In particular Article 4.2 of the TEU requires that “national identity” of the Member States of the EU must be respected. See also Plomer, \textit{supra} note 60, 127. See also Mansnérus, et al., \textit{supra} note 34, 61.
As discussed in Research Article II, it also appears that the moral exclusion under Article 6.2.c which was purported to be applied strictly and narrowly to encompass only industrial and commercial uses of human embryos has been deliberately extended by the ECJ in *Bristle*, far beyond its initially intended literal scope to cover not only industrial and commercial uses of human embryos but also cell cultures and cell lines obtained by the destruction of human embryos, as well as all downstream therapeutic products utilising hESCs. This raised concerns about proportionality of the restriction.

In conclusion, there is no uniform European consensus on the scientific and legal definition of the beginning of life and margin of appreciation for the EU Member States. As for the predicted future developments affecting the margin of appreciation in patent law, the granting of a unitary patent by the EPO opens the possibility of national revocation proceedings in EU Member States which in turn provides an opportunity to seek guidance from the ECJ, and may provide the ECJ with the potential to control the margin of appreciation exercised by Member States regarding morality restrictions on biotechnology patenting. Such a revocation would take effect under the law of the contracting state. When that State is an EU Member State, it is also bound by community law and hence by the morality exceptions in the Biotech Patent Directive.

The unitary patent system may in future promote legal certainty with the involvement of the ECJ in questions regarding interpretation of the morality exception as applied by the Member States. Most EU Member States and the European Parliament have agreed on a legislative initiative which comprises two regulations (unitary patent protection and translation arrangements) and an agreement on the Unified Patent Court (the UPC). These regulations entered into force in January 2013; however, they will become applicable from the date of entry into force of the Agreement on the UPC (and the signing of the agreement is still pending). The Agreement on the UPC establishes a specialised patent court with exclusive jurisdiction for proceedings relating to European and unitary patents. As the UPC will have the competence to interpret European patent law with effect for most EPC contracting states and EU Member states, it is an important measure that aims to resolve the problem of divergent national interpretations on EU patent law. It still remains to be seen however how well the patent system will adjust and encounter the substantive and procedural challenges posed by the European patent law system.

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292 Plomer, *supra* note 60, 131.
294 Hellstadius, *supra* note 50, 150.
295 The Agreement was signed by 25 EU Member States on 19 February 2013. It will need to be ratified by at least 13 states, including France, Germany and the United Kingdom to enter into force.
296 Hellstadius, *supra* note 50, 150-150. The Unitary Patent route (i.e., a European patent with unitary effect within the EU) will be an option additional to European patents within the EPC-system and national patents. The EPC becomes substantive law via the (patent) regulation and UPC Agreement. After the EPO decision of a grant, a unitary effect for the territory of the participating states will be given upon the patentee’s request. The system presupposes only procedural and administrative amendments to
future of the unitary patent system is uncertain following the U.K.’s 23 June 2016 membership referendum with 52 percent voting to leave.

Whatever challenges the new unitary patent system will present, there will still a need to keep the patent law morality provision confined within its indicated limits; otherwise it will be difficult to justify it from a strictly legal point of view. In particular, it appears reasonable to voice the concern that the alteration of the established patent principles risks becoming detrimental for the patent system because the assessment of the morality exclusion renders it difficult to accommodate against the background of the system’s functions.

There might be certain benefits involved in keeping moral limitations to the acceptable minimum standard already set by the pharmaceutical regulatory system. However, this does not mean that the patent examination procedure should be purely technical and/or insensitive towards ethical considerations. It is evident that patenting regime on hESCs has the power to control and stimulate or suppress and delay innovation on regenerative therapies. High quality patents also have the potential to act as facilitators in the translational process. They indeed have a vital role in ensuring that the patent system supports an adequate balance between the interest of patent holders and the public at large benefitting from the invention. In particular, it has been argued that the incentive function of the patent system necessitates that patent protection be available to promote investment in product development, despite there being no certainty that such investments will be profitable.

There is a concern that if the European patent system maintains a restrictive or irregular application of the moral exception in context of patents on novel health technologies (such as hESC innovations), the potential benefits of such technologies are at risk of becoming lost to Europe. If patent protection is not available in the EU, the inventor may be able to obtain it elsewhere in some of the major countries for stem cell research (e.g. China, Japan, Singapore, Israel or the U.S.). That would not optimally promote the internal

the substantive law. However, this seems quite optimistic, as a number of outstanding issues still remain to be resolved, in addition to established national variations.

Hellstadius, op.cit., 412.

Hellstadius has argued that broadening of the scope of the morality exclusion by including more factors to be assessed under a wider umbrella, may lead to a situation which the patent system is not able to handle simply due to its limited possibilities to practically affect the actual exploitation of inventions in society.

Under the current system, there is by default an obligation for examiners to address morality under Article 53(a) of the EPC.


Hellstadius, supra note 50, 34.

Barfoot, et al., supra note 84, 5 report that the USA and China produced the highest volume of stem cell publications in 2008-2012. The number of Japanese and Singaporean publications was also relatively high in relation to the global average (Singapore representing 1.8 times the global level, the USA (1.61
market objectives that constitute the underpinning rational of the Biotech Patent Directive. Overly restrictive and irregular application of the moral exception in hESC patents, in breach of the internal market objectives and the respect of plurality of European values, risks rendering Europe’s legislative landscape unattractive and discouraging for investments that may yield new technological advancements in healthcare.

times the global level), Japan (1.53 times the global level), and Israel (1.52 times the global level). Interestingly, Italy which is the most country in terms of hESC research had a very high relative publication rate (1.65 times the global level). In Barfoot, et al.’s study “relative activity for a specific year is calculated as: the proportion of country X’s publications that are stem cell research in that year divided by the proportion of total world publications that are stem cell research in the same year. A value of 1.00 indicates that the country’s stem cell research effort corresponds to the world average.”
5 Dimensions of dignity in translational research

5.1 Dignity as empowerment and constraint

The notion of human dignity often appears as a crucial perspective in any discussion of human rights in terms of ATMPs. Being an unavoidable concept perspective does not make it unambiguous, however. First of all, the relationship between human dignity and human rights is both disputed and unclear. Dignity provides the basis for human rights in the Universal Declaration on Human Rights (1948). Likewise dignity might be perceived as a right itself, as in the Hungarian Constitution. Dignity might also serve as an interpretative value in a human rights scheme, a value that may influence the interpretation of other rights. This perspective suggests that human dignity may be best perceived as an ethical value; in this sense, it may function as a legitimate reason to restrict the use of certain types of novel health technologies or even restrict the exercise of rights.

Brownsword has identified two versions of dignity: dignity as empowerment that is associated with human rights and dignity as constraint that restricts certain applications of biomedical technology. Dignity as empowerment rests on the idea that everyone possesses an inherent dignity that constitutes the foundation of inalienable human rights (such as the autonomy of an individual).

Whilst dignity as constraint means that human dignity and fundamental human rights must be safeguarded and hence science (such as biomedical sciences) should develop with respect for these important values and constraints should be applied to protect human dignity. Human dignity as empowerment can be seen as one of the foundational ideas in the Universal Declaration of Human Rights, as well as the Covenants on Economic, Social and Cultural Rights (1966) and on Civil and Political Rights (1966). Human dignity as a constraint has developed in contemporary bioethics and its influence can be seen in the Biomedicine Convention (1997), the UNESCO Universal Declaration on the Human Genome and Human Rights (1997), and it is also expressed in Recital 16 of the Biotech Patent Directive (1998).

Research on hESC-based ATMPs elicits viable examples of different dimensions of dignity and the role of dignity as empowerment and as a constraint. First, origin of the primary material (hESCs) raises the question of respect for human life i.e. whether an in vitro embryo can possess full personhood and be considered as a potential human being.
that possesses human dignity and has a right to life pursuant to Article 2 of ECHR and whose life should be protected from the moment of conception. Approaches to this question range from considering a research embryo as biological risk waste to perceiving it as a potential human being with full personhood status that should have the same rights as live-born individuals. Second, the hESC research triggers the question of how freedom of research should be balanced against the dignified treatment of research embryos and, more specifically, whether and how freedom of research can be limited if research embryos are perceived to possess human dignity. Third, the research on materials of human origin raised questions about the rights of the human tissue donor. Donation of human tissues triggers among other things questions about individual autonomy and respect of privacy type of right, such as the right to decide on the donation of embryonic tissue for research purposes and the right to have one’s privacy protected as donating the tissue involves sensitive personal data (i.e., genetic information on the donor). And finally, it raises issues relating to the need to relieve human suffering, respect for life and the dignity of the patient needing the treatment; the need for protection of public health; as well as questions about justice and beneficence (i.e., access to health and allocation of scarce resources). When balancing between these interests and justifying specific limitations, they should be proportional to the potential benefits a specific action that is limited may confer.

5.2 Impact of the strongly ’dignity-oriented’ Biomedicine Convention

Disagreement about dignity is not limited to questions regarding its relationship with human rights. There is no definitive consensus about what dignity means. Furthermore, the controversy surrounding the legal status of embryos relates to another problematic aspect of dignity: there is no agreement on who is entitled to dignity – this could be the human individual, or the human species. Dignity might also apply to biological entities that are not autonomous humans.309 Depending on the perception of dignity, one may talk about the dignity of the severely incapacitated, embryos, cadavers, etc. The Biomedicine Convention and its Protocols constitute the most important convention in the EEA regulating the field of biomedicine. The Convention sets out the minimum level of protection in medical and biological applications, but it does not prevent the Member States from providing a broader scope of protection.310 The Biomedicine Convention draws attention to some of these tensions and extends the human dignity to

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309 O’Connell, et al., supra note 233, 64.
310 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Article 27: “None of the provisions of this Convention shall be interpreted as limiting or otherwise affecting the possibility for a Party to grant a wider measure of protection with regard to the application of biology and medicine than is stipulated in this Convention.”
potential humans such as embryos as members of human species by highlighting the collective and individual notion of dignity.

The prevailing moral perceptions of the notion of “human dignity” have evolved in course of the novel scientific advancements and opportunities that have also simultaneously posed new challenges to the perception of different forms of life. Human dignity is perceived as a universal, inalienable source of human rights in international human rights instruments. The UNESCO’s Universal Declaration of the Human Genome and Human Rights (1997) with related instruments, the Biomedicine Convention and the Charter of Fundamental Rights included in the Constitution for Europe, all rely on the primacy of human dignity over the interests of scientific research and technological innovation. Article 2 of the Biomedicine Convention states that: “The interests and welfare of the human being shall prevail over the sole interest of society or science.” In addition, when it comes to the dignity and protection of clinical trial subjects, Recital 1 of the Clinical Trials Regulation requires that:

[i]n a clinical trial the rights, safety, dignity and well-being of subjects should be protected and the data generated should be reliable and robust. The interests of the subjects should always take priority over all other interests.

Also Recital 8 of the ATMP Regulation refers to respect of fundamental rights and observation of the principles reflected in the Charter of Fundamental Rights of the EU and the Biomedicine Convention. Yet, no more specific references are made to human dignity in the ATMP Regulation. Whilst the parent directive of EUCTDs (Directive 2004/23/EC) refers to the Charter and the Biomedicine Convention in its Recital 22 and to dignity in its Recital 16 that requiring that dignity of a deceased donor must be respected.

Like the Biomedicine Convention, the Charter of Fundamental Rights of the EU represents an update of human rights in the light of changes in society and scientific and technological developments. However, it should be noted that none of these legal instruments has provided an exact definition of the term human dignity. The text of the ECHR, unlike the Biomedicine Convention, does not explicitly mention the term dignity. Only Protocol 13 has a preambular reference to this notion. Despite this, ECtHR has increasingly incorporated dignity as a value in its judgments and individual opinions over recent decades. As for dignity in the Biomedicine Convention, Article 1 of the Biomedicine Convention states that:

“[p]arties to this Convention shall protect dignity and identity of all human beings and guarantee everyone, without discrimination, respect to their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine.”

311 Agovic, supra note 54, 263-266.
312 Furthermore, Recital 27 requires that “[h]uman dignity and the right to the integrity of the person are recognised in the Charter of Fundamental Rights of the European Union (the ‘Charter’). In particular, the Charter requires that any intervention in the field of biology and medicine cannot be performed without free and informed consent of the person concerned”.
313 Roscam Abbing, supra note 128, 20-21.
314 O’Connell, et al., supra note 233, 66.
Interestingly, origins of this article can be found in Kantian and Stoic philosophies, as well as in the French revolution, which promoted and popularised the idea of human dignity.\textsuperscript{315} Furthermore, the preamble to the Biomedicine Convention emphasises the need to prevent misuse in biotechnology which may result in acts that endanger human dignity, and requires the Member States to “[t]ake such measures as are necessary to safeguard human dignity and the fundamental rights and freedoms of the individual with regard to application of biology and medicine.” Furthermore, the explanatory report to the Biomedicine Convention perceives the concept of human dignity as an essential value to be upheld.\textsuperscript{316} According to Raimo Lahti, the partial importance of the Biomedicine Convention and its Protocols is that they provide even more detailed priority and assessment norms for conflicting constitutional and human rights principles.\textsuperscript{317} While the United Nation’s previous human rights instruments ascribe the right to human dignity to living persons, the Biomedicine Convention appears to extend human dignity to potential humans such as embryos as members of the human species.\textsuperscript{318} According to the Explanatory report to the Biomedicine Convention, the initial intention of the drafters was to extend the protection of human dignity to cover risks related to genetic research and its applications not only to living human individuals, but society and the human species itself. It is stated in the Explanatory report to the Biomedicine Convention that “[i]t is not the individual or society that may be at risk but the human species itself.”

One might also ponder whether the Biomedicine Convention represents an explicit step in pronouncing a common European consensus on human dignity. However, very irregular ratification of the Biomedicine Convention makes it very difficult to demonstrate that it represents such a view.\textsuperscript{319} Even if it is very hard to argue that the Biomedicine Convention expresses a pan-European consensus on human dignity, the dignity orientation still seems very strong in the Biomedicine Convention.\textsuperscript{320} The invocation of human dignity as a restriction in the Biomedicine Convention has also provoked some significant criticism. Among others, Susan Millns perceives the reliance on dignity as “remarkable” and “fuzzy”,\textsuperscript{321} whereas Gilbert Hottois has argued that the Biomedicine Convention contains “techno-scientophobic” suggestions and enshrines value judgments that are not universally accepted.\textsuperscript{322}

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\textsuperscript{315} Agovic, supra note 54, 265.
\textsuperscript{317} Lahti, supra note 261.
\textsuperscript{318} Agovic, supra note 54, 265.
\textsuperscript{319} By September 2015, only 29 of 47 Council of Europe contracting states had ratified the Biomedicine Convention.
\textsuperscript{320} O’Connell, et al., supra note 233, 66.
\end{flushleft}
Despite the criticism surrounding the notion of dignity as a constraint as stipulated in the Biomedicine Convention, it has still influenced the national laws of the Member States regulating embryo research. For instance, Raimo Lahti has claimed that the special emphasis on the human rights stipulated in Article 1 of the Biomedicine Convention in which “protection of humans” is paralleled with “protection of human beings” indicates some type of change in the existing priority rankings in the prevailing ideas of constitutional and human right norms in Finland. More specifically, the emphasis on protection of human beings seems to represent some change in the protected values as, according to Lahti, it may be understood as “a reason for increased legal protection of the human embryo”.

To illustrate this, the threat of imprisonment for violations against fetuses, embryos and the human genome was incorporated into the Finnish Penal Code. Furthermore, it has also been important to investigate how the use of SCNT techniques should be regulated subsequent to the ratification of the Biomedicine Convention. As a starting-point, Article 18.1 of the Biomedicine Convention emphasises the need to protect embryos in research settings by stating that “Where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo,” whereas Article 18.2 of the Biomedicine Convention bans creation of embryos for research purposes.

In his Concurring Opinion in the ECtHR’s Parillo v. Italy case, Judge Pinto de Albuquerque points out that this provision affirms the application of the subsidiarity principle by establishing that the primary legal parameter to consider is the domestic law of the contracting state in question. According to his interpretation of the provision, paragraph 18.1 establishes a mandatory legal status “that must be secured to the embryo, which must benefit from “adequate protection”. Therefore, he argues that

“The use of embryos for scientific purposes must not be assessed on a casuistic basis, but subjected to a principled evaluation of the “adequateness” of the protection provided to the embryo, according to the European legal parameter.”

As the Biomedicine Convention complements the ECHR in the field of biomedicine and genetic science, Judge Pinto de Albuquerque has noted that two consequences follow from this. First, the ECtHR is the ultimate interpreter and guarantor of the rights, freedoms and obligations set out in the Biomedicine Convention (Article 29 of the Biomedicine Convention) and consequently, the “adequateness” of the protection provided to the embryo, especially regarding genetic engineering techniques contrary to

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323 Lahti, supra note 261.
325 Concurring Opinion of Judge Pinto de Albuquerque in Parrillo v. Italy (App. no. 46470/11), 27 August 2015, at para 24.
human dignity. Second, Judge Pinto de Albuquerque’s view is that the ratification of the Biomedicine Convention and its Protocols by a large number of contracting states is a strong indication that a growing European consensus has been built around its provisions. However, it appears quite difficult to agree with his latter perspective as, since the adaption of the Biomedicine Convention in 1999, only 29 of the 47 Council of Europe member states (that are party to the ECHR) have ratified it thus far. In particular, there is no consensus regarding Article 18.2 of the Biomedicine Convention.

This problematic provision has resulted in divergent ratification approaches among the Council of Europe’s Member States. When it comes to the impact of Article 18.2 on national regulations, in Finland, for instance, therapeutic cloning is allowed, but Finland has not established a reservation as stipulated in the Article. Accordingly, only reproductive cloning is prohibited in Finland. Hence, the Finnish legislation has not been clarified in that respect. In contrast, Sweden deemed it necessary to make a reservation in Article 18.2 upon the ratification of the Biomedicine Convention to allow for therapeutic cloning. It was made permissible by an amendment in law on 1 April 2005, in which legislation was amended to cover research on ova and the results of somatic cell nuclear transfer. Semantically, the notion of “human being” seems to be broader than the concept of “human”; hence, it may cover earlier stages of a human life in which the human being is not an independent legal entity, i.e., an individual, in addition to the type of “human” that is a legal subject. If a live-born individual human can be seen as a legal subject, it is still unclear that when an embryo may possess so much human dignity than it can be considered as a human being on which that dignity also may confer rights.

Human dignity is also very frequently mentioned as a criterion for evaluating the legal status of the human embryo in some of the EU Member States’ legislations. For instance, many European countries (such as France, Germany, the Netherlands, Spain, Italy, Austria and Ireland) refer to human dignity in their legislative texts, albeit with different connotations. Among others, Portugal and Spain set out to safeguard human dignity in the context of biomedical research and some IVF practices. Likewise, the notion of human dignity appears in Estonian, Finnish, Swedish, and Swiss embryo research policies that prohibit abusing or damaging the embryo with the purpose of safeguarding its dignity. Furthermore, the EGE has found the principle of respect for

327 He further points out that the above-mentioned problem of the distinction between “therapeutic” techniques and techniques aiming at the “enhancement of normal characteristics” is not always apparent only increases the need for careful oversight by the ECtHR.
328 The Convention (ETS no. 164) was adopted on 4 April 1997 in Oviedo, Spain, and entered into force on 1 December 1999.
329 Proposition p. HE 27/II.
330 Walin, supra note 96, 11-13. See also Lahti, supra note 97, 257.
331 See e.g., Knoppers, et al., supra note 34, 36–43.
333 Estonia, Embryo Protection and Artificial Fertilisation Act (1997); Finland, Medical Research Act, no. 488/1999 (1999); Sweden, Act 1991:115 on Measures for Purposes of Research and Treatment Involving
human dignity to be a fundamental ethical principle governing stem cell research. A similar position has been adopted in the EU’s Sixth and Seventh Framework Programmes, in which research projects (including stem cell research) must be conducted in compliance with fundamental ethical principles, including the protection of human dignity. It is also noteworthy that the European Commission has maintained its position not to finance research projects that involve destruction of embryos under the Seventh Framework Programme and Horizon 2020.

Despite the notion of protection of human dignity often being mentioned in the national laws governing biomedical research in the EU Member States, statements by the EGE and EU research funding policies, these political and legal instruments fail to specify how exactly the concept of human dignity should be understood or applied in the hESC research context. Furthermore, the ECtHR has not been able provide a uniform European interpretation of how respect for human dignity translates into respect for embryonic life. Instead, the ECtHR has acknowledged the great diversity of national legal and moral norms and perceptions regarding protection of human embryos and human dignity. It has shifted the final decision-making power to them by granting a wide margin of appreciation to its contracting states in important value-choice questions.

5.3 Dignity as an amorphous universal concept

Differences over the relationship between human dignity and human rights, the meaning of human dignity, and the subject of human dignity make universal consensus on human dignity impracticable. The concept of human dignity may work best as a universal declarative principle in international conventions where parties are usually states. It is therefore not surprising that some commentators such as Walin have argued that the concept of human dignity may work as a universal concept if it is left undetermined. As we saw, there are distinct national differences in how human dignity should be perceived. The lack of a specific meaning seems very problematic, as some
commentators deem that this concept risks becoming hopelessly nebulous and too amorphous to be useful or being interpreted so disparately in different circumstances or contexts. Liisa Nieminen has pointed out that the concept of human dignity appears to have produced different content in different circumstances or contexts.\textsuperscript{339} The absence of a generally agreed meaning has also been perceived to be problematic as it may be misused as a conversation stopper in moral debate.\textsuperscript{340}

Furthermore, despite harmonisation attempts within the EU, patenting of pluripotent hESC innovations is still a controversial matter that has resulted in diverging regulatory approaches. However, the EGE has specified a number of fundamental values and principles common to all EU Member States that should guide the EPO’s decision-making process for patenting innovations involving hESCs. Those common principles include 1) respect for human life/dignity; 2) the relief of human suffering; 3) justice and beneficence; 4) freedom of research; 5) individual autonomy; and 6) proportionality.\textsuperscript{341} However, the EGE does not further specify the origin of these core values and it also fails to provide any further reasoning for these principles or values. Yet the EPO recognises a certain hierarchy between these principles by asserting: “\textit{amongst the fundamental ethical principles that ought to guide this ethical evaluation, priority should be given to the principle of the respect due to human life}...”\textsuperscript{342}

The EGE does not further explain why ‘the principle of the respect due to human life’ should be given the highest priority or whether that principle has priority over other core principles in each and every case.\textsuperscript{343} However, no further clarification is provided on whether \textit{the principle of the respect due to human life} should extend to cover all forms of life, even potential human beings; more specifically, whether the lives of potential human beings should be valued as high as the well-being of a living individual with full personhood status. The EGE also refers to the principle of non-commercialisation of the human body that is not included in the EGE’s listing of core values. The EGE has stated that this principle has its origin in the Charter of Fundamental Human Rights\textsuperscript{344} and the Biomedicine Convention, which prohibit profit-

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\item[\textsuperscript{340}] Agovic, \textit{supra} note 54, 257.
\item[\textsuperscript{341}] These common principles are mentioned in European Group on Ethics in Science and New Technologies to the European Commission (EGE), Ethical Aspects of Patenting Inventions Involving Human Stem Cells Opinion No 12, 2 February 2010.
\item[\textsuperscript{342}] European Group on Ethics in Science and New Technologies to the European Commission (EGE), Ethical Aspects of Patenting Inventions Involving Human Stem Cells Opinion No 12, 2 February 2010.
\item[\textsuperscript{344}] Article 3 of the Charter of Fundamental Rights states: “1. Everyone has the right to respect for his or her physical and mental integrity. 2. In the fields of medicine and biology, the following must be respected in particular: the free and informed consent of the person concerned, according to the procedures laid down by law, the prohibition of eugenic practices, in particular those aiming at the
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making activities from human bodily parts. More specifically, it is stated in Article 2 of the Biomedicine Convention that “[t]he human body and its parts shall not, as such, give rise to financial gain.”

We do not know with certainty how the European regulatory landscape for governance of novel health technologies such as hESC-based ATMPs will develop. However, it appears quite likely that if the current trends endure they will result in a greater reliance on human rights norms in the field of biomedicine. The hESC-patenting regime has been forced to address challenges arising out of “pro-life activism”, and the normative conflicts that arise where patenting norms and human rights norms encounter each other. Recital 16 of the Biotech Patent Directive emphasises the importance of the dignity and integrity of the person and affirms that the human body as such cannot be a patentable subject matter. Strong discourses regarding human rights and ethics (especially human dignity and the Judeo-Christian notion of integrity of the human body as an “Imago Dei”) can be found in some interpretations of the scope of the morality clause of the Biotech Patent Directive. The Brüstle case in particular represents an interesting example of complexity of these discourses. In Brüstle, Advocate General Yves Bot arguably construed an oppositional duality as between the markets approach and ethics by opposing “different philosophies and religions and the continual questioning of science” and by opposing “the economic functioning of the market and competition” on the one hand, and “the cost of sacrificing fundamental values of the Union” on the other. This kind of oppositional duality is rather unusual in official EU discourse. For example, the EGE tends to avoid placing either the science or markets perspective in opposition to ethics, usually seeking to reconstruct a mutually supportive relationship between these interests.

5.4 The penal code setting the ultimate boundaries for the freedom of science

In light of Wintgen’s legisprudential approach, the very inconsistent application and amorphous use of human dignity as a constraint may raise concerns about impaired normative coherence. The legisprudential principle of principle of alternativity assuming that individuals are initially free and capable of rationally organising their freedom in a context with others means that paternalistic criminalisations in embryo research raise particular concerns. Aligning freedom of science, criminal law, human

348 Please refer to Section 3.4.2. of this study regarding application of Wintgen’s legisprudential principles of 1) coherence; 2) alternativity; 3) temporality; as well as 4) necessity and normative density.
dignity and modern biotechnology is difficult. New criminalisations in the biotechnology sector require the legislator to proceed with the greatest diligence. It is especially important to specify what exactly is being restricted by means of criminal law. As to the effectiveness of the preventive function of criminal law, it has been argued that the intention to prevent activities that involve merely undetermined risk and injury to “legal goods” distracts criminal law from the harm principle. Consequently, criminal law risks becoming just a punitive means of managing risks associated with novel health technologies, and thus may transform into a kind of “administrative law”. Carlos Maria Romeo-Casabona has argued that if criminal law proceeds this way, it is open to losing its preventive effect and will be reduced to a merely symbolic function, through which it renounces its authenticity. Whilst Sakari Melander has addressed a relevant concern that in using human dignity as a principle for criminalisation, the risk of paternalistic criminalisations is always present.

Criminalisations in the field of modern biotechnology also seem questionable given the legisprudential principle of the necessity of normative density, in accordance with which rules should not automatically contain sanctions as the strongest from of normative density. Hence, if sanctions are involved, this requires a specific and supplementary justification of why weaker (non-coercive, but persuasive) alternatives are not used. Tarmo Miettinen has specified the elements of the freedom of science as follows: 1) the right to conduct research; 2) the right to choose one’s own research topic and methodology, 3) the right to information needed for the research; 4) and the right to decide on the publication of research results. According to Walin, the right to choose one’s own research topic and methodology seems most interesting for the stem cell research community. However, the responsibility of the researcher constitutes a counterbalance against that freedom. Miettinen has asserted that the responsibility of the researcher covers the relevance of the study, the liability to comply with the ethical code of conduct in science, and to respect others’ rights and the environment. As an example from Finnish constitutional law, Walin raises an important question with respect to the limitations of the freedom of science as a constitutional right granted by the Finnish Act on Research, section 11 § that also contains a prohibition on conducting embryo research without the permission of the National Supervisory Authority for Welfare and Health, and Section 13 of the Finnish Act on Research generally imposes restrictions on research on embryos as follows:

“[t]he production of embryos exclusively for the purpose of research shall be forbidden. Embryos that have been used for research may not be implanted in a human body or be kept alive for longer

353 Walin, supra note 96, 54.
than 14 days from their formation, not including any time during which they have been kept frozen. Research may use embryos that have been stored for up to 15 years, after which the embryos must be destroyed."

This prohibition may derive from Article 18.1 in the Biomedicine Convention that requires adequate protection for embryos. Section 15 of the Finnish Act on Research mandates that:

"[r]esearch on embryos and gametes for the purpose of developing procedures for modifying hereditary properties shall be prohibited, unless the research is for the purpose of curing or preventing a serious hereditary disease."

This prohibition derives from Article 13 of the Biomedicine Convention. Walin has specified that this is one of those Articles from which derogations cannot be made. The penalty for unlawful intervention on the embryo is imposed under Chapter 22, Section 3, of the Finnish Penal Code and the penalty for unlawful intervention on the genome under its Chapter 22, Section 4. From the perspective of the freedom of science, Walin finds Section 4 of the Chapter 22 of the Finnish Penal Code on unlawful manipulation of genetic inheritance the most problematic. This prohibits the cloning of a human, the generation of a human by combining embryos or the generation of a human by combining human germ cells and animal genetic material on pain of two years’ imprisonment.355

Walin especially directs her criticism towards the scarcity of argument in preparatory materials with respect to the said prohibitions, in which it has been only stated that some actions are against human dignity in the sense that they should be criminalised.356 That type of restriction of the freedom of science (Section 16 in the Constitution of Finland) may restrict the researcher’s right to work and to engage in commercial activity that is guaranteed in Section 18 in the Constitution of Finland. Walin points out that when evaluated purely on scientific criteria, the said experiments might be relevant and their prohibition could hinder a researcher from making his/her living in the best possible manner.357 It appears very problematic that the concept of “human” has been left undetermined in the Finnish Act on Research. The prohibition of cloning is also ambiguous at best.358 Under the Finnish law it apparently covers merely reproductive cloning. Walin has claimed that a “human” refers to a born, living human individual who has reached legal personhood status.359 Walin’s reasoning seems to be consistent with the ECtHR case law.360

355 Walin, supra note 96, 53.
356 Walin, supra note 96, 54.
357 Ibid.
359 Walin, supra note 96, 55.
However, it should be noted these liberalistic perspectives have not gained universal acceptance. For instance, Resolutions of the Congresses of the International Association of Penal Law have adopted a more restrictive approach when it comes to boundaries of freedom of science and criminal law in relation to modern bio-medical techniques. 361 Section II 5.2 of Resolution of the 14th Congress of the International Association of Penal Law acknowledges that the basis and scope of legal protection of the unimplanted human embryo largely depends on its moral status. Furthermore, it is stated that irrespective of the lack of a universal consensus on its moral status

“there is unanimity that -whatever may be said of possible restrictions- in principle human life is worthy of being protected from the very moment of conjugation of gametes, without regard to whether the early embryo has to be considered a "person" or as a being possessing its own fundamental rights.”362

Yet it seems that no universal consensus exists on the scope of the protection that should be granted to such research embryos. However, Resolution of the 14th Congress of the International Association of Penal Law has chosen to deny “[a]ny sort of "ownership" or property rights of gamete donors in embryos”. According to the Resolution, this prohibition does not exclude the possibility of getting the consent of the donor of the embryo to authorise research on that embryo.363

As the notion of human dignity seems open to substantial legal manipulation depending on the circumstances in which it is used, it is important when the human dignity argument is invoked that it must be also clearly stated where exactly the threat to human dignity relates to the action that is being restricted.364 Limitations on freedom of science should be proportional when they are balanced against the potential benefits of the research. In the light of the legisprudential principle of temporality, limitations on freedom of science must be justified as “on time”. Walin perceives human dignity as a concept whose content differs not just in space, but also in time. She has pointed out that:

(App.53924/00, Judgment of the Grand Chamber of 8 July 2004; (2005) 40 EHRR 259). These ECtHR judgments indicate that it is neither desirable nor even possible to answer the abstract question of whether the unborn child is a person for the purposes of article 2 of the ECHR. The ECtHR’s decisions mean that a Contracting State enjoys a margin of appreciation to decide under its domestic law when the right to life begins.

362 Interestingly, Section II of Resolution of the 14th Congress of the International Association of Penal Law touched upon the boundaries of the freedom of science in the context of modern bio-medical techniques and criminal law. Among other things, the Resolution points out that regulations and sanctions ranging up to penal provisions may be found necessary to deal with the prohibition on producing embryos for purposes other than human procreation. The Resolution also states that “experiments aimed at developing hybrids and chimera creatures by means of karyogamy of human cells with those of animals must be criminalised.” Resolutions of the Congresses of the International Association of Penal Law (1926-2004) Available at: http://www.penal.org/sites/default/files/files/NEP%2021%20anglais.pdf. Accessed 21 June 2016.


Walin; supra note 338, 254.
“[w]henever human dignity is invoked in order to restrict individual rights, or to impose new obligations in individuals, a level of conceptual non-ambiguity is required such that the use of the concept has to be limited to a defined geographical area over a given period of time.”

As far as human dignity is concerned in the ATMP field, there is an obvious need for regulators to engage in new and innovative legislative approaches, as they are expected to create facilitating and proactive legislation in cooperation with all stakeholders. Greater reliance on legisprudential approach would permit stepping away from paternalistic criminalisations, as it significantly relies on non-coercive, flexible, self-regulatory measures (such as reliance on guidelines on research ethics and ethics committees’ interpretations thereof in light of the most recent scientific understanding) that can smoothly adjust to varying conditions over time and place. The notion of human dignity is a noble concept; however, it is most valuable and useful where it deals with the promotion of the well-being of living human persons. To protect and promote human dignity, the regulators should focus more on safeguarding the human dignity of severely ill patients awaiting novel therapies than on protecting the human dignity of research embryos.

365 Ibid.
366 Mansnérus, supra note 34, 164.
6 Stakeholder participation influencing the legislative landscape of ATMPs

Upon the emergence of the European ATMP scene, the industry representatives and policy-makers stated that there was an urgent need for EU-wide legislation to safeguard the interests of public health and the security of patients. The industry lobbied for an EU-wide regulatory scene for ATMPs, as the EU is exclusively competent for economic perspectives (health care services cannot be automatically subordinated to the internal market). However, in the case of “common safety concerns in public health”, both the EU and its Member States are authorised to act, but the Member States may take action only if the EU does not act or decides not to take action. The proportionality and subsidiary principles mean that the “common safety concerns in public health in an area in which application of existing EU legislation and additional national measures have proven insufficient”, were the only backdoor for the European Commission to regulate the ATMPs. Concerns regarding the apparent lack of regulatory governance in this field were raised and a need for a new harmonised regulation was widely but not unanimously acknowledged. The industry particularly argued that the nonexistence of EU-wide legislation of ATMPs risks harming patients who are denied the potential benefits of these regenerative medicines. EuropaBio supported harmonised regulation, as it was anticipated to create predictability and help companies make informed investment decisions, facilitating their investment in the R&D of ATMPs. Harmonised regulation would also be more cost efficient, as it would reduce the expenses arising from meeting diverse quality, safety, efficiency, and marketing requirements.

Subsequently, a working group consisting of specialists in the fields of organs, tissues and cells convened a meeting to discuss the human cells and tissues regulatory regime in Europe in June 2000. A survey based on questionnaire-guided interviews on the existing regulation in the Member States disclosed a number of disagreements on some ethical aspects, a great deal of similarities regarding safety issues as well as an evident lack of regulation in many Member States. It was concluded that there is an urgent need for a single EU regulation on the quality, safety, traceability and vigilance of human cells and tissues. Furthermore, they outlined a preliminary framework in

367 Pirnay, et al., supra note 22, 554. See also Mansnérus, supra note 22, 431.
368 Pirnay, et al., op. cit., 554.
370 Pirnay, et al., supra note 22, 538. See also Mansnérus, supra note 22, 431.
371 Pirnay, et al., op. cit., 534. See also Geesink, supra note 170 for a general overview of the industry hearings.
372 Kent, et al. supra note 177, 43. See also Pirnay, et al., op. cit., 538.
373 Pirnay, et al., op. cit., 535. Reference is made to Working Group’s written reports from the “Meeting on the Therapeutic Use of Human Organs and Tissues” held in Porto, on 14 -16 June 2000.
374 Pirnay, et al., op. cit., 535, 529, (Table 1., section 2.4).
which an umbrella directive would set out general principles, whereas more detailed appendices would address some particular issues (such as quality and safety). In addition, they identified a need for standards regulating each type of tissue or cell.\(^{375}\) The working group also emphasised that the shortage of organs and tissues should be taken into consideration in enacting new legislation, and no legislation limiting the availability of living or cadaver donors should be passed.\(^{376}\) Thereafter, health ministers of the Member States reached a similar outcome by supporting the idea of a directive that imposes requirements for high safety and quality standards for the procurement, testing, processing, storage, and distribution of human tissues and cells to ensure the safety of the patients.\(^{377}\)

An evaluation study conducted by DG Sanco in 2003 reported that as TEPs differ in many respects from medical devices and pharmaceuticals, they are not appropriately covered by the existing EU legislative framework.\(^{378}\) TEPs were actually clearly excluded from the scope of Medical Devices Directive and the Medicinal Products Directive (which covers GTMPs and CTMPs among other things, but leaves TEPs beyond of its scope).\(^{379}\) As the EUCTDs were drafted in the spirit of public health arguments (Article 152 of the Amsterdam Treaty), in contrast to the existing European Commission procedures regarding approximation of legislation relating to medical products, the EUCTDs do not have specifying rules for the marketing of cell human cell and tissue-based products and therapies as their primary objective.\(^{380}\) The impact assessment report the ATMP Regulation notes that the EUCTDs do not pursue an “internal market” objective. Efficiency criteria are not mentioned either.\(^{381}\) In this dual approach adapted by the European Commission, the EUCTDs were formed to encompass tissues and cells that are not a part of a biotechnological process and hence “substantially manipulated” (i.e., predominantly, “traditional transplants”), while the ATMP Regulation was created to cover products and therapies that are subject to biotech processes that necessitate both specific regulation and comprehensive harmonisation of requirements to accelerate their path to the EU market.\(^{382}\) Consequently, the degree of manipulation in this dual approach regulates whether a graft is classified as a traditional transplant or a commercial product. Generally speaking, ‘substantial manipulation’ means that the biological characteristics, functions,  

\(^{375}\) Pirnay, et al., *op.cit.*, 535, 529, (Table 1., section 2.5).

\(^{376}\) *Op.cit.*, 535, 529, (Table 1., section 2.8).


\(^{378}\) Bock, et al., *supra* note 77,3.


\(^{382}\) Pirnay, et al., *supra* note 22, 535.
or properties relevant for the therapeutic effect have been altered.\textsuperscript{383} Several stakeholders had raised a terminological issue about the significance of the concept ‘engineered’, arguing that it should be more exactly defined to avoid borderline problems with other cell-based products.\textsuperscript{384} The European Commission responded to these concerns by providing a definition that actually followed the FDA approach to defining non-substantial manipulations of TEPs.\textsuperscript{385} Certain manipulations of the cells and tissues were defined as not substantial. According to Annex 1 of the ATMP Regulation, these include (tissue) cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilisation, irradiation, cell separation, concentration or purification, filtering, freezing, cryopreservation, and vitrification.\textsuperscript{386} It seems that from the very beginning the European Commission had decided to leave TEPs beyond the scope of the EUCTDs and regulate them by the specific ATMP Regulation.\textsuperscript{387} This regulatory pathway leaving TEPs outside the scope of the EUCTDs resulted in an intentional regulatory gap.

To illustrate the emergence of a broader legislative landscape for ATMPs, the emergence of the Clinical Trials Regulation and the Biotech Patent Directive need to be discussed briefly. The Clinical Trials Regulation that was created to ensure consistency of clinical trials in the EU and to promote transparency to foster innovation affects the commercialisation landscape of ATMPs in the EU. Some questions that have arisen in connection with public consultations regarding the Clinical Trials Regulation will be briefly discussed in Section 6.3 below. Furthermore, the emergence of the Biotech Patent Directive, which has resulted in disharmonised implementations of the so-called morality clause (Article 6.2.c. in particular affecting the patentability of hESC based innovations) will be briefly discussed in Section 6.4 below.


\textsuperscript{384} Pirnay, et al., \textit{supra} note 22, 535-536.

\textsuperscript{385} Geesink, \textit{supra} note 170, 29. See also Pirnay \textit{op. cit.}, 535-536.

\textsuperscript{386} See also European Medicines Agency. \textit{Reflection paper on classification of advanced therapy medicinal products}, \textit{supra} note 70 for further details.

\textsuperscript{387} Pirnay, et al., \textit{supra} note 22, 538. See also Eucomed ATMP Backgrounder, \textit{supra} note 170,1 that refers to the regulatory gap.
6.1 EUCTDs – as an important step towards higher quality and safer use of cells and tissues of human origin for therapeutic purposes

The EUCTDs proposal drafted by DG Sanco in 2002 considered Article 152 of the Amsterdam Treaty, which required high standards of quality and safety to be set for substances of human origin. Furthermore, the Biomedicine Convention was taken into account. Many consultations also took place with technical specialists, representatives of the Member States and some relevant organisations active in the field. The EUCTDs proposal sets out requirements for the procurement, testing, processing, storage, and distribution of human tissues and cells intended for application in humans. The proposal declares that it would apply to all elements of the human body used for transplantation, excluding cells and tissues utilised as autografts within the same surgical procedure and autologous cells utilised for medicinal products.

Unlike EU Regulations, EU Directives constitute a minimum standard for the Member States, allowing them to maintain or introduce stricter protective measures to safeguard public health. As the EUCTDs were seen as predominantly technical directives setting EU-wide quality and safety standards, they avoided wider public debates. It should be noted that the existing formal impact assessment process applying to all major EU policies since 2005 has been mandatory. Thus, the impact assessment of the EUCTDs proposal was not comprehensive; assessment of its influence on SMEs was restricted. It was predicted that the EUCTDs requirements are likely to increase the expenses for starting materials utilised by SMEs; however, no specific provisions were envisioned for them.

The EUCTDs proposal was submitted to the European Parliament and the Council on 26 June 2002 and was processed via the standard legislative process in which the European Parliament together with the Council approves the EU legislation, whereas the European Commission is responsible for drafting and implementing it. Quality, safety and ethical concerns were the main topics of debate during a parliamentary

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389 EUCTDs Proposal, supra note 170, recital 13. See also Pirnay, et al., supra note 22, 536.
390 Among others, the following organisations were invited to stakeholder meetings: the European Association of Tissue Banks, the European Association of Musculoskeletal Transplantation, the European Eye Bank Association, the European Group for Bone Marrow Transplantation, the Donor Bone Marrow Association, the Eurodonor Foundation and the International Alliance of Patients’ Organizations. Eucomed medical technology, the European Federation of Pharmaceutical Industry Associations and Baxter BioScience were consulted as representatives of the industry.
392 EUCTDs Proposal, supra note 170, shows that no specific provisions have been envisaged in the proposal to accommodate needs of SMEs. See also Pirnay, et al., supra note 22, 530, (Table 1., section 3.7.).
393 Kent, et al., supra note 177, 49. Pirnay, et al., supra note 22, 536.
hearing in 2003, where representatives of the industry (Eucomed and EuropaBio), scientists, EU officials, non-governmental organisations, private blood banks, religious groups and bioethics organisations were present. The opinion of the European Parliament was forwarded to the European Commission on 10 April 2003. The majority of the amendment proposals addressed the need to strengthen the EUCTDs in ethical respects (for instance concerns were raised regarding the use of hESCs as a primary material, commercial uses of altruistically donated materials etc.). The possible relevance of these ethical perspectives notwithstanding, the European Commission could not incorporate them into the EUCTDs draft as ethical considerations are not covered by Article 152 the Amsterdam Treaty. An amended proposal was transmitted by the European Commission on 30 May 2003. Subsequent to the amendment proposals, the scope of the EUCTDs was extended to cover autologous cells to be used for medicinal products. In a common position adopted on 22 July 2003, the majority of rather technical considerations were approved, whereas the lack of an adequate legal basis meant that ethical amendment proposals were rejected.

Upon adoption of the parent directive of the EUCTDs, by the European Parliament and the Council in 31 March 2004, in the final version of the EUCTDs subsidiarity principle was applied to avoid ethical debate and to enable accommodation of national interests. Despite, the industry succeeded in lobbying for amendments to the EUCTDs to allow them to procure, store and process cells and tissues and to be qualified as biobanks, in some Member States it is still very difficult for commercial

394 Kent, et al., ibid.
397 In Article 2.b. of the initial EUCTDs Proposal, supra note 170, it was stated that this Directive does not apply to “autologous cells to be used for the manufacturing of medicinal products”. Whilst in the final version single surgical procedure remained as the only exeption for the use of autologous cells, Recital 8 states that “[ ]Tissues and cells used as an autologous graft (tissues removed and transplanted back to the same individual), within the same surgical procedure and without being subjected to any banking process, are also excluded from this Directive.”
actors to perform comprehensive biobanking activities.\textsuperscript{400} This is due to the reason that the subsidiarity principle allows the Member States to exceed the requirements of EUCTDs when implementing them into national law. Based on ethical arguments some Member States have imposed some further national requirements to prevent industry’s direct access to human cells and tissues.\textsuperscript{401} For instance, in Belgium only tissue banks exploited by a hospital can obtain direct access to human cells and tissues for allogeneic use.\textsuperscript{402} Consequently, SMEs access to primary material, which was the underlying objective of the EUCTDs, is not equally granted in all Member States.\textsuperscript{403} For instance, in some Member States companies cannot access primary material, unless they are registered as a biobanks. Some countries do not allow companies to act as biobanks. According to EuropaBio, this situation may lead to patients being denied promising novel therapies. Despite these issues, enactment of the EUCTDs was an important step towards higher quality and safer use of cells and tissues of human origin for therapeutic purposes.\textsuperscript{404}

6.2 ATMP Regulation – heavily lobbied by the industry whilst academia and public tissue establishment were underrepresented

Two public consultations lead by Directorate General for Enterprise and Industry (DG Enterprise) in 2002 and 2004 disclosed a non-consensus on whether there is a need for a specific TEP legislation or whether amendments to the existing EU legislation on medical devices or medical products would be more suitable.\textsuperscript{405} The EU officials and the EMA preferred using the existing regulatory framework for medical products that could be complemented by the framework for medical devices. A completely new legal framework for TEPs was strongly supported and heavily lobbied by the industry.\textsuperscript{406} Despite policymakers are required to consult all affected stakeholders, public institutions and academia appeared to have underestimated the scope and impact of this EU legislation and, hence they became underrepresented in the consultation process.\textsuperscript{407} While 117 tissue engineering companies from 14 Member States were actively involved in the consultation process, a very limited number of interviews were conducted with representatives from public hospitals and tissue establishments of U.K., Germany and France only.\textsuperscript{408} The participation and influence of the industry players in policymaking

\begin{footnotesize}
\bibitem{400} Pirnay, et al., supra note 22, 529. See also Mansnérs, supra note 22, 433.
\bibitem{401} Kent, et al., supra note 177, 53.
\bibitem{402} Pirnay, et al., supra note 22, 546. See also Mansnérs, supra note 22, 433.
\bibitem{403} EuropaBio Stakeholder Meeting Report, supra note 170, 6.
\bibitem{404} EurActiv, supra note 399. Pirnay, et al., supra note 22, 545. See also Mansnérs, supra note 22, 433.
\bibitem{405} Kent, et al., supra note 177, 49.
\bibitem{406} Pirnay, et al., supra note 22, 552. See also Mansnérs, supra note 22, 434.
\bibitem{407} EurActiv, supra note 399.
\bibitem{408} Bock, et al., supra note 74, 14.
\end{footnotesize}
process was very strong.\textsuperscript{409} The distinctiveness of the TEPs was especially emphasised by the industry actors that perceived TEPs as a heterogeneous class of medical products for which the existing regulation would be too restricted and costly, and predicted long marketing authorisation process times would impede the ability of SMEs and other industry actors to launch these innovative products to the market.\textsuperscript{410} As an outcome of the public consultations, a need for a specific legislative framework for TEPs was identified. The idea of a dual regulatory approach that takes the level of risk into consideration was supported; products and therapies that are subject to biotech processes should not be covered by the EU CTDs as TEPs were seen to require specific regulation and a comprehensive harmonisation of requirements to accelerate their path to the EU market.\textsuperscript{411}

Subsequent to the public consultations, the DG Enterprise provided a draft ATMP Regulation to bridge the regulatory gap as described in the DG JRC-IPTS evaluation studies.\textsuperscript{412} The main objectives of draft ATMP Regulation were to harmonise and facilitate access to the internal market and foster competitiveness whilst securing a high level of health protection.\textsuperscript{413} The DG Enterprise also addressed the free movement of products within the internal market (Article 95 of the Amsterdam Treaty). Provisions relating to production in accordance with GMP and compliance with marketing authorisation requirements and rules on post-marketing pharmacovigilance were included.\textsuperscript{414} It was emphasised in the impact assessment report of the ATMP Regulation that the GCP and GMP guidelines should be drafted in a close cooperation with all stakeholders and, especially with the industry.\textsuperscript{415} In addition, Eucomed pointed out that GMPs for medical products are not directly applicable to TEPs and hence, they need to be adapted. Especially, the European Commission’s proposal on the centralised marketing authorisation process was very positively welcomed by industry actors.\textsuperscript{416} Furthermore, the draft ATMP Regulation proposed reinforcement of requirements for risk management and traceability of cell, gene, and tissue-based treatments, and provided special incentives for SMEs developing ATMPs.\textsuperscript{417}

\textsuperscript{409} Pirnay, et al., \textit{supra} note 22, 540. See also Mansné rus, \textit{supra} note 22, 434.

\textsuperscript{410} Kent, et al., \textit{supra} note 177, 50.

\textsuperscript{411} Pirnay, et al., \textit{supra} note 22, 540.


\textsuperscript{413} European Union (2005) European Commission (DG Enterprise & Industry), \textit{op.cit.}


\textsuperscript{415} ATMP IA Report, \textit{supra} note 170, see section 4.1.6. \textit{“Advanced Therapies approach”}.


In 2005, the second evaluation study conducted by the DG JRC-IPTS identified and assessed the economic, social and environmental effects of the regulatory solutions presented in the draft ATMP Regulation. Its contents contributed to the official impact assessment report. While the draft ATMP Regulation was submitted for a further public consultation in May 2005, the European Commission decided to expand its scope to cover GTMPs and CTMPs, in addition to TEPs. Both the DG JRC-IPTS and the formal impact assessment report emphasised that the absence of a uniform EU legislation would result in different approaches across the EU as to the legal classification and marketing authorisation procedures of ATMPs. Such regulatory gap would hamper free movement of ATMPs within the internal market, deprive patients’ access to treatment regimens using ATMPs, and finally constitute hurdles for safeguarding a high level of public health protection in the Member States. Finally, lack of uniform regulation could impair the development of a robust tissue engineering field in the EU and adversely affect the EU competitiveness in that field. It was concluded in the impact assessment report that a uniform ATMP Regulation would be significantly beneficial for all stakeholders. Among other things it was predicted to provide legal clarity and certainty by harmonising quality and efficacy standards for ATMPs. That would ameliorate the competitiveness of SMEs and other actors and improve the confidence of patients and healthcare professionals.

The ATMP Regulation was processed via the standard co-decision procedure between the European Parliament and Council. Despite the wording of the ATMP Regulation was agreed at the first hearing, it raised some significant debate on ethical issues when it passed through the European Parliament. Especially, concerns regarding commercialisation of altruistic cell and tissue donations, integrity of the person and the inviolability of human dignity were discussed and lobbied. Also the status of hESC-based ATMPs was discussed. The European Parliament Committee on Legal Affairs (JURI) tried to exclude the hESCs-based ATMPs from the scope of the ATMP Regulation by arguing that:

“Legislation in force in Member States concerning the use of certain types of cells, such as embryonic stem cells, varies considerably. The regulation of advanced therapy medicinal products at Community level should not interfere with decisions made by Member States on whether to allow the use of any specific type of cells. It should also not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of or derived from these cells. Moreover, it is impossible to assess when, if ever, research on these cells will reach the stage at which commercial products made from these cells could be placed on the market. In order to respect the basic principles and the proper functioning of the internal market and to ensure legal certainty, this

418 Bock, supra note 74. ATMP IA Report, supra note 170, see section 2.2 “A disrupted internal market”.  
419 ATMP IA Report, see section 2.2. Pirnay, et al., supra note 22, 545. See also Mansnérus, supra note 22, 435.  
420 ATMP IA Report, see section 2.2.  
Regulation should apply only to products made of cells, for which marketing is feasible in the near future and which do not raise major controversies. Yet, the proposed amendment was not possible because it would have left hESC-based ATMPs unregulated (i.e. not covered by the mandatory quality and safety requirements). Consequently, the proposed ethical amendments were left outside the scope of the final dossier. The ethically neutral ATMP Regulation that entered into force on 30 December 2008 required that the existing ATMPs or such products under development to comply with its requirements by 30 December 2012 at the latest.

6.3 Clinical Trials Regulation – aiming at ensuring consistency of clinical trials in the EU and promoting transparency to foster innovation

The EU legislation on clinical trials has gone through some significant modifications during the last decade. These changes started in 2004 with the implementation of the Clinical Trials Directive and continued in 2005 with the publication of the Good Clinical Practice Directive (Directive 2005/28/EC). More recently the legislative landscape for clinical trials was updated by the Clinical Trials Regulation that is scheduled to become effective by October 2018 at the latest. The main objective of the Clinical Trials Directive is to ensure that: the rules for conducting clinical trials are consistent throughout the EU; and information is made publicly available on the authorisation, conduct, and results of each clinical trial carried out in the EU. The Clinical Trials Regulation also strives for increasing transparency of clinical trials in the EU, from the point of authorisation of the trials to the publication of the results. Hence it seeks to improve the availability of information to patients, caregivers and healthcare professionals on ongoing clinical trials. Transparency is also expected to foster
innovation and stimulate research. It is also predicted to help avoidance of unnecessary duplication of clinical trials, and repetition of trials that have been terminated due to major safety or efficacy concerns.\textsuperscript{428} The Clinical Trials Regulation will apply to interventional clinical trials on medicines once the Clinical Trial Regulation is in operation, and to all trials authorised under the previous Clinical Trials Directive and still ongoing three years after the Clinical Trials Regulation has entered into force. After the Clinical Trials Regulation has become effective, the Clinical Trials Regulation requires the EMA to develop and maintain a clinical trial portal and database to be used for the submission, authorisation and supervision of trials in the EU. Yet, authorisation and oversight of clinical trials remains the competence of EU Member States. The portal and database is purported to serve as source of public information on the clinical trial applications assessed, and all clinical trials conducted in the EU.\textsuperscript{429}

Article 82(1) of the Clinical Trials Regulation requires the EMA to draw up the functional specifications together with the time frame for their implementation, in collaboration with the Member States and European Commission. The EMA consulted on its proposals with EU Member States, the European Commission and stakeholders representing non-commercial and commercial clinical-trial sponsors, healthcare professionals and patient groups. To finalise the functional specifications, the EMA released a draft proposal for public consultation from 10 October to 31 October 2014. A total of 47 individuals and organisations submitted more than 500 comments.\textsuperscript{430} To get further perspectives on its proposals for implementing the transparency requirements, EMA released a draft documents for public consultation from 21 January to 18 February 2015.\textsuperscript{431} Over 80 different individuals and organisations submitted more than 1100 comments.\textsuperscript{432} Beyond comments of technical nature, concerns were raised


\textsuperscript{429}Ibid.


regarding unclear scope of the applicable exceptions to the publication requirements and protection of personal data in an automated system.

Under the Clinical Trials Regulation the information on all clinical trials must include the key features of the trial; details of treatment population and number of subjects; inclusion and exclusion criteria, main objectives and endpoints; the dates of the start and end of recruitment; substantial modifications made to protocol during the trial; the end date of the trial and, 12 months later, the summary of results and a lay summary. Furthermore, for clinical trials included in a marketing authorisation application in the EU, clinical study reports will also be published 30 days after the procedure for granting the marketing authorisation has been completed or the applicant for marketing authorisation has withdrawn the application. Despite the Regulation states that information on clinical trials shall be publicly available, confidential information do not need to be disclosed. The Clinical Trial Regulation defines that confidentiality is justified for following reasons: protection of personal data; protection of commercially confidential information (considering the marketing authorisation status of the medicine, unless there is an overriding public interest); as well as protection confidential communication between Member States in the preparation of their assessment; and ensuring effective supervision of the conduct of clinical trials by Member States. Yet, no specific examples of information from registration or summary results that should be commercially confidential have been provided. Specific

433 Clinical Trials Regulation, Recital 67 states that: “In order to ensure a sufficient level of transparency in the clinical trials, the EU database should contain all relevant information as regards the clinical trial submitted through the EU portal. The EU database should be publicly accessible and data should be presented in an easily searchable format, with related data and documents linked together by the EU trial number and with hyperlinks, for example linking together the summary, the layperson’s summary, the protocol and the clinical study report of one clinical trial, as well as linking to data from other clinical trials which used the same investigational medicinal product. All clinical trials should be registered in the EU database prior to being started. As a rule, the start and end dates of the recruitment of subjects should also be published in the EU database. No personal data of data subjects participating in a clinical trial should be recorded in the EU database. The information in the EU database should be public, unless specific reasons require that a piece of information should not be published, in order to protect the right of the individual to private life and the right to the protection of personal data, recognised by Articles 7 and 8 of the Charter. Publicly available information contained in the EU database should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.”

434 Clinical Trials Regulation, Recital 68 states that: “For the purposes of this Regulation, in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, the application for marketing authorisation has been withdrawn. In addition, the main characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorisation of a clinical trial, the decision on the authorisation of a clinical trial, the substantial modification of a clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general, should not be considered confidential.”

435 Article 81, para. 4.
concerns were also raised that sponsors of clinical trials do not wish to disclose information on new indications and/or formulations for authorised products early, as this may affect patent protection. Furthermore, particular concerns were raised regarding endeavors to automate considerations of confidential commercial information and publication of anonymised of personal data.  

6.4 The Biotech Patent Directive - resulting in disharmonised national implementations

The drafting history of the Biotech Patent Directive reveals that the Biotech Patent Directive was a very heavily lobbied legislative instrument. It was indeed one of the most heavily lobbied Directives that ever that had passed through the EU legislative process, according to Porter.\textsuperscript{437} The Biotech Patent Directive was approved by the Council of the EU and the European Parliament in the co-decision procedure on 6 July 1998. It was an outcome of ten years of hard and intense negotiations, and it followed the European Parliament’s rejection of an earlier draft in 1995.\textsuperscript{438} The objective of the Biotech Patent Directive was to “improve the competitiveness of the European biotechnology industry by clarifying and harmonizing European patent laws”. As a result of negotiations between the legislators, “morality clause” in the form of Article 6 was included in the final version to give a more significant role for ethics and morality as assessment norms within European patent law.\textsuperscript{439} The insertion of Article 6 (that provides a non-exhaustive list of specific examples to be excluded from patentability on the grounds of ordre public or morality) represents a political compromise between the Council of Ministers and the European Parliament which exercise the legislative power under the co-decision procedure.\textsuperscript{440}

In October 1988, the first version of the Biotech Patent Directive was introduced by the European Commission.\textsuperscript{441} That time the main justifications for the Biotech Patent

\begin{itemize}
  \item European Medicines Agency. “Overview of comments on EMA/641479/2014 Draft proposal for an addendum, on transparency, to the “Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014”, supra note 432.
  \item Porter, supra note 65, 3.
  \item Porter, op.cit., 3–4.
  \item The current wording of the Article 6 reads as follows: 1. Inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation.2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable: (a) processes for cloning human beings; (b) processes for modifying the germ line genetic identity of human beings; (c) uses of human embryos for industrial or commercial purposes; (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.
  \item Plomer, supra note 439, 17.
\end{itemize}
Directive were mostly economic ones, as the European Community needed to take strategic steps to maximally benefit from the opportunities for the creation of prosperity and employment that the prospective growth of the biotechnology sector offered. Harmonised patent legislation was seen to play a pivotal role in this development. In the Commission’s view the risk of the fragmentation of European patent laws was seen as a potential impediment for the growth of the European biotechnology industry. Initially, there was especially a need to clarify the distinction between inventions and discoveries in patent law. It was agreed that biological material in its natural form would remain an unpatentable discovery, whereas artificially produced biological material or biological material that has been isolated from its surroundings would be patent-eligible subject matter, even if the structure of that element is identical to a natural element. This clarification envisioned to provide legal certainty required for the European biotechnology sector to grow and to compete with the US and Asian markets.

The Biotech Patent Directive was not initially purported to drastically alter the European patent system, as the European Commission’s proposal of October 1988 was constructed upon the prevailing general principles of patent law. It intended to clarify how they should be applied throughout Europe in a harmonised way to satisfy the requirements of novelty, inventive step and industrial application. The very first draft of the Directive was relatively straightforward, and it mainly framed the problem in light of these terms. According to Porter, it mainly reflected the permissive approaches of the United States Patent and Trademark Office (UPSTO) and Japanese


444 Article 52.1 EPC allows patents for inventions that are new, involve an inventive step and are capable of industrial application, whereas Article 52.2 EPC specifically prohibits the patenting of “discoveries”. The lack of guidance from Article 52 EPC and national patent laws on how to deal with this issue meant that European researchers and companies were not sure if their inventions could be eligible for patent protection within Europe or not. See Porter, supra note 65, 5-6. See also Crespi, R.S. The Biotechnology Patent Directive is approved at last! Trends Biotechnol. 1999 Apr;17(4):139-42.

445 Legal basis of the Commission’s proposal was Article 95 EC of Treaty on European Union, Rome, 25th March 1957, as revised 1st July 1987, 1st November 1993, and 1st May 1999. See also Plomer, supra note 439, 19.
As a starting point the Biotech Patent Directive would clarify the scope of the patentable subject matter and distinction between unpatentable discoveries and patentable inventions by specifying that biological material that has been isolated from its surroundings or produced in an artificial way would be patentable even if the structure of that element were identical to a natural element.

Yet, already during the very first hearing the European Parliament took the position that the Biotech Patent Directive should consider “moral and ethical aspects” of biotechnology patenting in greater detail. The European Commission’s first draft was criticised the Economic and Social Committee, which in its opinion dated 26 April 1989 emphasised that there is a need to draw “ethically appropriate boundaries” as regards to what may and may not be commodified. It was also noted that human beings as such were not expressly mentioned in the Biotech Patent Directive draft as unpatentable subject matters. A number of amendments were proposed by the European Parliament and the Commission agreed to incorporate some of them to their new draft Directive in April and October 1992, which aimed at clarifying the ambiguities arising out of life science patents. The amended draft took certain ethical issues into account by referring to Article 53.a EPC, which prohibits patents in invention whose exploitation would breach *ordre public* or morality. Despite the extensive redrafting, the Council rejected the European Parliament’s amendments to the draft version in September 1994, which resulted in mandatory conciliation proceedings between the Council and the European Parliament. Thereafter, a joint version produced by the Conciliation Committee was finally disapproved by the European Parliament on the 1st March 1995.

Subsequent to the rejection of the draft Biotech Patent Directive, a second amended proposal was submitted by the Commission to the European Parliament on 25th January 1996. This version placed greater importance on public policy and morality.

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450 Decision on the joint text approved by the Conciliation Committee for a European Parliament and Council Decision establishing the Community action programme 'SOCRATES' (C4- 0049/95 - 94/0001(COD)) (Codecision procedure: third reading), OJ C 68 of 20.3.1995. According to Plomer that was indeed the first time that the EP had used its veto powers to reject draft legislation. See also Plomer, *supra* note 439, 19.


452 See Porter, *supra* note 65, 17.
proposal included a clearer wording addressing the discovery/invention distinction in biotechnology patent law, and welded this distinction with the moral prohibition on the ownership of the human body. However, in this version no reference was made to the exclusion of human embryos from patentability. It only mentioned two types of “immoral inventions” that should be unpatentable: (i) methods of human treatment involving germ line gene therapy and (ii) processes for modifying the genetic identity of animals which are likely to cause them suffering or physical handicaps without any substantial benefit to man or animal, and also animals resulting from such processes, whenever the suffering or physical handicaps inflicted on the animals concerned are disproportionate to the objective pursued.

Consequently, the Parliamentary Committee on Legal Affairs and Citizens' Rights suggested in its report on the Draft Biotech Patent Directive (dated 25th June 1997) that “methods in which human embryos are used” to be unpatentable on moral grounds. Despite, the most of amendments proposed by the Parliamentary Committee on Legal Affairs and Citizens' Rights were accepted by the European Parliament (on 16th July 1997) and by the Commission (29th August 1997) respectively, the Council decided in its Common Position (of 26th February 1998) to narrow the scope of the proposed patentability restriction to cover “uses of human embryos for industrial or commercial purposes” only. That wording of Article 6.2.c remained in the final version of the Biotech Patent Directive, which was finally adopted by the Council and the Parliament on 6th July 1998. However, it should be noted that during the time of drafting the Biotech Patent Directive, the hESC technology was still its infancy. Very soon after adoption of the Biotech Patent Directive, new kind of stem cell technologies emerged. Since the first isolation and culturing of hESCs by Wisconsin scientist James Thompson in November 1998, hESCs have become a topic of vivid bioethical debate. Therefore, that debate was still not ongoing when the final version of the Directive was approved.

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454 The Report acknowledged the EP’s Resolution on the Protection of Human Rights and Dignity with regard to the Application of Biology and Medicine, OJ C 320, of 28.11.1996, p. 268. The Resolution stated that “all trade in human embryos, fetuses and foetal tissue without exception must be prohibited by law” and also that “consumptive research on and the production of human embryos for research purposes must be prohibited”. In addition, reference was made to Opinion No. 8 of the Group of Advisers on Biotechnology (GAIEB), para. 2.3 stating that: “The human body, at different stages of its constitution and development, as well as its elements, do not constitute patentable inventions. Such exclusion does not come only from the usual conditions of patentability, but it is also inspired by the ethical principle of non-commercialisation of the human body. Therefore no patent can be given on the human body or on its elements…” See also Plomer, supra note 439.
458 See Porter, supra note 65, 22.
In the final version of the Biotech Patent Directive a clear distinction was made between the unpatentability of the human body in its natural state as opposed to elements isolated from the human body (which could constitute a patentable invention, provided that they meet other patenting criteria i.e. novelty, inventive step and industrial application). Furthermore, some Recitals addressing ethical perspectives were included in the Biotech Patent Directive. The very active stakeholder participation did not however result in harmonised legislation that could satisfy all parties involved. Despite the specific list of examples of 6.2 was purported to facilitate the interpretation and implementation of the morality provision, remarkable differences in interpretations and national legislations have emerged, especially in case of Article 6.2.c. Also, as discussed in Research Articles II and III further interpretations regarding the scope of the exemptions have been sought.


<table>
<thead>
<tr>
<th>Implementation strategy</th>
<th>Jurisdiction</th>
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<tbody>
<tr>
<td>Exact, translated wording implemented</td>
<td>Belgium, Croatia, Cyprus, CzechRepublic, Denmark, Finland, France, Greece,</td>
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<tr>
<td></td>
<td>Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway,</td>
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<td>Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, the U.K.</td>
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<tr>
<td>Implemented with minor alterations</td>
<td>Switzerland</td>
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<tr>
<td>Implemented with wider scope</td>
<td>Austria, the Netherlands</td>
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<tr>
<td>Implemented with narrower scope</td>
<td>Estonia</td>
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Reference: Please refer to table of legislation of this study for further details regarding national laws implementing Article 6 of the Biotech Patent Directive.

459 Recitals 14, 19, 39.
7 Results and discussion

This Chapter aims at analysing how well the ATMP Regulation meets its objectives and expected benefits. Predictive views presented in the preparatory material of the legislation are retrospectively matched against the current implications of the ATMP Regulation to identify benefits and possible shortcomings with the ATMP Regulation. In addition, some other aspects constituting impediments for the market entry of these innovative therapies will be presented. These aspects include among other things availability of research funding, patentability prospects of a particular technology, difficulties with getting (pre)clinical trial authorisations as well as research governance and pricing and reimbursement of ATMPs.

Despite the primary objective of this study has been to analyse how the ATMP Regulation has affected the market-entry of ATMPs under development, it would not be accurate to conclude that the low number of ATMPs is only a consequence of the ATMP Regulation. When it comes to other aspects affecting market entry of these innovative products, a number of legal an ethical considerations pertaining to fragmented legislative landscape covering among other things the ATMP Regulation, EUCTDs, clinical trials legislation and intellectual property rights constitute jointly essential, but not only obstacles for an accelerated market-entry of ATMPs. There are also a number of other relevant factors beyond legal considerations affecting commercialisation of ATMPs. One of these aspects, the impact of research funding policies has been discussed as an indirect way of steering research priorities and market-entry of ATMPs. Furthermore, reimbursement of ATMPs has been discussed as an essential factor influencing commercialisation prospects of these products. Other relevant aspects include biomedical hurdles that prevent basic research findings from being tested in a clinical setting as well as organisational indolence preventing proven interventions from becoming standard practice. Yet, both of these latter biomedical and human resources related considerations of have been left outside the actual scope of this regulatory study.

In conclusion, in this Chapter commercialisation process of ATMPs is presented as a stagewise process involving following major roadblocks:

1) the availability of research funding;
2) the challenges with the IP protection;
3) the access to primary materials and data protection;
4) the disharmonised classification of ATMPs;
5) the difficulties with accommodation of niche production with industry-scale GMP requirements;
6) the difficulties with getting pre-clinical and clinical research authorisations;
7) the burdensome marketing authorisation procedure; and finally
8) the high cost of ATMPs and difficulties with getting reimbursement.
7.1 Research funding policies steering research priorities

Research funding (along with patentability prospects and reimbursability of medicines) constitutes an indirect means for influencing whether certain types of research should be conducted or not. The EU wide research funding policies affecting stem cell research is a viable example of the steering function of public funding policies. The European Commission maintains its position on not financing research projects that involve destruction of embryos under its current Framework Programme for Research and Innovation Horizon 2020, in accordance with the ECJ’s Brüstle judgment.

The third paragraph of Article 19 of EU Regulation 1291/2013, establishing Horizon 2020 specifies a range of research activities that should not be financed under Horizon 2020: (a) research activity aiming at human cloning for reproductive purposes; (b) research activity intended to modify the genetic heritage of human beings which could make such changes heritable; and (c) research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of SCNT. However, it should be noted that under fourth paragraph of Article 19 “research on human stem cells, both adult and embryonic, may be financed, depending both on the contents of the scientific proposal and the legal framework of the Member States involved.” Pursuant to Horizon 2020, however, no funding shall be granted for research activities that are forbidden in all EU Member States and no activity shall be funded in a Member State where a particular activity is prohibited.

Quite recently, Horizon 2020, the EU Funding Programme for Research and Innovation, was challenged via the mechanism of the European Citizens Initiative to call on the European Commission to propose legislation on matters of the EU competence regarding funding hESC research. The arrangers of “Embryo, One of Us” initiative referred to the Brüstle ruling in which the ECJ provided a broad definition of a human embryo. However, the European Commission rejected the request by the “Embryo, One of Us” initiative, which was sought the prohibition of any research involving the destruction of human embryos. The initiative was supported by more than 1.7 million signatures collected across seven Member States. The European Commission’s refusal rejected the equivalence of human persons and embryos, its view being that the existing funding framework is appropriate and respects EU Treaties and the Charter of Fundamental Rights of the EU.

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461 Kaisi, supra note 221, 189-190.
A so-called “triple lock” system has been applied by the European Commission in Horizon 2020 regarding research on hESCs. First, national legislation applied by the Member States is respected; second, each project must pass both a scientific evaluation in order to assess whether the use of hESCs is necessary and an ethics review organised by the European Commission; and third, European funds may not be used for the creation of new stem cell lines or for research that necessitates destruction of human embryos. In its response to the organizers of “Embryo, One of Us” the European Commission has further emphasised that it does not particularly publish calls for research proposals on hESCs and the scientists may suggest the best possible methods for a specific study. The European Commission also clarified that the implications of the ECJ’s Brüstle ruling applied merely to the patentability of hESC-based inventions and did not deal with the question of whether such research can be conducted or funded. Hence, the legality of hESC research was confirmed by the European Commission even subsequent to the ECJ’s ruling in Brüstle and a clear distinction was drawn by the European Commission between the permissibility of the hESC research and the patentability of its findings. Furthermore, in terms of internal market objectives, the Regulation on Horizon 2020 emphasises how research and innovation is important for the economic growth of the European Union and for attracting private investment, whereas patents have been deemed to play a vital role in commercialisation of hESC research. 462 As for private hESC research funding, it is likely that patentability restrictions will not encourage big pharmaceutical companies to invest in R&D in hESC therapies, at the very least. A relevant question is whether they would do so otherwise, as investments in companies developing hESCs have been perceived as a risky investment.463

As discussed in Research Article I, beyond the issues of availability of research funding and patentability in the stem cell field, an interesting general remark can be made: It has been reported that a restrictive national regulatory approach does not necessarily lead to a lower publication rate. The relation between the policy and research practice actually appears to be more complicated than that. Beyond the regulatory policy, many other factors seem to influence the development of the field of hESC research. Globally speaking, the stem cell research field has grown very rapidly over the past decade. The volume of research output, the number of publications, as well as citation frequency has increased significantly in hESC and iPSC related topics. An empirical study by Barfoot et al. examined the hESC publication data to compare

463 Mansnérs, supra note 34, 82. See for instance, Franz, S. Embryonic stem cell pioneer Geron exits field, cuts losses. Nature Biotech. 2012 Jan 9;30(1):12-3. Geron encountered a clinical hold due to the FDA’s concern about the carcinogenic potential of hESCs. Waiting for the potential payoff from hESCs research proved too far off for Geron, which did not have any licensed products. It would have cost USD 25 million on a yearly basis to continue its hESC programme.
recent trends in countries with contrasting policy positions.\textsuperscript{464} It was reported that, for instance, hESC research in both Germany and Italy demonstrated an above average publication and citation rate despite the restrictive stem cell policies of these countries, while the U.K. and Sweden, which have adopted a more liberal regulatory approach unexpectedly demonstrated a below-average publication and citation rate. According to Barfoot et al., this may depend on how legislative positions are transposed into regulation and practice. For instance, despite the legislation in the U.K. being permissive by default, there are some other relatively restrictive regulations (\textit{soft law instruments}) governing how and where the research may be conducted. Simultaneously, other aspects, including the stage of maturity of the field of research in different jurisdictions, and the availability of research funding may also significantly impact the prospect of conducting stem cell research.

Perhaps the above average number of stem cell publications and citations in restrictive countries implies that “\textit{where there is a will there is a way.}” More generally, in the case of advanced therapy medical products, Pirnay et al. have predicted that “\textit{medicine won’t stop on its way}” and “\textit{the field might evolve to circumvent legislation}”.\textsuperscript{465} The apparent increase in publications dealing with iPSCs may indicate that funding policies direct and encourage researchers to conduct research on iPSCs instead of hESCs, which are still deemed ethically more contentious by some.

7.2 The indispensable IP protection attracting research funding and capital investment to stimulate the growth of university spin-offs

IP protection is of great importance for the pharmaceutical industry. How IP rights are used by SMEs depends among other things on their business strategy, financial resources, innovative activities, competitive position and the field of expertise.\textsuperscript{466} Research-intensive SMEs that seek to develop new medicines often arise as spin-off companies from academia. They often rely heavily on the patent system to cover their R&D investment. Confidential information (protected as \textit{trade secrets}) is also important

\textsuperscript{464} Barfoot, et al., supra note 84, 34.
\textsuperscript{465} Pirnay, et al., supra note 22, 549.
for many SMEs and so is the valuable know-how or undisclosed test data regarding new or enhanced medicines.\textsuperscript{467}

Along with EU policies on research funding, patents can be seen as another type of indirect means of managing research priorities. For instance, from a regulatory perspective, moral exclusions constitute an indirect form of regulation for stem cell technologies, since the denial of patent protection for a hESC invention has no impact on the exploitation of the invention on the internal market; the actual use of the hESC invention cannot be prohibited by the refusal of patent protection. The intrinsic nature of patent protection constitutes a \textit{negative}, exclusive right; the holder of a patent can prevent others from using the patented invention, but the patent protection as such does not grant the holder the right to use the invention if its use is otherwise prohibited by law.\textsuperscript{468} In contrast, the actual use of inventions is regulated by rules beyond patent laws such as ATMP Regulation, which, inter alia, sets out for the rules for ATMP marketing authorisations via the mandatory centralised procedure. Hence, denial of patent protection only wields an indirect effect; resulting in a situation where the invention is free for everyone to use. Patent law represents just one element of the legislative environment for ATMPs (such as hESC-based health technologies) in Europe; other means such as trade secrets and marketing authorisation (and clinical data exclusivity) may be much more important for commercialising these technologies. When clinical data exclusivity applies upon the approval of a new medicine, no generic version of that product can be approved using the same clinical data used to support the original medicine for eight years.\textsuperscript{469} Hence, a generic version of product would be required to pass clinical trials or await the expiry of this eight-year period before applying for a mandatory marketing authorisation. It should be noted that patent law’s indirect regulation role is secondary to its primary purpose of legal protection of inventions.\textsuperscript{470}

However, since the patent law’s primary purpose is the legal protection of innovation only where this adapts to acceptable moral standards, the patent law must be

\textsuperscript{467} It should be noted that understanding the trademark system is also important for companies selling branded products. While industrial designs and copyright and related rights are generally less relevant to most SMEs in the pharmaceutical field, this could vary depending on the product line and strategy of the SME. These aspects of IP protection will be left outside the scope of this study, however.

\textsuperscript{468} Hellstadius, \textit{supra} note 50, 30 has pointed out that the purpose of the so-called regulatory system is to monitor and control technologies by means of ethical authorisation of research, clinical trials, and the specific requirements for commercialisation of innovations, whereas the primary purpose of the patent system is limited to granting exclusive rights.

\textsuperscript{469} After the eight years have expired, anyone can make use of the pre-clinical and clinical trial data of the original regulatory applications, but still cannot market their generic product. After a period of ten-years from the grant of the innovator’s marketing authorisation however, the generic company can also market their product, unless the innovator’s product qualifies for an additional one year of exclusivity. This additional term may be obtained if the innovator company is granted a marketing authorisation for a significant new indication. In such a case, the generic company can only market its product after eleven years have passed from the grant of the original marketing authorisation.

\textsuperscript{470} Odell-West, \textit{supra} note 51, 171.
unambiguous and certain to support the patent examiners and judges adequately in their analysis of the scope of the morality exclusions.\textsuperscript{471}

In any case, a strong patent position is often required to fund the very considerable development costs associated with development of ATMPs. First of all, as patents are used for raising capital, they have become increasingly important for SMEs and academia developing ATMPs. Patents may indicate quality as well as technical progress to capital markets or to venture capitalists and serve as collateral for bank loans.\textsuperscript{472}

According to Hellstadius, these new uses have made patents more attractive.\textsuperscript{473} By contrast Jens Andreason has found that “\textit{despite intellectual resources represent an immense value, these resources are only seldom collateralised}”. This is due to difficulties with valuation of these complex assets.\textsuperscript{474} Patent valuation may constitute challenges, as the value of a patent depends on a variety of factors that are often interdependent. The scope of patent protection affects value of the patent(s) significantly, and so may also patent portfolio positions.\textsuperscript{475}

Nevertheless apart from high impact publications, academia needs IP to attract investors for university spin-offs. It is essential that appropriate university invention policies and solid as well as flexible processes regarding administration of IP are in place to ensure that the know-how and patentable inventions are adequately protected to facilitate their transfer to a spin-off company or some partner.\textsuperscript{476}

It has been reported by the Finnish Ministry of Economic Affairs and Employment that the Finnish higher education and research institutions have a lot of innovation potential that remains inefficiently exploited and there is an urgent need to enhance cooperation between academia and industry to facilitate commercialisation of inventions originating in academia. Ideally, enhanced cooperation between academia and industry could boost the national economy overall. Another means of commercialisation that arises in connection with academic research is the transfer of patents and other IP to existing companies. The patenting frequency of academic

\textsuperscript{471} Ibid.
\textsuperscript{472} Hellstadius, supra note 50, 84-86.
\textsuperscript{473} Op. cit., 86.
\textsuperscript{476} The university invention policies are beyond the scope of this study. For further details from a Finnish perspective, please refer to Bruun, N., and Välimäki, M. \textit{Korkeakoulukeksinnöt.} (Helsinki: IPR University Center), 2007.
institutions remains quite low, only approximately 80-100 university spin-offs arising per year.477

Simultaneously, the competitive patenting environment has become increasingly challenging from the perspective of SMEs and academia. Among other things, it has been noted that the trend towards the lowering standards for the inventive step requirement has increased transaction costs, which has mainly affected SMEs, whereas larger companies may benefit from such developments.478 When academia suffers from a relatively low patenting frequency and scarce resources, it also risks difficulty with such increased transaction costs. Nikolaus Thumm has suggested that the approach to patents in the life sciences sector is quite ambiguous in that large corporations usually use patenting more frequently as a means of IP protection than SMEs, while the average number of patents per SME employee is significantly higher than the patent density of larger corporations. SMEs also appear to use trade secrets to protect their intellectual assets more than larger companies.479 Despite these challenges, according to a recent study by Eurostat SMEs have been reported to account for approximately 17% of patent applications filed by companies from the EU, and SMEs’s ‘market share’ ranks as high as 20% of patents in biotechnology related fields (including biotechnology, pharmaceuticals and the analysis of biological materials).480

Both companies and academic research institutions invest in acquiring, developing and applying know-how and information which can provide a competitive advantage. Other than patents, trade secrets are an important means of appropriating the results of innovation to protect access to and exploit knowledge valuable to the entity and not widely known. Under the recently adopted Trade Secrets Directive 2016/943 (adopted on 27 May 2016) such valuable know-how and business information, that is undisclosed and intended to remain confidential, is referred to as a trade secret.481 According to Recital 2 of the Trade Secrets Directive, an important objective is to


478 Hellstadius, supra note 50, 84-86. See also Andreasson, supra note 474, 128-129.


481 European Commission. Directive of the European Parliament and the Council on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure.
strengthen the protection of trade secrets. This is indeed particularly important for SMEs. The Trade Secrets Directive harmonises the definition of trade secrets in accordance with existing internationally binding standards. It also outlines the relevant forms of misuse and explains that reverse engineering and parallel innovation must be ensured, as trade secrets are not a form of exclusive IP. Without establishing criminal sanctions, it harmonises the civil means through which victims of trade secret misappropriation can seek protection (e.g., stopping the unlawful use and further disclosure of misappropriated trade secrets; the removal from the market of goods that have been manufactured on the basis of an illegally acquired trade secret and the right to compensation for the damage caused by the unlawful use or disclosure of the misappropriated trade secret). Trade secrets can be used to protect a wide range of know-how and business information. They may be used to complement or as an alternative to other intellectual property rights. They also allow innovators to derive profit from their innovation and are therefore particularly important for competitiveness as well as for research and development, and the innovation-related performance of SMEs.482

Despite SMEs being generally seen as a heterogeneous group of companies, the main asset of such companies is typically their technology, which is only protected by means of patents.483 Furthermore, the interests of SMEs in patent protection may substantially differ from those of larger corporations. For instance, a multinational corporation may want certain patentable research tools to be placed in the public domain, whereas a SME would prefer patent protection to attract venture capital or a potential acquirer.484 In the case of academia, this situation may appear more even ambiguous. The researchers wish to publish their remarkable research findings in high impact publications as soon as possible to acquire research public funding or funding from charities. However, in some cases publishing may contradict a patenting strategy and ruin the chance of patent protection if a publication can be seen to constitute a prior state of the art in assessing the absolute novelty of an invention. Therefore, it is essential to ensure that solid publication policies are in place in university and industry partnerships to mitigate the risk of patentable research findings being released to the public domain before a patent application has been filed. Furthermore, protection of trade secrets may be as important as protection of patentable innovations for a university spin-off company. In incorporating a spin-off company, ensuring that the academic institution and all researchers involved have transferred their relevant IP to the spin-off company adequately and in a documented way is very important. When venture capitalists are involved, due diligence will often be done to ensure that the spin-off company really has the right to use its IP and title to its IP and adequate agreements, processes and policies (such as non-disclosure agreements, IP transfer agreements, IP licence agreements, employee invention policies including details about any

482 Recital 3.
483 Hellstadius, supra note 50, 84-86.
484 Hellstadius, ibid.
compensation paid or pending under such policies, details about registrations, etc.) are in place to protect its intellectual assets.

In addition, the presence and strong position of large multinational pharmaceutical companies has made it especially challenging for SMEs (including small university spin-offs) to compete in the biotechnology sector. SMEs developing ATMPs often operate in multiple jurisdictions, and hence have some need for patent protection similar to multinational corporations in many states. However, SMEs often encounter difficulty with access to investment capital in innovation, as they have smaller financial resources for creation of patent portfolios or even for protection of a single patentable invention in many jurisdictions. The same applies to the university spin-offs. Furthermore, big corporations possess comprehensive patent portfolios with overlapping patent claims, which makes it very difficult for SMEs (or academia) to compete. Consequently, there is a risk of patent litigation with big pharmaceutical companies, which is often expensive both in terms of financial resources and personnel. Bruun et al. have argued that universities should also take patent litigation risk management aspects into consideration and they should avoid financial liabilities that may arise in the event of a patent infringement. Since patent litigations also are often very complicated and sometimes lengthy, management of such conflicts not only requires in-house resources, but also usually necessitates assistance from external counsel. A SME or an academic institution rarely has the financial resources to invest in conflict management or the personnel that can deal with complex litigations. Hence, the increased focus on IP protection may constitute financial impediments for SMEs and academia that may render the commercialisation of ATMPs even more challenging.

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486 Bruun et al., supra note 476,144.
7.3 Challenges with access to primary materials and data protection

7.3.1 Inefficient distribution of cell lines and other biological materials

Some Member States have imposed some further national requirements to prevent industry’s direct access to human cells and tissues due to ethical reasons. Access to primary materials is not equally granted in all Member States.487 For instance, in some Member States companies cannot access primary material, unless they are registered as a biobanks.488 Some countries do not allow companies to act as biobanks.489

Availability and limitations on uses of hESC represents a viable example of how a great plurality of approaches to research governance and ethics remains across the EU. Recital 7 of the ATMP Regulation states that the ATMP Regulation should not interfere with decisions made by Member States on whether to allow the use of any specific type of human cells (such as hESCs) and it should not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of or derived from these cells. There is a great ambiguity in the set of rules regulating the protection of embryos, which has resulted in a large margin of appreciation in Article 18.2 of the Biomedicine Convention at the European level. According to Roscam-Abbing, the prohibition of creation of human embryos for research purposes stipulated in Article 18.2 has been perceived to express the concern for preserving dignity and human identity.490 Simultaneously, this prohibition has raised the question of whether or not it is justified in the event that hESC research were the sole method of finding ways of preventing and curing very serious diseases.491

As mentioned in Research Article II, differences in the application of Article 18.2 can be seen in the different practices of European countries, ranging from a total ban on in vitro embryo research to permitting SCNT.492 Hence, European regulatory approaches to hESC research governance vary substantially from one Member State to another. These varying approaches ranging from restrictive ones to intermediate and permissive ones are influenced by different value systems, religions, traditions and specific research economic circumstances and priorities of the Member States. Restrictive regulatory approaches are characterised by critical attitudes towards

488 Kent, et al., supra note 177,53.
489 See for example Pirnay et al., supra note 22, 456.
490 Roscam Abbing, supra note 128, 21.
491 Ibid.
492 Mansnérus, supra note 34, 145.
scientific discoveries and, thereby, they adopt a prohibitive approach to a wide range of research practices and technologies, such as therapeutic cloning or research on embryos is regulated by means of strict regulations or blanket bans. Countries applying restrictive policies often support strong government supervision and intervention with the objective of protecting human embryos and the society from the potential negative effects and predicted dangers of these technologies. The liberal approaches pursue the promotion of scientific and medical development from a starting point that is beneficial to humanity. In addition to societal matters, this approach aims to regulate the interest of patient and public health. For instance, the Spanish Law on Biomedical Research makes these objectives clear by stipulating that “research shall be undertaken in accordance with the precautionary principle in order to prevent and avoid risks for life and health.” The intermediate regulatory approaches adopted by most of the Member States aim at providing efficient and safe mechanisms for conducting hESC research. The necessity of proportionality requirements as denominators for respect for the human embryo have been found to appear as common requirements in the intermediate position of the majority of Member States.

When it comes to recent developments facilitating hESC research governance in Europe, the relaunch of the Human Pluripotent Stem Cell registry (hPSCreg) in 24 June 2015 represents a positive sign, as hPSCreg attempts to solve the debated cross-disciplinary (i.e. legal, ethical and technical issues) arising in connection with governance of hESC research. It also represents an indication of the European desire to reach a consensus of very controversial and sensitive moral issues miring hESC research. It was originally established as a response to the ethical controversies relating to hESC research governance. Recently, this global registry has been enhanced and expanded to offer more in-depth information and analysis on human pluripotent stem cell lines, including hESCs and adult derived iPSCs. It is a freely accessible, continuously maintained resource for the research community, legislators, regulators and international public. As hPSCreg operates in line with the European policy (hence, it is committed to ensure that fundamental ethics principles are met and no cell lines that fall within the non-fundable activities can be registered), it currently constitutes a vital governance tool for European Commission-funded research, as it provides formal cell line certification which is required for European Commission project approvals.

493 Knoppers, et al., supra note 34, 40 refer to legislation adopted in Austria, Georgia and Italy that prescribes that fertilised human oocytes and cells can only be used for medically assisted procreation. See also Mansnérus, supra note 34, 143.

494 Knoppers, et al., ibid refers to instrumentalisation and commodification of potential human life, as well as exploitation of women and children.


498 Knoppers, et al., supra note 34, 42.


500 It is funded by the European Commission in partnership with the UK Stem Cell Bank (NIBSC-MHRA), Charité University Medicine in Berlin and the Center of Regenerative Medicine in Barcelona (CMR[B]). Human pluripotent stem cell registry. Available at: http://hpscreg.eu/. Accessed 21 June 2016.
In addition to ethical considerations, some propriety interests and commercialisation norms may be conducive to impede collaboration and commercialisation of research of ATMPs. In particular, inefficient distribution of cell lines and other biological materials has been recognised as a significant problem. It has been noted that encouraging research institutions to adopt material transfer agreement templates had proved to be an insufficient measure to improve access to biological materials. Therefore, the leaders of research initiatives should pursue making efficient exchange of materials a stronger standard within the research community and commercial partners participating in ventures. As an alternative to material transfer agreement that are drafted and negotiated between individual parties of a venture, standardised terms and conditions could be created to facilitate and streamline exchange of biological materials.

In addition, developers of ATMPs could also benefit from greater levels of data-sharing. However, due to the risk of “parasitic patenting” many ventures have decided to make data available under so-called “click-wrap” licenses instead of releasing the data into the public domain. However, some commentators deem that the risk of “parasitic patenting” is overstated and the need for broader data-sharing is a more significant issue. Hence, there is a need for research initiatives to balance the risk of “parasitic patenting” in relation to the possible benefits to be gained from improved data-sharing. As a final point, to accelerate stem cell research into advanced therapies, large-scale initiatives should promote a practice of not patenting “fundamental inventions”, as patents on foundational inventions may significantly impede research progress.

7.3.2 Wider ethical aspects of donation evaded in the ATMP Regulation

The paradigm of translational research imposes new regulatory challenges in situations where stem cell research is translated from bench to bedside, in particular in terms of tissue donors’ right to self-determination and privacy. As discussed in Section 6.2. of this study, despite some significant ethical concerns were raised and discussed during the legislative process of the ATMP Regulation regarding commercialisation of altruistic cell and tissue donations, integrity of the person and the inviolability of human dignity,


505 Herder, supra note 501, 282. Herder refers to WARF’s rigid control of its hESC patented cell lines illustrates patenting inventions that are perceived foundational to a field of inquiry can impede research progress.

506 Hartlev, supra note 135, 258-260.
the proposed ethical amendments were left outside the scope of the final version of the ATMP Regulation due to the fact that such ethical considerations are outside the scope of the EU’s legislative mandate.

Yet, the Recital 8 of the ATMP Regulation states that fundamental rights and principles reflected in the Charter of Fundamental Rights of the EU and the Biomedicine Convention have been observed. Article 3.1 of the Charter requires among other things that everyone has the right to respect for his or her physical and mental integrity. In addition Article 3.2 specifies that in the fields of medicine and biology the free and informed consent of the person concerned, according to the procedures laid down by law the following must be respected. Also under Article 10.1 of the Biomedicine Convention everyone has the right to respect for private life in relation to information about his or her health. In addition, more specifically, Recital 15 of the ATMP Regulation notes that “[a]s regards the donation of human cells or tissues, principles such as the anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient should be respected”. Therefore, human cells or tissues contained in ATMP should be procured from voluntary and unpaid donation. Also, Recital 19 of the ATMP Regulation notes that the summary of product characteristics, labelling and the package leaflet of an ATMP should comply fully with the patient’s right to know the origin of any cells or tissues used in the preparation of ATMPs, while respecting donor anonymity.

Furthermore, as it will be discussed in Section 7.3.3., the new EU Data Protection Regulation imposes specific requirements for controlling and processing of personal data. Also the Recital 28 of Clinical Trials Regulation specifies consent requirements for clinical trials for re-use of data collected for purposes of clinical trials:

“[i]t is appropriate that universities and other research institutions, under certain circumstances that are in accordance with the applicable law on data protection, be able to collect data from clinical trials to be used for future scientific research, for example for medical, natural or social sciences research purposes. In order to collect data for such purposes it is necessary that the subject gives consent to use his or her data outside the protocol of the clinical trial and has the right to withdraw that consent at any time. It is also necessary that research projects based on such data be made subject to reviews that are appropriate for research on human data, for example on ethical aspects, before being conducted.”

Especially, in case of commercial stem cell repositories, it should be noted that tissue donors may have a particular interest in self-determination and privacy protection in regards to those samples. Such legitimate interests of the donors should be balanced against the interests of other actors, including but not limited to patients that can potentially benefit from the donated samples and the society at large benefiting from creation of new scientific knowledge. The Report of the Unesco International Bioethics Committee (IBC) on the ethical aspects of human embryonic stem cell research emphasises the importance of prior, free and informed consent of hESCs:

507 See e.g. Hartlev, supra note 135, 254.
“Whatever form of research involving embryos is allowed, steps should be taken to ensure that such research be carried out within the framework of a State-sponsored regulatory system that would give due weight to ethical considerations, and set up appropriate guidelines. When authorisation of donations of supernumerary pre-implantation embryos from IVF treatments for therapeutic embryonic stem cell research is under consideration, particular attention should be given to the dignity and rights of both parental donors of embryos. Thus, it is essential that the donation be made only after the donors should have been given full information as to the implications of the research and have given their prior, free and informed consent. The purposes for which such research is carried out, and the way of its performance, should be subject to assessment by the appropriate ethics committees, which should be independent of the researchers involved. This assessment should include ex post facto ethical evaluation of such research. ...”

To safeguard interests of tissue donors and potential patients in need of advanced therapies, it would be very important to acquire prior, written, informed consents from donors to ensure that the persons who donate tissues for research also consent to possible secondary uses of the donated tissues. In addition, the donor should be adequately informed about his/her rights to revoke the consent for any reason and the possible use of personal data after such revocation if such use is after revocation of the consent allowed by a law under some specific circumstances. Furthermore, it is relevant to consider whether anonymisation of a tissue sample (that still contains genetic information of the research subject) takes the interests of the research subject adequately into consideration. Hartlev has argued that anonymisation as such may not be a sufficient measure. Regarding the perspective of recognition of the principle of self-determination, for some the possibility to define or decide for which purposes their tissue samples are being used may also be a matter of even greater significance.

509 For instance, according to Section 6 the Finnish Medical Research Act No. 488/1999, as a main rule medical research on persons may not be conducted without the research subject’s informed consent in writing. When it comes to revocation of consent: “[r]esearch subjects shall be entitled to withdraw their consent at any point prior to the completion of the research. They shall be informed of this right before the start of the research. Withdrawal of consent and resulting withdrawal from the research shall not involve any negative consequences for the research subject.” However, subsequent to a recent amendment to (inclusion of a new Section 6a), the personal data of the patient may be used for purposes of the study for which the clinical trial subject has given his/her consent under some specific circumstances even after revocation of the consent. Requirements for such use of personal data are following: the use of personal data is necessary for assessment of use, properties or effects or efficacy of a medicine, medical device or a method, or for purposes of quality assurance, effectiveness or safety of a medicine, medical device or a method, and the research subject knew when giving his/her consent that such personal data would be processed as a part of compilation of research data.
510 Hartlev, supra note 135, 260-261.
7.3.3 The EU Data Protection Regulation imposing requirements for processing of research data

Despite a wider analysis of implications of the new EU General Data Protection Regulation 2016/679 (the GDPR)\(^5\) is left outside the primary scope of this study, there is a need to briefly outline some aspects that influence data controlling and processing in context of clinical trials and traceability aspects of ATMPs in particular. Compliance with data protection requirements is of paramount importance for protection of the privacy and integrity of participants of clinical trials or donors of materials of human origin. Yet, it should be noted that compliance measures needed to comply with more stringent EU-wide, mandatory data protection requirements may cause additional financial burden for SMEs that are struggling with limited financial and human resources.

As a starting point the protection of natural persons in relation to the processing of personal data is a fundamental right. Article 8(1) of the Charter of Fundamental Rights of the EU and Article 16(1) of the TFEU provide that everyone has the right to the protection of personal data concerning him or her. GDPR shall apply to any processing of personal data in the context of the activities of an establishment of a controller or a processor of data in the EU, regardless of whether the processing itself takes place within the EU or not.\(^5\) Pursuant to the GDPR, the definition of personal data is defined as “any information related to an identified or identifiable natural person or data subject.” An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that person.\(^5\) The definition of sensitive personal data has been expanded to cover genetic data and biometric data processed to identify a person uniquely.\(^5\) The GDPR shall not be applicable to anonymised data. Yet, it should be noted that the GDPR recognises that there is category of data between anonymised and personally identifiable data. Such category is called pseudonymised data, personal data that has been processed in such a way that the data can no longer be related to a specific data subject without the use of additional information as long as such additional information is kept separate and

\(^5\) It was finally formally approved by the EU Parliament on 14 April 2016 after more than four years of debate, lobbying and negotiations. GDPR is expected to be published in the Official Journal of EU in June 2016, which will begin a two-year transition period. During that transition period, the data processors should review and adjust their data processing practices in order to meet the new requirements imposed by the GDPR.

\(^5\) See Article 3. Entities processing personal data on behalf of a data controller will have direct and independent obligations to comply with particular data protection requirements which previously only applied to data controllers.

\(^5\) Article 4.1.

\(^5\) Article 9.1.
subject to technical and organisational measures to ensure that is not attributed to an identifiable person.\textsuperscript{516}

The transparency and publication requirements of arising out of Clinical Trials Regulation raised some data protection related issues to be resolved in a public consultation of the Clinical Trials Regulation. Specific concerns have been expressed that presentation of information in documents that are sent to the clinical trials portal, or errors in the Member States’ or sponsors’ redaction in such documents, may result in involuntary publication of either protected personal data or confidential commercial data.\textsuperscript{517} For instance, clinical trial result summaries may include information that indirectly can be associated with individuals (despite the information about adverse reactions is structured according to Annex IV and V) or notice and summary of a serious breach may also include similar personal data.\textsuperscript{518} Especially, in case of an orphan disease the patient population may be so small that despite anonymisation, the data risks becoming attributable to a specific patient. The EMA’s legal responsibilities as data controller regarding the content of the database needed further clarification. As a starting point, the EMA is responsible for ensuring that no such information will enter the public domain. In an automated system, it may not be possible for the EMA to manually review all submitted documents to ensure that they do not contain such confidential information or personal data. Therefore it would be advisable for the EMA to e.g. issue templates or specific guidelines for submission of data in the different situations where a risk of inadvertent publication of confidential business information or personal data exists.\textsuperscript{519} Also concerns were expressed that the definition of commercially confidential information, as no specific examples of information from registration or summary results that should be commercially confidential have been provided.\textsuperscript{520}

When it comes to relation between the transparency requirements of the Clinical Trials Regulation and the Trade Secrets Directive\textsuperscript{521}, pursuant to the Trade Secrets Directive the public interest prevails over private interest and care subject to legal obligations to disclose information of public interest, e.g. in pharmaceutical sector. According to the Trade Secrets Directive, regulations ensuring a high level of

\textsuperscript{516} Recital 26.
\textsuperscript{518} Ibid.
\textsuperscript{519} Ibid.
transparency will not be affected. Hence, trade secrets may not be used to negatively affect protection of public health.\textsuperscript{522}

As mentioned in Section 7.3.2 above, tissue donors may have a particular interest in self-determination and privacy protection in regards to those samples. The GDPR imposes more stringent consent requirements: consent for the processing of personal data must be clear and have an unambiguous indication of a data subject’s agreement to the processing of their personal data. A request for consent must be “clearly distinguishable” from any other issues in a written document, and it must be provided “in an intelligible and easily accessible form, using clear and plain language”.\textsuperscript{523} Thus, consent may not be “veiled” within other contractual documents. If consent obtained prior to the application date of the GDPR does not meet the requirements set forth in the GDPR, new consent should be sought from the data subjects. The GDPR also imposes an obligation to appoint a data protection officer in certain circumstances, such as large scale processing of sensitive personal data.\textsuperscript{524} Furthermore, the GDPR requires that data controllers provide more detailed information to the data subjects.\textsuperscript{525} The GDPR also confers new rights for individuals. These include, for example, the right to have personal data deleted and data portability.\textsuperscript{526} Data controllers and processors will be obliged to use appropriate and organizational measures taking into account “the state of the art and costs of implementation” and “the nature, scope, context, and purposes of the processing as well as the risk of varying likelihood and severity for the rights and

\textsuperscript{522} The interfaces of the Trade Secrets Directive and the Clinical Trials Regulation that aims at promoting transparency of clinical trials via publication of research results in a centralised database have been left outside of the scope of this study. Yet these considerations would require further clarification.

\textsuperscript{523} Recital 32.

\textsuperscript{524} Under Article 37 data protection officer shall be appointed i) if the processing is carried out by a public authority; ii) if core activities of the controller or the processor consist of processing operations which, require regular and systematic monitoring of data subjects on a large scale; or iii) if sensitive data is processed on a large scale. The wording of the GDPR does not contain any quantitative thresholds (e.g. in terms of number of data subjects) with respect to an obligation to appoint a data protection officer.

\textsuperscript{525} The GDPR contains an extensive list of information that controllers are obliged to provide to data subjects. Information requirements slightly vary depending on whether the personal data is to be obtained directly from the data subject (Article 13) or indirectly from somewhere else (Article 14). Information must be provided in a concise, transparent, intelligible and easily accessible way using clear and plain language. The GDPR also requires data controllers and processors to maintain records relating to their respective processing activities. Such records must be made available to the supervisory authority upon request.

\textsuperscript{526} Under Article 17 data subjects shall have the right to request the deletion of personal data, e.g. if i) the data is no longer needed for the purposes by which it was collected; ii) the data subject withdraws consent; iii) the data subject objects to the processing; or iv) the data was processed unlawfully. If the data controller has an obligation to erase data, it must also take reasonable steps to inform other controllers that are processing the data about the person’s objection. The GDPR contains a list of exemptions to the right to be forgotten. Whereas data portability requires the data controller to provide the data subject with the personal data concerning him/her in a structured, commonly used, machine-readable and interoperable format. Data portability under Article 20 applies only to data that has been provided to the data controller by the data subject where the processing is based on the data subject’s consent or data is being processed to fulfill a contract.
freedoms of individuals. The GDPR also includes a notification obligation in case of a breach of personal data and penalties arising in case of non-compliance.

The GDPR also requires controllers and processors to conduct a privacy impact assessment of the impact of the envisaged processing operations if the processing poses a high risk for the rights and freedoms of individuals. In this assessment, the nature, scope, context and purpose of the processing and the sources of the risk should be taken into account. In the GDPR, a systematic and extensive evaluation of personal aspects related to natural persons that is based on automated processing as well as processing of sensitive personal data on a large scale is mentioned as an example of high risk processing. If a privacy impact assessment indicates a high risk, consultation with a supervisory authority is mandatory.

When it comes to protection of personal data in transatlantic context, the European Commission has recently adopted the so-called “Privacy Shield” arrangement by issuing an adequacy decision on 12 July 2016. It provides an additional mechanism for European companies to legally transfer personal data from the EU to the U.S., and it will replace the Safe Harbour Agreement invalidated by the ECJ (case C-362/14) in October 2015.

527 Article 32.1. of the GDPR provides a list of security measures that may be regarded as “appropriate”: pseudonymisation and encryption of personal data; the ability to ensure ongoing confidentiality, integrity, availability and resilience of systems and services processing personal data; the ability to restore the availability and access to data in a timely manner in the event of a physical or technical incident; a process for regularly testing, assessing and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing.

528 Under Article 33 of the GDPR, in the event of a personal data breach, data controllers must notify the appropriate supervisory authority without undue delay and, where feasible, not later than 72 hours after becoming aware of the breach. Notice is not required if the personal data breach is unlikely to result in a risk to the rights and freedoms of individuals. Minimum content requirements for notice are provided for in the GDPR. In the event that a data processor experiences a personal data breach, it must notify the controller but does not have an obligation to notify the data protection authority. The GDPR also requires a data controller to inform data subjects without undue delay about the breach if the breach is likely to result in a high risk to the rights and freedoms of individuals.

529 Under Article 83 of the GDPR, the supervisory authorities may impose administrative fines on data controllers and processors for non-compliance with provisions of the GDPR. There will be two tiers of fines:
a) Max 10M EUR / 2% of total worldwide turnover, e.g. for a breach of obligations related to the implementation of organizational and technical measures to protect privacy; the use of data processors; data breach notifications; appointment and responsibilities of data protection officers. b) 20M EUR / 4% of total worldwide turnover, e.g. for a breach of obligations related to fundamental data processing principles; the requirements for obtaining consent from data subjects; data subjects’ rights regarding access to information, the right to be forgotten, the right to restrict the use of data, data portability obligations and the right to object to automated data decision-making; the transfer of personal data to third countries; and non-compliance with an order from a supervisory authority. Fines may be imposed instead of or in addition to other measures available for supervisory authorities. Such measures include warnings, reprimands, bans and suspensions. Any fines imposed by the supervisory authorities must be effective, proportionate and dissuasive. For example, the nature, gravity and duration of the violation, actions taken by the data controller to mitigate the damage, the degree of responsibility of the controller or processor and the type of personal data affected by the violation should be taken into account when imposing the fines.

530 Article 35.

531 Yet, there is a risk that like its predecessor, the Privacy Shield may also be challenged before the ECJ. Therefore, European companies should not rely on the new Privacy Shield as the only mechanism for
All in all, the data protection requirements imposed by the GDPR play an important role in protection of privacy of research subjects. They also simultaneously constitute additional administrative and financial burden for SMEs and academia, as adequate processes and personnel need to be in place to comply with the requirements. Data protection constitutes an essential element of a quality management system of a company developing medicines. As clinical trials rely on data, business continuity planning is a critical aspect to protect data during the required retention time. Escrow agreements with providers of escrow services are likely to become more and more common means to ensure that such relevant pieces of information and audit trail can still be accessed in the case of an unanticipated event.

7.4 Lack of harmonised classification of ATMPs

It appears that the clarity in the ATMP Regulation is impaired when its scope is further explored. The ATMP Regulation introduced a new mutual term of “advanced therapies”. However, the use of cells within its sphere of activity is also very often used for non-therapeutic purposes (e.g. as models for toxicology screenings or for an *in vitro* study of mechanisms of particular diseases). Broadly speaking, tissue engineering covers the use of cells and tissues to repair or replace existing malfunctions in components of the human body. Despite the term “tissue engineering” has been often used as an alternative to “regenerative medicine”, it appears that the latter has become synonymous with stem cells. It has been also reported by Barfoot et al. that nearly half transferring personal data from the EU to the U.S. but also continue to adhere to the existing transfer mechanisms (such as the Standard Contractual Clauses and Binding Corporate Rules). There is no certainty whether the Privacy Shield will be greeted with satisfaction by the Article 29 Working Party, a body representing all EU data protection authorities, which is predicted to issue its opinion on the new arrangement shortly.

Pursuant to Article 15.1 the ATMP Regulation, the holder of a marketing authorisation for an shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used. The marketing authorisation holder shall keep such data for a minimum of 30 years after the expiry date of the product, or longer if required by the European Commission as a term of the marketing authorisation (Article 15.4).

Among other things following aspects need to be addressed: Are trial master files sufficiently safe if the company goes out of the business? If a site or contract research organisation closes down, who keeps information (e.g. informed consents)? If the contract research organisation closes who conducted the study goes out of business, how the access to all of the standard operating procedures can be ensured in such circumstances?

of all stem cell papers use keywords related to “drug development” or “regenerative medicine”. Currently “tissue engineering” is usually used to describe the creation of parts of the human body, covering even entire organs. As a consequence, “tissue engineering” that by using cells or tissue to create tissue or body parts or whole organs for transplantation is a term that intersects with three related forms of technology: antisense technology (utilising RNA to interrupt a cell’s ordinary function, meaning a technology that interrupts the production of proteins, but cannot e.g. result in the production of a different protein), somatic gene therapy (utilising DNA to genetically alter an adult cell’s normal function) and stem cell technology (utilising a stem cell that divides and can be reprogrammed to a specific cellular function). As for application of these three forms of health technologies, tissue engineering overlaps with transplantation and therapy. When it comes to antisense technology, it is restricted to a form of therapy for its application. As for somatic gene therapy, it is evidently therapeutic, however the products used in the therapy can be used e.g. to manufacture bio-pharmaceuticals, or they can be utilised as models for toxicological screenings. When it comes to the stem cell technology, it can be used in any of the applications described above. Furthermore, due to the rapid scientific advancements in the field, it is important to keep the definitions of ATMPs under continuous assessment. New innovative products, which are not explicitly covered by existing provisions (such as combination products that comprise of an ATMP and a medical device), may emerge.

Consequently, the ATMP Regulation fails to be clearly accessible, due to the absence of standardised terminology and disregarding the standard terms when such exist. Despite these technologies are often referred to by using different terms, they are scientifically very closely related or even interlinked depending on their context of application. This makes scientific classification and regulation of ATMPs a very difficult task for the regulators and especially for those applying for marketing authorisations. The rapid advances in the ATMP field, risks to resulting in a lack common scientific terminology, which may in turn result in fragmented use of these ATMP classifications. That may significantly hamper commercialisation of these innovative medicines.

535 Barfoot, et al supra note 84,5. According to Barfoot et al. 47% of stem cell publications used keywords related to regenerative medicine, whilst 2% used keywords referring to drug development.
536 Warren-Jones, supra note 36, 83.
537 Recital 18 of the ATMP Regulation notes that ATMPs may incorporate medical devices or active implantable medical devices. Those devices should meet the essential requirements laid down in Council Directive 93/42/EEC of 14 June 1993 concerning medical devices and Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, respectively, to ensure an appropriate level of quality and safety. Pursuant to the Recital 18 of the ATMP Regulation the results of the assessment of the medical device part or the active implantable medical device part by a notified body in accordance with those Directives should be recognised by the EMA in the evaluation of a combined ATMP carried out under the ATMP Regulation. Please refer to Article 6, 7 and 9 of the ATMP Regulation for further details.
538 Warren-Jones, supra note 36, 83.
There are some significant issues with the uneven practices of national competent authorities regarding ATMPs classifications despite the definitions of “CTMP” and “GTMP” are provided in Annex I to Medical Products Directive and “TEP” is defined in the ATMP Regulation, respectively. It appears paradoxical that even if a developer of an ATMP requests for a classification from the CAT, it is not legally binding, and national competent authorities of Member States frequently classify the same product differently. This concern has been also raised in a public consultation of the European Commission. It was reported by the European Commission that:

“the possibility that the same product may be subject to different requirements across the EU implies that the level of public health protection is different according to the place of residence of the patient. That the same product can be marketed under different regulatory regimes is not only undesirable from a public health standpoint but it also undermines the incentives to develop ATMPs. First, the uncertainty as to the market potential for a product discourages investments. Secondly, divergent classification of the same product distorts competition between developers. Finally, the application of different regulatory requirements across the EU hinders the free movement of these products.”

This constitutes a significant barrier to commercialisation of these medicines. For instance, ChondroCelect is already facing this problem in some Member States where academic and hospital facilities are permitted to produce an autologous chondrocyte preparation in direct competition with this licensed medicine. Another example is a case of three similar products comprising of human natural killer (NK) cells expanded and activated in ex vivo culture over many weeks as an anti-cancer immunotherapy. In France, these products were deemed “not substantially modified” and thus were not regulated as medicines, whereas Spain, Germany and Switzerland classified these products as ATMPs. The U.K. authorities classified a significantly less-manipulated NK cell product in which the cells were simply activated and not expanded as an ATMP. As for the future development of these products, those regulated as medicines could presumably follow a drug development trail to generate necessary data for a marketing authorisation application to the EMA, whereas in the case of the NK cell product that is perceived a ‘non-substantially modified’ preparation, it is unclear how this might be developed if the clinical trials were successful. This product does not appear commercially valuable, as it cannot follow a drug development pathway. In the absence of adequate efficacy trials that are systematically organised and controlled, these non-medicinal products cannot be provided to a wider group of patients.

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Furthermore, the licensed NK cell medicine would not be legally protected from competing unlicensed products. Notwithstanding, the issues relating to divergent classifications by national competent authorities, classification is helpful as such, because it provides the developers of ATMPs the possibility to share a preliminary understanding of particular issues applicable to their medicine in development (GMP and GCP requirements depend on the ATMP’s subclass). Yet, the national competent authorities cannot use the classification procedure when they face difficulties with classification of ATMPs.

7.5 Challenges with adaptation to industry-scale requirements

GMP compliance plays an essential role in ensuring the quality of ATMPs. Yet, the inherent characteristics ATMPs (including, but not limited to e.g., variability of the starting materials, small batch sizes, short shelf-life etc.) constitute particular challenges for the manufacturing process of these innovative products. Furthermore, early phases clinical research may take often place in hospitals that operate under quality systems that differ from those of the pharmaceutical sector. Article 5 of the ATMP Regulation requires the European Commission to draw up GMP Guidelines specific for ATMPs. Quality control is essential for ensuring the safety and efficacy of ATMPs. The ATMP manufacturer is responsible for safeguarding the quality of the product and the manufacturing process is adequate. GPM compliance constitutes an integral part of the pharmaceutical quality system. The European Commission has in its consultation document classified the main objectives of GMP as follows:

i. “the personnel is adequately trained and there is clear allocation of responsibilities;
ii. there is a good documentation system that ensures that appropriate specifications are laid down for starting and raw materials, as well as intermediates and bulk products, that the production process is clearly understood, and that appropriate records are kept;
iii. the production process is adequate to ensure the quality of the product, that measures are in place to identify any process deviation, and that appropriate action is taken in such cases;
iv. there is a quality control system which is independent from production;

quality defects are identified as soon as possible, the causes investigated, and appropriate measures are taken; and

vi. The premises and equipment are suitable and that there is appropriate maintenance."

Furthermore, it has been stated by the European Commission that self-inspections should be conducted for purposes of (i) monitoring compliance with GMP; (ii) ensuring that the specific requirements provided for in the marketing authorisation or clinical trial authorisation are fulfilled; and (iii) to take corrective measures if needed.

The following Sections 7.5.1 and 7.5.2 discuss the specific challenges SMEs, universities and public hospitals encounter with adaption to industry-scale standards. Also some of the recently proposed adaptations to the GMP requirements will be briefly discussed.

7.5.1 Industry’s strong influence on levelling the playing field

The ATMP impact assessment report discloses that the representatives of the industry found the originally suggested wording of “placing on the market” as inadequate, as it did not encompass ATMPs produced and utilised in the same facility (e.g. in-house use in hospitals).

It appears that the vast majority of the parties involved supported a view that public tissue establishment, research units in the academia and other local players should be required to comply with the same regulations as companies. It should be noted that this view was apparently biased, as the great majority of consulted specialists were actually representing, or affiliated with pharmaceutical industry.

In the initial draft of the ATMP Regulation, it was envisioned that it shall not be applicable to:

“[a]ny ATMP that is prepared by a qualified and licensed professional, such as a pharmacist, physician, or trained and certified biologist, on an exceptional basis, in order to comply with a medical prescription for an individual patient; the product must be prepared in full at the site of treatment of the patient, and without using standardised or patented processes.”

Eucomed lobbied successfully to eliminate this exclusion and expressed that:

“[w]e believe that the European Union should be a level playing field for those researching, designing and manufacturing hTEPs, but overall, we believe that patients should be entitled to have access to hTEPs based on the highest safety, quality and efficacy standards. This cannot be reached

545 Ibid.
546 ATMP IA report, supra note 170, see 5.1. “Economic and competitiveness impacts”. See also Pirnay, et al., supra note 22, 546. Mansnérus, supra note 22, 436.
547 ATMP IA report, op. cit., see 8.2.1 “Overall strategy”.
548 Pirnay, et al., supra note 22, 546.
549 Eucomed ATMP Regulation Proposal, supra note 170, Article 1.2.a of the intial draft, “The point under (a) would not ensure equal access for patients to high level safety, quality and effective hTEP”, in Eucomed’s view.
if different rules apply depending on the nature of the business of the manufacturer. For this reason, we oppose the creation of special rules for 'one-off, non-industrially manufactured' hTEPs.\footnote{Eucomed ATMP Position Paper, \textit{supra} note 170, 2.} 

In addition, Eucomed insisted on scope of the ATMP playing field that:

“\[p\]atients should be assured that the treatments they receive are safe, are of high quality, and perform as intended, no matter who prepares the treatment. The text needs to be amended to ensure that this is the case. Currently the proposal is worded in such a way that hospitals might be able to avoid complying with the provisions of the regulation, whereas industrial manufacturers of similar products would bear the obligations of compliance.”\footnote{Eucomed ATMP Backgrounder, \textit{supra} note 170, 1.}

Whilst, the parties representing health care professionals and academia voiced a concern that the exclusion was too constricted. Also the definition of an “industrial manufacturing process” was perceived as too ambiguous. In addition, it was argued that hospitals and academia should not be imposed superfluous regulatory requirements (e.g. marketing authorisation requirements).\footnote{ATMP IA Report, \textit{supra} note 170, see 4.1.4 “Semi-centralised and 2-tier authorisation procedure”.} These views notwithstanding, it was finally resolved that any ATMPs, also those produced and used for treating single patients in hospitals, shall be covered by the ATMP Regulation. The DG JRC-IPTS evaluation studies reveal that the data available regarding the extent of the tissue engineering activities of public tissue establishments was very limited.\footnote{Bock, et al., \textit{supra} notes 74 and 77. Pirnay, et al., \textit{supra} note 22, 540. Mansnérus, \textit{supra} note 22, 437.} These evaluation studies incorrectly assumed that hospitals conducted research or produced fairly simple, autologous TEPs for in-house treatments and considered tissue engineering merely as a future strategic opportunity, but did not yet produce any TEPs yet. Furthermore, tissue-engineering in Europe market in EU was found to be “characterised by young, small, research-based and technology-oriented companies, most of them SMEs with less than 50 employees.”\footnote{Fisher, M.B., Mauck, R.L. Tissue engineering and regenerative medicine: recent innovations and the transition to translation. \textit{Tissue Eng Part B Rev.} 2013 Feb;19(1):1-13. Hourd, P., Chandra, A., Medcalf, N. and Williams, D. J., Regulatory challenges for the manufacture and scale-out of autologous cell therapies (June 30, 2014), \textit{StemBook}, 2 (ed.) The Stem Cell Research Community, StemBook, doi/10.3824/stembook.1.96.1.} According to Eucomed’s position paper on ATMPs, in addition to SMEs that represented the great majority of producers of TEPs, also larger corporations were interested in investing in this promising field of medical technology.\footnote{Eucomed ATMP Position Paper, \textit{supra} note 170, 2.}

As for the current state of the ATMP market, the research and development in ATMPs is maturing.\footnote{Eucomed ATMP Position Paper, \textit{supra} note 170, 2.} Yet, it appears that the big pharmaceutical companies have generally a rather limited interest in investing in R&D of ATMPs or acting as a sponsor in clinical trials involving those products. Especially, big Pharmaceutical companies seem to be reluctant to engage in so-called high risk early investigational clinical
trials. Some commentators believe that this situation is changing. However, it appears that in the EU the major stakeholders involved in development of ATMPs are hospitals, academic institutions, non-profit organisations and SMEs. Especially, academic and clinical centres with GMP compliant manufacturing facilities are becoming more common across the EU and they now play an important role in translation of research to GMP compliant research protocols. They are also a significant provider of pre-clinical and clinical trial GMP-grade material.

When it comes to the current clinical pipeline of the ATMPs, according to a recent report issued by the European Commission, the majority of research in ATMPs is conducted by small companies and entities that operate on a non-for-profit basis. Almost 70 percent of sponsors for clinical trials on ATMPs reported in EudraCT are non-for-profit organisations or SMEs; big pharmaceutical companies account for less than 2 percent of all sponsorships. Likewise, it has been reported that the majority of applications for scientific advice to the CAT are also submitted by SMEs. There is a concern that if big companies are not interested in development of ATMPs, it may become financially very difficult for SMEs to organise the late scale clinical trials, as they usually cannot afford so comprehensive clinical trials needed for marketing authorisations.

As for the current pipeline for cellular therapies in particular, the development of new cell therapies appears predominantly investigator-led in the EU (as well as in the U.S) and it has been noted that the Europe is currently still lagging behind the U.S in terms of number of cellular therapies in clinical trials.

Foley et al. have reported that based on the information acquired from the U.S. National Institute of Health’s global clinical trial data base there are two prominent groups of the cellular therapies in development; first type clinical trials are investigator led autologous cellular therapies that focus mainly on procedures (i.e. therapies with complex routes of administration) representing 63% of all clinician-led trials (number of trials:437) and the second type of clinical trials are company-led cellular therapies that are mainly allogeneic and product-focused (i.e. therapies where intervention is minimal) representing 44% of all company-led trials (number of trials:66). According to Foley

561 European Commission, supra note 6,3.
562 Hourd, et al., supra note 556,2.
et al., only 22 of 66 company-led trials involve autologous therapies (33%), whereas 333 of 437 clinician-led trials (involving both procedures and products) are autologous (76%). All in all, Foley et al. report that of the 503 trials sampled and estimated, 437 are conducted by clinicians (87%) and 66 by companies (13%), and 149 (30%) are products and 354 (70%) are procedures. Furthermore, the global industry data compiled by the Cell therapy Group shows that by August 2012 there were 48 later stage industry-sponsored clinical trials of cell therapies in Phases III or Phase II/III, of which 59% were autologous. In Europe, where the U.K. is one of the leading countries in Europe developing ATMPs (together with Germany and Spain), the U.K. data suggests that by April 2013 there were 34 ongoing cell therapy clinical trials in the U.K. (mainly in Phases I/II or II), of which 23 were autologous (68%). The majority (76%) of these clinical trials were sponsored by a research institution with only 6 were sponsored by industry.

Not surprisingly, these findings seem to be in line with the recent report issued by the European Commission demonstrating that the majority of research in ATMPs is conducted by SMEs, charities and academia. Among others Hildebrandt et al. have suggested that IP and reimbursement related issues do not encourage big pharmaceutical companies to invest in R&D of ATMPs. The IP and reimbursement aspects of ATMPs have been discussed in Section 7.2. and 7.8 of this study. Especially, the recent case law of the ECJ (and subsequent decisions of the EPO’s Boards of Appeal) limiting patentability of human embryonic stem cell applications constitutes an additional hurdle for commercialisation therapies of embryonic origin. Hildebrandt et al. also mention the fact that ATMPs are more closely related to transplantation, a field that does not interface much with traditional industrial R&D.

Furthermore, as the costs of launching a new medicine to the market are very high pharmaceutical companies tend to focus on potential blockbuster medicines instead of

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564 Foley, et al., op.cit.
566 Maciulaitis, et al., supra note 559, 481 (see Figure 3.). Hourd, et al., supra note 556.4.
569 European Commission, supra note 6.9.
571 Case C-34/10 Oliver Brüstle v. Greenpeace e.V. [2011] OJ C 362/5 Judgment of the Court (Grand Chamber) of 18th of October 2011. The case is a reference for a preliminary ruling under Article 267 TEU from the German Bundesgerichtshof made decision 17 December 2009 on the interpretation and scope of application of Article 6.2.c of Directive 98/44/EC. See also T2221/10, Technion Research and Development Foundation Ltd., 4 February 2014. See also T 1441/13, Embryonic stem cells, disclaimer /ASTERIAS), 9 September 2014.
572 Hildebrandt, et al., supra note 570, 3.
niche applications.\textsuperscript{573} While the global revenue of leading cell therapy medicines have been estimated to be rather modest in relation to their significant R&D costs.\textsuperscript{574} Currently, it appears that ATMPs are usually developed by academia or hospitals and SMEs in a nearly complete absence of big pharmaceutical companies that predominantly develop conventional medicines.\textsuperscript{575} Furthermore, it should be noted that unlike incorrectly assumed in the DG JRC-IPTS evaluation studies, public tissue establishments have supplied the great majority of grafts that have become ATMPs today.\textsuperscript{576} Pirnay et al. find SMEs and especially public biobanks essential for ATMP development and production, as they are the only actors targeting grafts on niche markets, which appear less appealing for large corporations.\textsuperscript{577} However, their vital function as drivers for the R&D and production of ATMPs seems to be disregarded.\textsuperscript{578}

More recently the EMA has acknowledged that the complexity of the existing EU-wide legislation is inhibiting providers of ATMPs from launching their therapies to the market, as their resources are insufficient to comply with the regulatory requirements.\textsuperscript{579} The EMA has expressed its willingness to foster the development of ATMPs by strengthening the dialogue with the stakeholders involved and providing further assistance to them.\textsuperscript{580} As for hospitals performing cellular therapies, it has been argued that their clinical routine should be taken into account by the revision of the applicable legislation.\textsuperscript{581} Concerns have been expressed regarding the irremediable harm that is being done as some hospitals and SMEs are abandoning their endeavours in ATMP field due to insurmountable regulatory and financial obstacles.\textsuperscript{582} As a remedy to this situation, it has been proposed that the ATMP Regulation should be urgently revised to focus on delivering affordable therapies to all needy patients without necessarily going to the market. Especially, it has been argued that a level playing field


\textsuperscript{574} Pirnay, et al., \textit{ supra} note 22, 554. Reference is made to Bredin, P. Avis HMRA—Keratinocytes—2012.


\textsuperscript{576} Hildebrandt, et al., \textit{ supra} note 570.4. See also Pirnay, et al., \textit{ supra} note 22, 547. Mansnérus, \textit{ supra} note 22, 438.

\textsuperscript{577} Pirnay, et al., \textit{ op.cit.}, 548.


\textsuperscript{580} Op.cit.


\textsuperscript{582} Pirnay, et al., \textit{ supra} note 22, 549. See also Mansnérus, \textit{ supra} note 22, 439.
is appropriate for public institutions and SMEs providing tailor-made and/or niche ATMPs. Pirnay et al. have expressed that these actors:

“[s]hould not face requirements that go beyond the accreditation system and the quality and safety standards laid down in the EUCTDs and this for all aspects of their existence, from donation to distribution. Unless the EUCTDs are proven to be insufficient to ensure patient safety (not market access), these non-commercial ATMPs should be kept outside of the scope of the Medicinal Product Regulation.”

To reach this it was suggested that the European Commission could issue interpretative guidelines on placing on the market of ATMPs. Yet, an adequate level of public health protection should prevail over economic interests. Very recently, the European Commission has actually, provided draft GMP Guidelines that suggest some ATMP specific adaptations to GMP standards. These draft Guidelines will be discussed in further detail in Section 7.5.3 below. Interestingly, despite the transition to GMP manufacture added significant costs; a study by Pearce et al. confirms that most of the interviewed research centres agreed that it was a necessary process and that these complex therapies needed regulation. Actually, none of the 50 European academic research centres that responded to Pearce et al.’s study supported the concept of a lower standard of GMP for ATMPs than for conventional medicines, nor did they think that academic groups should be allowed to work to a lower GMP standard than industry. However, all interviewees supported risk-based approach to comply with pharmaceutical standards in the development of ATMPs.

Moreover, there is a concern that unnecessarily strict EU-wide legislation is not beneficial for the emergent European ATMP market. Too stringent regulations may also result in forum shopping, as to maximise on revenues pharmaceutical companies tend to outsource their R&D and manufacturing facilities to off shore jurisdictions, where the regulatory atmosphere is not predominantly risk averse. Pearce et al. report that the regulatory burden in the EU has not yet put academic clinical investigators at a significant disadvantage in relation to their overseas competitors. However, it was noted that patients are traveling to another Member State to gain access to experimental ATMPs that are in the absence of regulatory approvals unavailable in their local centre. Concerns have been raised that the non-harmonised regulation drives patients to seek for novel therapies in jurisdictions where the ethical oversight might be inferior to the EU standards. Stem tourism has been expressed as a serious ethical and health

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583 Pirnay, et al., supra note 22, 553.
584 Ibid.
585 Pearce, et al., supra note 540, 295.
586 Op.cit., 294
587 Ibid.
588 Pirnay, et al., supra note 22, 553. See also Mansnérs, supra note 22, 440.
589 Pearce, et al., supra note 540, 295.
concern by the International Society for Stem Cell Research, which deems that excessively positive information on benefits of unproven stem cell therapies has been provided. Concerns has been expressed that stem cell tourism constitutes a major problem in the field of treatment of degenerative diseases that damages patients and their relatives and slows down the serious development of effective stem cell therapies. For the responsible application of stem cell therapies in patients with degenerative diseases, it would be important to define clinical roadmaps (i.e. major milestones in basic and clinical research that need to be achieved, and the ethical, regulatory, societal and financial issues that need to be addressed). Properly controlled clinical trials play a vital role in the battle against stem cell tourism.

In addition, subsidiary principle constitutes another challenge, as each Member State may prohibit the use of certain therapies (e.g. therapies using certain cell types, e.g. hESCs) on its territory for ethical reasons. Hence, despite a granted centralised marketing authorisation, commercialisation of some medicines may turn out to be impossible in some Member State.

7.5.2 Incompatibility of industrial standards with tailor-made and niche applications

It was already noted in the Report from EuropaBio’s Industry Hearing that in the U.K, as well as in some other EU countries tissue engineering R&D takes place on a very small developmental scale in many small spin-off companies and specialist research hospitals. Richard Woodfield from the MHRA states that R&D of ATMPs is very strongly iterative and characterised by a gradual emergence of efficacy. He also pointed out that another concern, the issue of hospital production, is of particular

593 See e.g., Lindvall, et al., op.cit., 3-13.
595 See e.g., Barclay, supra note 590.
596 EuropaBio Stakeholder Meeting Report, supra note 170, 10.
597 Ibid.
importance. Furthermore, he addressed the technical requirements of a tiny scale hospital production: ‘‘clearly these need to be risk-based and fully proportionate, to reflect the characteristics of the individual product.’’598 This particular iterative nature of R&D and risk-proportionate approaches in ATMP context will be discussed in further detail in Sections 8.2 and 8.3 of this study.

Eucomed ATMP Backgrounder raised a concern that some ATMPs that were prior to implementation of the ATMP Regulation authorised by national competent authorities in the Member States risk to be taken away from patients.599 It has been reported by Pirnay et al. that some public tissue establishments had to discontinue the production of their established therapies due to stringent regulatory requirements following from the ATMP Regulation.600 There is a problem that today some regenerative therapies are exclusively provided by the public sector under the hospital exemption. As some actors in public sector are not capable of implementing the requirements of the ATMP Regulation, valuable established therapies are risking becoming unavailable in some Member State.601

Pirnay et al. mention as an example Belgian keratinocyte banks that had been supplying human keratinocytes for the treatment of burns and chronic skin wounds since 1980s to more than 1000 severely burnt patients were notified by the national competent authorities that their products are perceived as ATMPs and that the administration of these products to patients as used it to be performed (i.e. exclusively under the scope of the EUCTD’s) has not been permitted after 30 December 2012. They were not allowed to continue administration of their grafts to patients despite the fact that periodic inspections by the authorities had not revealed significant quality or safety issues, which caused some established operators to exit the market.602

When patients are denied access to some established therapies, the ATMP Regulation risks to have a direct adverse impact on health care professionals’ ability to treat them.

As discussed above, the big pharmaceutical companies seem to have only a limited interest in investing in R&D of ATMPs. Hence, there is much hope associated with R&D activities of SMEs that are better suited to pursue niche markets. However, as mentioned, there are currently only six ATMPs on the EU market that succeeded in going through the ATMP Regulation funnel and successfully completed the mandatory centralised marketing authorisation procedure. (However, as mentioned there are currently only four ATMPs still on the market). It should be also noted that most of the ATMPs currently being developed by research units in academia and SMEs have not reached a phase of clinical trials yet, which implies a burdensome marketing authorisation process under the ATMP Regulation.603 Improving the availability of

599 ATMP Backgrounder, supra note 170,2. See also Pirnay et. al., supra note 22, 551.
600 Pirnay, et al., supra note 22, 553. See also Mansnérous, supra note 22, 450.
601 Pirnay, et al., supra note 22, 551. See also Mansnérous, ibid.
602 Pirnay, et al., supra note 21, 551. See also De Corte, et al., supra note 5. See also Mansnérous, supra note 22, 451.
603 Pirnay, et al., supra note 22, 551. See also Mansnérous, supra note 22, 451.
ATMPs to patients in the EU is predominantly, but not merely a regulatory task. A granted authorisation procedure does not guarantee that patients will be able to access the ATMP affordably and timely, so much work remains to be done by patient organisations and other stakeholders to lobby for access issues in the EU.

Subsequent to the implementation of the EUCDTs the number of actors operating in the ATMP field decreased significantly due to the more stringent regulatory requirements. Now the same actors are encountering challenges with the ATMP Regulation that imposes another level of costly pharmaceutical industry standards (such as marketing authorisation and GMP requirements), irrespective of whether their tailor-made niche products reach the EU market or not. In particular, it has been criticised that these requirements have been imposed without robust scientific support (e.g., lack of evaluation of quality and safety under the EUCTDs). Especially, progress towards production and commercialisation of tailor-made autologous ATMPs faces considerable translational challenges under the existing regulatory framework. Hourd et al. point out that distinction between autologous and allogeneic therapies influences the product safety and efficacy model, as well as the approaches to manufacturing, logistics and clinical administration of the ATMP, which respectively affects the technical and regulatory requirements for development and commercialisation of safe and effective cell-based ATMPs at the required scale and cost. Among other things they have found that manufacturing and supply of more-than-minimally manipulated autologous cell-based ATMPs encounters numerous specific challenges caused by complex supply logistics and the need to scale-out production to multiple manufacturing sites or potentially near to the patient within hospital settings. Especially, they argue that the requirement to establish and maintain comparability risks to become under a single market authorisation an insurmountable burden for the roll-out of manufacturing processes to more than two or three sites.

The drafting history of the ATMP Regulation reveals that these mandatory requirements were created for and in close cooperation with big pharmaceutical companies, which usually manufacture large amounts of medicines to be used by vast masses of patients. Hourd et al. specifically note that in contrast to allogeneic therapy or traditional pharmaceuticals or biologics production, manufacturing and supply of autologous ATMPs is characterised by complicated supply logistics and the need to

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606 See e.g. Pirnay, et al., supra note 22, 549. Pirnay, et al. refer to number of bone banks that was reduced by a third.

607 Hourd, et al, supra note 556, 1.


609 Pirnay, et al., supra note 22, 551. See also Mansnérus, supra note 22, 444.
scale-out rather than scale-up production.\textsuperscript{610} Whilst it has been noted that the great majority of companies seem to pursue highly profitable business models involving mostly scalable allogeneic therapies that follow a conventional business and supply model similar to that of the conventional biopharmaceuticals.\textsuperscript{611} In contrast, it has been reported that autologous ATMPs are developed in smaller quantities and they need to adapt to alternative manufacturing and distribution methods, depending on the ATMP (for instance, indication and prevalence of the disease), the method of preservation of the ATMP and the fit with the systems in place at the hospital where the ATMP will be finally administered. \textsuperscript{612} Pearce et al. have also expressed a view that as most of ATMPs are personalised to individual patients or produced in very small batch sizes “\textit{it is unlikely that many will fit the conventional pharmaceutical model of a single batch providing treatments for thousands of patients.}”\textsuperscript{613} A centralised marketing authorisation may provide an incentive for companies; however other actors such as hospitals, public tissue establishments and academic research units do not usually pursue marketing authorisations.\textsuperscript{614} Furthermore, it has been argued that standards designed in cooperation with big pharmaceutical industry actors are not compatible with niche applications where it is hard to benefit from economies of scale, or with tailor-made single patient procedures with restricted time frames.\textsuperscript{615} Both SMEs and public tissue establishments encounter this problem, as for instance GMP facilities are only profitable when manufacturing medicines on a larger industrial scale.\textsuperscript{616} The DG JRC-IPTS evaluation study anticipated the current trend of concentration due to adaptation to national and EU standards will continue:

\begin{quote}
“\textit{[a]dapting to and compliance with the regulation could tie up resources that might otherwise be available for investment in R\&D. This is felt to be particularly likely in the case of SMEs. As well as delaying the launch of hTEPs and limiting the range a given company develops and produces,}
\end{quote}

\begin{thebibliography}{9}
\bibitem{610} Hourd, et al. \textit{supra} note 556, 5. Hourd, et al. report that Japan and South Korea have considered different regulatory evaluation approaches based on adaptive licensing or conditional marketing approvals. According to Hourd et al. these approaches are based on stepwise learning and iterative phases of data accrual and regulatory re-evaluation, which allows commercial sale in certain instances whilst pivotal trials are being conducted.
\bibitem{613} Pearce, et al., \textit{supra} note 540, 294.
\bibitem{614} Pirnay, et al., \textit{supra} note 22, 549. See also Mansnérus, \textit{supra} note 22, 445.
\bibitem{616} Pirnay, et al., \textit{op.cit.}, 549. See also Mansnérus, \textit{op.cit.}, 445.
\end{thebibliography}
this could tip the scales in favour of larger firms better able to target pan-European markets. This could then lead to market consolidation in the form of takeovers or product licensing.\textsuperscript{617}

In case of academia, it has been criticised that the administrative challenges GMP and GCP compliance constitutes a true hurdle for small academic manufacturers.\textsuperscript{618} Open access availability of common procedures and reagent/process validations would be extremely valuable for them. It has also been reported that research funding bodies do not seem to understand the burden of paperwork relating to GMP/GCP compliance and do resource them sufficiently.

There is also a specific issue that the formal release of IMP ATMPs in the EU necessitates appointment of a qualified person. In many Member States national competent authorities approve routine pharmaceutical qualified persons for release of complex ATMPs. As many qualified persons experience that these innovative products fall outside of their general area of expertise, they are reluctant to take the risks of releasing IMP ATMPs. The ones conducting clinical trials may encounter difficulties regarding the release of IMP ATMPs. It has been reported that essential adequate training for pharmacy qualified persons in the production of ATMPs is currently lacking. The U.S. authorities do not require qualified persons for a release of IMP ATMPs. It is apparent that the evident lack of proficient qualified persons also results in substantial additional costs in ATMP production, coupled with the fact that these products are usually produced in very small quantities or even in single product batches. The problems arising out of the mandatory qualified person requirement are stressed, as many ATMPs are tailor-made for a single patient and necessitate the final dosing right before administration. Unfortunately, a qualified person required for release of each and every single batch is tremendously expensive and sometimes logistically impossible.\textsuperscript{619}

In addition to the impact of the ATMP Regulation to SMEs, a concern has been expressed that due to the more stringent requirements many hospitals and tissue banks may need to abandon their ATMP efforts in the near future.\textsuperscript{620} Yet, Pirnay et al. predict that:

“[t]o safeguard some life-saving therapies, and because medicine won’t stop on its way, the field might evolve to circumvent legislation and find refuge under the umbrella of the ‘Declaration of Helsinki’ or the ‘single surgical procedure’ rule (e.g. peri-operative processing of cells).\textsuperscript{621}”

\textsuperscript{617} Bock, et al., supra note 77, 10.
\textsuperscript{618} Pearce, et al., supra note 540, 295.
\textsuperscript{619} Ibid.
\textsuperscript{620} Pirnay, et al., supra note 22, 549. The single surgical procedure under EUCTDs is perceived as an easier opportunity to pursue medical advances, but it was found deficient in terms of some quality and safety considerations and the oversight of ATMPs manufactured and supplied by cell and tissue establishments. See also Mansnérus, supra note 22, 446.
\textsuperscript{621} Pirnay, et al., ibid. Recital 8 of Directive 2004/23/EC so-called, EUCTDs parent directive states that: “[...]Tissues and cells used as an autologous graft (tissues removed and transplanted back to the same individual), within the same surgical procedure and without being subjected to any banking process, are also excluded from this Directive.”
Notwithstanding the criticism regarding the introduction of the supplementary GMP requirements for ATMPs, it has been reported that actually experienced research centres which were involved in the initial development of new ATMPs were also those who successfully achieved GMP-compliant production for clinical trials. A study by Pearce et al. states that this connection between development success of ATMPs and translation to GMP compliant production was confirmed by an observation: those who produce know how to develop. They also noted that the centres that successfully translated to clinical trials were those that interacted actively with regulatory authorities. It appears that either their advice is essential for successful conversion to GMP and trial or only facilities that are already skilled in GMP manufacturing or trials designs are confident enough to approach the regulatory authorities. It was also reported that some academic research centres experienced in ATMP development regularly pass GMP inspections, as they know how to comply with GMP standards and are comparable with and potentially competitive with industry actors. Many of these proficient research centres had previous experience in manufacturing nonmedical, minimally manipulated cell therapies and they have existing quality systems for compliance with national regulations and were better resourced than are purely academic laboratories developing ATMPs in isolation. In any case, it appears very difficult for new research facilities to enter the field under current regulations because of the investments required in GMP manufacturing resources. There is still a considerable a lack of GMP-compliant research centres in academia that can participate in this field of translational research.

7.5.3 Possible ATMP-specific adaptations to the GMP requirements

As a starting point Recital 17 of the ATMP Regulation requires that the ATMPs manufacture should comply with the GMP principles, as set out in Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of GMP in respect of medicinal products for human use and investigational medicinal products for human use. Yet, it allows for adaptations where necessary, to reflect the specific nature of ATMPs. Furthermore, Recital 17 requires that guidelines specific to ATMPs should be drawn up by the European Commission, so as to properly reflect the particular nature of their manufacturing process. Yet, regulators have encountered challenges with creation of GMP standards for ATMPs and some developers of ATMPs have faced significant difficulty in some Member States in obtaining approval for manufacture of specific products because of unrealistic expectations of product qualification by their national competent authorities.

For instance, the study by Pearce at al. mentions a classification problem with bone marrow-derived mesenchymal stromal cells that are commonly produced for therapeutic use across the EU. Some Member States do not classify them at all as medicines, whereas in those Member States where they are classified as ATMPs, most authorities accept release criteria on the basis of sterility, four-

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622 Pearce, et al., supra note 540, 296.
623 Ibid.
parameter immunophenotype as definition and above 80 percent viability. It was reported that one national competent authority had required chromosomal stability assays on all mesenchymal stromal cell cultures, which in practice renders the trial unsustainable.625

To address the need for ATMP-specific adaptations to GMP requirements, the European Commission recently arranged targeted stakeholder consultations on GPM requirements for ATMPs.626 These consultations cover so-called “commercial ATMPs” (i.e., licenced products) as well as so-called “investigational ATMPs” (i.e., ATMPs used in clinical trials). ATMPs produced under hospital exemption were however left out of this consultation under the first consultation document. Stakeholders involved in the development, manufacture and/or commercialisation of ATMPs were invited to share their perspectives on the GMP requirements that should apply to ATMPs.627 The consultation document proposed some adaptations to GMP requirements applicable to ATMPs. The majority of respondents supported the approach in the first consultation document (whilst the second consultation is currently ongoing). In particular, SMEs and academia found it well-adapted to the specific characteristics of ATMPs, and useful and beneficial for the development of the field. Some of the proposed adaptations were also expected to reduce manufacturing expenses. Some respondents perceived that the flexibilities proposed for ATMPs would improve EU competitiveness in the global setting.628 Yet 20 percent of the respondents (mostly representing the industry sector) had a negative view of the development of a self-standing guideline. Some industry sector representatives were concerned that this guideline would create double standards depending on whether ATMPs are manufactured by industry or academia/hospitals. Now the second consultation document clarifies that the risk-based approach is equally applicable to all type of operators.629 According to the European Commission, a substantial number of respondents objected to the principle that the guideline would not apply to the hospital exemption. Whilst the second consultation document has been amended in this respect and it does not exclude manufacturing under hospital exemption. Clarification regarding the scope of the guidelines and links with general GMP rules was also requested.

From a regulatory perspective the proposed GMP guidelines on ATMPs appear quite casuistic. However, it seems to be unavoidable as further clarity and practical examples have been requested by the developers of ATMPs to standardise risk proportionate approaches to GMP and clinical trials. In short, the following general observations can be made based on the first consultation:

i. the proposed, more flexible risk-based approach was strongly supported, but a need for additional guidance regarding the application of this approach was expressed (as presented below second consultation document provides now further clarifications in this respect);

ii. some of the respondents (mostly from academia) supported the proposed opportunity to recognize to the quality systems established under the parent directive of EUCTDs (Directive 2004/23/EC) and/or the JACIE accreditation system (the second consultation document now provides further clarification regarding ATMPs that are not that are not subject to substantial manipulation);

iii. regarding the premises, academia gave strong support to the possibility of accepting the use of a clean room with a background of C or D grade for early phases of clinical trials for TEPs and CTMPs (but there was no consensus on whether this flexibility should extend beyond the early phases of clinical trials and whether GTMPs should be also covered). Furthermore, a very large number of respondents from all sectors noted that this possibility should also be extended to the manufacture of ATMPs in closed systems or when isolators are used and that flexibility for the use of semi-closed systems should also be considered. Criticism was directed towards the requirements for dedicated production facilities (manufacture can take a long time and it may not be economically possible to have dedicated facilities);

iv. the requirements adapted for raw materials were widely supported among respondents from all sectors. In particular, the principle that ATMP manufacturers should not be required to audit blood and tissue establishments authorised and supervised in accordance with Directives 2002/98/EC and 2004/23/EC was supported;

v. most proposed requirements regarding production were considered well-adapted, but a number of adaptations were suggested (e.g., some respondents from all sectors objected to the principle that simultaneous manufacture of various viral gene therapy vectors in the same area is not acceptable, as well the principle of cleaning validation between the manufacturing of different batches for cell-based products). The need for additional guidance regarding the possibility of re-processing in exceptional cases, where the treatment of patients requires the re-administration of autologous materials, was also expressed;

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630 Under Article 16 of Directive 2004/23/EC tissue establishments shall take all necessary measures to ensure that the quality system includes at least the following documentation standard operating procedures: guidelines, training and reference manuals, reporting forms, donor records and information on the final destination of tissues or cells.


632 Additional adaptations were suggested such as the use of raw materials that are covered by a marketing authorisation (e.g., cytokines). As for the sterilisation of starting materials, many found that the preference for heat over other sterilisation methods should be reconsidered.
vi. respondents from all sectors generally agreed that a pragmatic approach is required to \textit{process validation};

vii. the approach adopted on \textit{qualified person} oversight and release regarding products from third countries has been generally considered useful. Many also requested that the guideline should require that the professional qualifications/experience of the qualified person should be specifically adapted to the characteristics of ATMPs;

viii. most respondents supported the approach adopted on sampling and testing. (However, additional flexibilities and more detail have been requested and second consultation documents provides some clarifications in this respect as presented below);

ix. it was also noted that in small organisations (hospitals, in particular), teams are multi-skilled and trained in both quality control and production activities. While recognising the importance of securing the independence of the quality control from the production activities, need for accommodation of constraints on small organisations was expressed;

x. the approach to \textit{reconstitution} suggested in the consultation document was widely supported across all sectors\textsuperscript{633}; and

xi. it was noted that the GMP obligations should be adapted to ATMP manufacture by means of \textit{automated devices/systems} (the second consultation document provides clarifications in this respect).\textsuperscript{634}

All in all, these proposed adaptations in ATMP-specific GMP Guidelines were widely welcomed in the first public consultation and represent a leap forward to a more flexible risk-based approach to the manufacture of ATMPs. To provide further clarification of how the risk-based approach should be applied to ATMPs DG SANTE launched a new public consultation and issued a new consultation document on 28 June 2016 that has been elaborated based on the issues raised in the first consultation.\textsuperscript{635} In particular, this new consultation document provides further examples and suggest guidance regarding risk-based approach to GMP manufacture of ATMPs.

As for investigational ATMPs, it emphasises that the safety of the product needs to be ensured from the first stages of development. Yet, it also notes that due to a gradual increase in the knowledge of the product additional flexibilities may be possible in early phases of clinical trials. Manufacturing procedures and control methods are expected to become more specified during the more advanced phases of the clinical trial.\textsuperscript{636} It also emphasises that it is important to ensure that data obtained from the early phases of

\textsuperscript{633} Reconstitution covers activities required after batch release and prior to the administration of the ATMP to the patient, and which cannot be considered as a manufacturing step.

\textsuperscript{634} European Commission. Summary of responses to the targeted stakeholder consultation on the development of good manufacturing practice for advanced therapy medical products pursuant to Article 5 of Regulation, 5.

\textsuperscript{635} European Commission. Consultation Document. Good Manufacturing Practice for Advanced Therapy Medical Products (v.2), supra note 626.

clinical trial can be used in later phases of development.\textsuperscript{637} It encourages developers to seek early advice from the competent authorities in connection with the implementation of the risk-based approach for IMP ATMPs (especially regarding early phases of clinical trials). The draft GMP Guidelines provide examples of possible adaptations that are acceptable in case of IMP ATMPs as follows:

- For first-in-man clinical trials, production may take place in an open environment in a critical clean area of grade A in a background clean area of grade C. It is however required that there are appropriate controls of microbiological contamination, separation of processing procedures, and validated cleaning and disinfection. Also, risk-analysis study should be conducted to demonstrate that the implemented control measures are adequate to ensure aseptic manufacturing.\textsuperscript{638}

- In early clinical trial phases I/II when the manufacturing activity is very low, annual calibration, inspection or checking can be limited to the facility, cabinets, incubators, isolators, freezers, air sampler and particle counters, unless a lower frequency is justified due to periodicity of use. Yet, the rest of equipment could be tested less frequently based on a risk analysis and the production activity. The suitability for use of all equipment should be verified before it is used.\textsuperscript{639}

- The level of formality and detail for the documentation should be adapted to the stage of development.\textsuperscript{640}

- During early phase I/II clinical trials specifications can be based on wider acceptance criteria taking due account of the current understanding of the risks.\textsuperscript{641}

- Also some additional flexibilities regarding qualification of premises and equipment, process validation, and validation of analytical methods.\textsuperscript{642}

As for licensed ATMPs, marketing authorisation is the starting point for the application of the risk-based approach in GMP manufacture of ATMPs. Hence, any specific limitations should be agreed as part of the marketing authorisation. The specific characteristics of the product or manufacturing process can be taken into consideration to justify deviation from standard expectations when providing the description of the manufacturing process and process controls in the marketing authorisation application. In addition, regarding aspects that are not specifically covered by the marketing authorisation, it is mandatory for the manufacturer to document the reasons for the approach implemented when the risk-based approach is applied, and to justify that all of the measures applied are adequate to ensure the quality of the product.\textsuperscript{643}

\textsuperscript{637} Ibid. According to the second Consultation Document, a too immature quality system risks to compromise the use of the study in the context of a marketing authorisation application. Furthermore, a weak quality system may compromise the approval of the clinical trial if the safety of trial subjects is at risk.

\textsuperscript{638} Op.cit., 11.

\textsuperscript{639} Ibid.

\textsuperscript{640} Ibid.

\textsuperscript{641} Ibid.

\textsuperscript{642} Op.cit., 11, 44–49.

When it comes to risk-based approach to ensuring the quality of the raw materials, it is required that the manufacturer has a good knowledge of the role of the raw material in the manufacturing process. Especially, understanding on specific properties of the raw material are vital for the manufacturing process and final quality of the product. Also the level of risk of the raw material due to the inherent properties thereof must be taken into consideration (e.g., basic media v. growth factors), or the use thereof in the manufacturing process (higher risk if the raw material is in direct contact with the starting materials). Finally, it must be assessed whether the control strategy (i.e. qualification of suppliers) is sufficient to eliminate the risks or to reduce them to an acceptable level.

As for risk-based approach to be applied in connection with the testing strategy, it is noted that in some cases it may not be possible to perform the release tests on the active substance or the finished product due to technical reasons or when the amount of available product is limited to the clinical dose. In such cases an adequate control strategy should be designed and explained in the marketing authorisation or clinical trials authorisation application based on the validation of the manufacturing process and the in-process controls. Following alternative measures have been proposed: (i) testing of intermediates (instead of the finished product) or in-process controls (instead of batch release testing) if the relevance of the results from these tests to the finished product can be demonstrated; or (ii) substituting routine batch testing by process validation. In addition following adapted approaches have been suggested: (i) it may be justified to waive the on-going stability programme for ATMPs with a very short shelf-life; (ii) the strategy regarding sterility assurance may need to be adapted if the application of the sterility test to test the final product is not possible due to the scarcity of materials available or it may not be possible to wait for the result of the test before the product is released due to short shelf-life; and (iii) the particulate matter test may be limited to foreign visible particles in case of cells in cell culture suspension that are not clear solutions, if alternative measures are implemented.

When it comes to cells or tissues that have not been subject to substantial manipulation, some flexibilities are suggested as such materials are typically associated with lower risks than the manufacturing of ATMPs that require complex substantial manipulation.

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645 For instance, it may not be possible to perform the release tests on the combined components of certain combined products due to time restrictions if the product needs to be administered immediately after completion of manufacturing.
647 *Op. cit.*, 9. It is noted that the process validation is usually not required for investigational medicinal products, it may be very important when routine in-process or release testing is limited or impossible.
648 A sterility test in accordance with the European Pharmacopoeia (Chapter 2.6.27).
649 Such adaptation may involve use of alternative methods for preliminary results, combined with sterility testing of media or intermediate product at following relevant points of time. If the results of the sterility test of the product are not available at release, appropriate mitigation measures should be implemented.
650 *Op. cit.*, 9. These alternative measures may include controls of input of particles from materials and equipment used during manufacturing, or the verification of the ability of the manufacturing process to produce low particle products with simulated samples without cells. 142
Yet, processes that are not qualified as “substantial manipulation” are not risk-free, especially if the processing of the cells involves long exposure of the cells or tissues to the environment. Therefore, there is a need for a risk analysis to identify the measures that are necessary to ensure the quality of the product in the manufacturing process. To avoid administrative burden in manufacturing process of ATMPs that do not involve substantial manipulation, premises and equipment that have been duly validated to process cells/tissues for transplantation purposes in accordance with standards that can be deemed comparable to those laid down in these draft GMP Guidelines for the same type of manufacturing operation do not need to be validated again. Yet, premises/equipment used to process cells/tissues under the same surgical procedure (derogation under Article 2(2) of Directive 2004/23) or for research purposes must be validated in accordance with these GMP Guidelines. Draft GMP Guidelines emphasise the responsibility of the manufacturer to ensure that the manufacturing of ATMPs takes place in aseptic conditions, also when the manufacturing process does not involve substantial manipulation. Yet, some adaptations regarding clean room facilities are allowed, but subject to risk assessment.

The Directorate General for Health and Food Safety, DG SANTE, has also recently (1st of June 2016) launched a public consultation to seek the views of stakeholders and other interested parties on the document regarding "Risk proportionate approaches in clinical trials" which has been drafted in preparation for the implementation of the Clinical Trials Regulation. However, the particularities of ATMPs have not been specifically addressed in this document. Whilst the second consultation document regarding risk-based approach to GMP manufacture of ATMPs specifies that

"the description of the manufacturing process and process controls in the clinical trial authorisation application should also describe, as appropriate, the quality strategy of the manufacturer when the risk-based approach is applied. For aspects that are not specifically covered by the clinical trial authorisation, it is incumbent upon the manufacturer to document the reasons for the approach implemented and to justify that the totality of the measures applied are adequate to ensure the quality of the product."

Yet, it should also be noted that none of the adaptations in the proposed GMP Guidelines (including the risk-based approach) should be seen as derogation of the marketing authorisation or clinical trial authorisation terms. The manufacturing requirements (e.g., specifications, manufacturing process, controls, etc.) specified in the

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653 Op.cit., 10. More specifically it is stated that “[w]hen manufacturing operations take place in an open environment in premises other than a critical room of grade A in a background clean area of grade B, a risk-analysis study should be conducted (particular consideration should be paid to the time that the product is exposed to the environment) and it should be demonstrated that the implemented control measures are adequate to ensure aseptic manufacturing. Under no circumstances it is acceptable to conduct manufacturing operations in premises with air quality classification lower than a critical clean room of grade A in a background clean area of grade D.”
654 European Commission, supra note 425.
marketing authorisation and clinical trial authorisation should always be followed. All things considered, these proposed adaptations in ATMP-specific GMP Guidelines represent a positive leap forward to a more flexible risk-based approach to the manufacture of ATMPs. They may alleviate the administrative burden and decrease the costs of GMP manufacture. It remains to be seen whether these facilitative measures will yield new licenced products to the EU market, as there are still a number of other factors influencing their market entry.

### 7.6 Challenges with conduct of preclinical and clinical trials

The development of novel therapeutic methods of treating diseases and debilitating injuries to the human body is an essential scientific endeavour. However, since scientific advances may not be pursued at any cost, medical products and processes need to be regulated at a level proportionate to the inherent risk in providing new therapeutic opportunities for those needing them. As a starting point Article 35 of the Charter of the Fundamental Rights of the EU requires that a high level of human health protection shall be ensured in the definition and implementation of all EU policies and activities, also those covering clinical trials. Whilst Article 15 of the Biomedicine Convention sets out for a general rule that scientific research in the field of biology and medicine shall be carried out freely, subject to the provisions of the Biomedicine Convention and the other legal provisions ensuring the protection of the human being. More specifically, Article 16 the Biomedicine Convention sets out for principles regarding protection of persons undergoing research by stipulating that research on a person may only be undertaken if all of the following conditions are met: (i) there is no alternative of comparable effectiveness to research on humans; (ii) the risks which may be incurred by that person are not disproportionate to the potential benefits of the research; (iii) the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of the research, and multidisciplinary review of its ethical acceptability; (iv) the persons undergoing research have been informed of their rights and the safeguards prescribed by law for their protection; (v) the necessary free and informed consent has been given expressly, specifically and is documented. Such consent may be freely withdrawn at any time. Whilst Article 17 of the Biomedicine Convention sets out for additional the rules regarding protection of persons not able to consent to research and

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Article 18 addresses aspects of protection of research embryos. As for research on ATMPs, Recital 16 of the ATMP Regulation requires that clinical trials on ATMPs should be conducted in accordance with the overarching principles and the ethical requirements of GCP laid down in Clinical Trials Directive (2001/20/EC). In addition it requires that Directive 2005/28/EC on GCP as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products should be adapted by laying down rules tailored to fully take into account the specific technical characteristics of ATMPs. Whilst Article 5 of the ATMP Regulation requires the European Commission to draw up GCP Guidelines specific for ATMPs.

As described in Section 6.3 of this study the EU-wide legislative landscape for clinical trials has undergone some significant changes during the last decade. Despite the legislation and guidelines (for instance ICH Guideline E6 for Good Clinical Practice) have been perceived relatively flexible, it has been noted ‘one size fits all’ approach to the design and conduct of clinical trials has been followed to meet up with the ethical and scientific requirements of GCP. Yet, the traditional clinical trial paradigm may not always be suited to accommodate the particularities of ATMPs. The traditional sequential trial (ranging from Phase I-III sequence of clinical drug testing) may turn out to be inefficient in development of niche and tailor-made ATMPs. The EMA has also noted in the recent years the practice for conducting first-in-human clinical trials has evolved towards a more integrated approach. In such approach sponsors conduct several steps of clinical development within a single clinical trial protocol (e.g. to assess single and multiple ascending doses, different age groups, interactions with nutrition, early proof of concept or early proof of principle etc.).

This is a structured approach to trials; incremental decisions on next steps are based on the data collected at each earlier step. According to the EMA it allows for adaptations for the specificities of each medicine, its mechanism of action, and intended therapeutic use.

Despite, the specific considerations regarding the clinical trial design are left outside the primary scope of this study, it should be noted that the Clinical Trials Regulation supports a proportionate approach to the design and conduct of clinical trials that allows for adaptations to the risk to the subject of the research. Yet, in case of first-in-human clinical trials on ATMPs, improved strategies are needed to identify and mitigate risks to trial participants.

658 See e.g. European Commission, supra note 626, v. 1.
7.6.1 Pre-clinical data provided for IMP ATMP dossier risking resulting in use of contrived animal models

Clinical trials are necessary for the development of ATMPs and without them patients may not have access to new medicines. EU and international guidelines on CCP are in place on to make sure that first-in-human clinical trials are conducted as safely as possible. These guidelines include the requirement for extensive studies, including animal trials, to collect information about an investigational medicine before it can be tested on humans. Recital 13 of the ATMP Regulation states that ATMPs should be subject to the same regulatory principles as other types of biotechnology medicinal products. However, it is noted that technical requirements, especially the type and amount of quality, preclinical and clinical data necessary to demonstrate the quality, safety and efficacy of the product, may be highly specific.

There is a concern that under the current ATMP Regulation the provision of pre-clinical data for purposes of the medicinal product dossier of IMP ATMPs frequently results in use of very contrived animal models.\textsuperscript{661} As pharmacological activity and unforeseen adverse side effects may be species-specific, there is a remarkable risk of underrating toxicity of human-specific biologic reagents when assessed in animal models.\textsuperscript{662} It has been noted that standard animal models may also not be adequately predictive of toxicity due to differences in life cycle and, as corresponding human applications cannot be simulated properly.\textsuperscript{663}

According to the CAT the choice of the most relevant animal model should be determined by the specific safety aspect to be evaluated.\textsuperscript{664} As the raw materials of animal origin often substantially differ from the human product, the testing of an “equivalent” ATMP originated from tissues of the experimental host becomes inadequate.\textsuperscript{665} Homologous animal models may often provide the most relevant system for proof-of-concept, but their predictability is restricted due to dissimilarities between animal and human cells or factors involved in the differentiation process.\textsuperscript{666} If immunocompromised and/or immunosuppressed animals are used, persistence or functionality may not be optimally translated to predict \textit{in vivo} performance of

\begin{itemize}
\item[\textsuperscript{661}] Pearce, et al., supra note 540, 295.
\item[\textsuperscript{663}] Pearce, et al., supra note 540, 295.
\item[\textsuperscript{665}] Pearce, et al., supra note 540, 295.
\item[\textsuperscript{666}] CAT, supra note 664, 8.
\end{itemize}
transplanted cells. The use of immunosuppressant may also influence tumour formation, whereas in an immunocompetent animal model the host immune system may reject the administered product resulting in a potentially false negative outcome of the trial. The CAT emphasises that the selection of animal models and the duration of animal studies should be adequate for evaluation of long-term effects taking into account the persistence and functionality of the cells.\textsuperscript{667} The development of ATMPs seems to necessitate a paradigm shift in the approach to pre-clinical testing needed for clinical trial authorisations.\textsuperscript{668} Another question is whether “smart” \textit{in vitro} testing could in some cases replace or complement the use of animal models. In any case regulators should consider benefits and limitations of novel development tools (such as organoids, modelling/simulation, biomarkers, etc.) to address non-clinical requirements.

When it comes to particular issues stem cell therapies encounter on their way from bench to bedside, it should be noted that, not any type or level of functional improvement in animal models is sufficient to justify clinical application in humans.\textsuperscript{669} As a starting point, to safeguard patients’ safety in clinical trials involving stem cells, the contemplated stem cell-based approach must have been demonstrated to induce substantial recovery of functional deficits that bear a resemblance to patients’ symptoms. Yet, there is a risk that the behaviour of stem cells and their derivatives after transplantation in animal models may only partly predict how these cells will behave in human patients, as the animal model may not illustrate all aspects of the pathology of the human disease, which may explain the lack of efficacy in the clinical trial of the stem cell-based product under development. In addition, the biological mechanism underpinning the observed functional improvement subsequent to a stem cell-based treatment should be determined in an animal model of the disease. As use of stem cells can result in a clinically valuable recovery via different mechanisms (e.g. cell replacement, trophic support, modulation of inflammation, stimulation of angiogenesis etc.), any stem cell based treatment should be explicitly demonstrated to work via one or more of these mechanisms before its clinical application in humans.\textsuperscript{670}

Beyond the ATMP regime, safety considerations of research subjects in first-in-man trials became a topic of vivid discussions after the tragic incident that took place during a Phase I first-in-human clinical trial on a fatty acid amid hydrolase inhibitor (code name: BIA 10-2474) in Rennes, France in January 2016.\textsuperscript{671} The EMA launched on 21 July 2016 a public consultation to gather perspectives on amendments needed to the

\textsuperscript{667} Ibid.
\textsuperscript{669} Lindvall, et al. \textit{supra} note 592,12.
\textsuperscript{670} Ibid.
EMA’s Guideline on first-in-human trials improve safety of first-in-human clinical trials. The existing guideline mainly focuses on non-clinical aspects of drug development and the use of animal data and reflects the practice at the time it was developed in 2007 which focused on a single ascending dose design for first-in-human trials. Yet, it has become more and more common to integrate non-clinical data available before first-in-human administrations and the pharmacokinetic, pharmacodynamic and human safety data arising during a trial. Subsequently, the integrated approaches, (in particular those involving multiple ascending dose trials) have emerged and many first-in-human trials are now conducted with integrated protocols that may combine different parts of a study. Despite particularities of clinical trial designs are beyond the primary scope of this study (and thus they would require more profound scrutiny), as a general note it can be concluded that further guidance regarding first-in-human trials on ATMPs is needed among other things regarding use of surrogate end-points (such as biomarkers in preclinical or early clinical trials predicting the safety an IMP ATMP) and especially regarding adaptive trial designs. In case of adaptive trial designs it would be especially important to investigate how the safety, integrity and validity of a trial can be ensured when changes are made to a study design in response to accruing data (for instance, guidance is needed regarding determination of proper intervals of time between dosing of successive volunteers, validation of toxicological data before escalating doses etc).

7.6.2 Difficulty in acquiring clinical trial authorisations from ethics committees for trials on ATMPs

Their complex nature means that some ATMPs being developed encounter further difficulty in acquiring ethical approvals for clinical trials. Article 6.1.4 of the Clinical Trials Regulation requires the reporting Member State to submit via the EU portal, the final Part I of the assessment report, including its conclusion, to the sponsor and to the other Member States concerned within 45 days from the validation date. The conclusion shall be one of the following in view of the requirements set out in the Clinical Trial Regulation: (a) the conduct of the clinical trial is acceptable; (b) the conduct of the

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673 In such trial a single dose of the investigational drug is given to each volunteer in a small group of clinical trial participants to assess the safety. Thereafter, if that is acceptable each participant in the next group receives a single dose at the next higher dose of the investigational drug. See European Medicines Agency, op.cit. for further details.
675 In multiple ascending dose trials, each subject is treated on many occasions at a given dose level. The treatment is then increased progressively to higher doses in successive groups of volunteers if the safety and tolerability at the previous dose is acceptable. European Medicines Agency. op.cit. for further details.
clinical trial is acceptable, but subject to compliance with specific conditions which shall be specifically listed in the conclusion; or (c) the conduct of the clinical trial is not acceptable. In case of clinical trial applications regarding IMP ATMPs, the assessment timeframe may be extented by further 50 days.

Yet, the possibly (and also likely) longer time frame is a minor problem in relation to some significant tensions (or even a risk of litigation) that may also arise in situations where there authorisation for a clinical trial has not been applied for (or granted) and physicians end up providing “experimental treatments” for patients instead.

For instance, in Finland physicians of a private hospital that used oncolytic viruses in experimental treatments “as a last resort” for single patients having different diagnosis of cancer and no option for conventional therapies were prosecuted for conduct of clinical trials without an authorisation to conduct a clinical trial. Such tailor-made, personalised treatments had been offered individually in a private hospital under the responsibility of a treating physician. The District Court of Helsinki found however, that despite experimental treatments generating new scientific data that had been published they cannot be perceived as clinical trials that require a clinical trial authorisation pursuant to Finnish Act on Medical Research.676

Despite this, it may appear obvious from an ethical perspective that therapeutic procedures that are not validated by clinical data should not be permitted; there may be acceptable reasons to allow the application of unproven treatments under certain specific conditions.677 In medical ethics and medical law, those procedures have been called “therapeutic experimentation” or a “therapeutic attempt”.678 Under the Declaration of Helsinki such attempts are regulated as a combination of research and care as well as treatments where proven interventions do not exist:

“[t]he physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of patients who serve as research subjects.”679

As for unproven interventions, it is stated in the Declaration of Helsinki that:

[i]n the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician’s judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.680

676 Ruling of District Court of Helsinki, Case R 13/8233, dated 2 October 2014.
677 See e.g. Fuchs, supra note 107, 143.
678 Ibid.
It should be noted that “experimental treatments” under Declaration of Helsinki are not exempt from the EU-wide GMP standards on quality. Despite those therapeutic attempts being justified in specific circumstances, it is very important to carefully consider individual cases, and especially the patient’s ability to give informed consent to any such unapproved intervention.\textsuperscript{681} The more unconventional a treatment is the higher the requirement is for physician to inform the patient about any potential risks involved with such an unapproved intervention. It would be highly undesirable if an unnecessarily high threshold to grant authorisations for clinical trials on ATMPs resulted in a situation where physicians end up proving experimental treatments instead of conducting systematic, controlled clinical trials. Since there is a need for more systematic assessment of the safety and efficacy of a product, data gained from experimental treatments cannot replace clinical trials. Therefore, national competent authorities should be vested with adequate knowledge on ATMPs to conduct risk-assessments of particular products and to be able to realistically assess risk-benefit balance of these products and sufficiency of quality system and risk management measures needed to eliminate or mitigate risks associated with clinical trials.

In addition, despite the EU-wide attempts to facilitate the administrative burden of clinical trials in multiple jurisdictions, it should be noted that the ethical assessment of clinical trials still remains within the competence of the national competent authorities of the Member States. Hence, the opportunity to conduct some types of research may differ from one jurisdiction to another. Ethical considerations that complicate the conduct of research range from access to primary materials to risk and safety related considerations of trials. Recital 18 of the Clinical Trials Regulation specifies that

\textquoteleft\textquoteleft[i]t should be left to the Member State concerned to determine the appropriate body or bodies to be involved in the assessment of the application to conduct a clinical trial and to organise the involvement of ethics committees\textsuperscript{682} within the timelines for the authorisation of that clinical trial as set out in this Regulation. Such decisions are a matter of internal organisation for each Member State. When determining the appropriate body or bodies, Member States should ensure the involvement of laypersons, in particular patients or patients’ organisations. They should also ensure that the necessary expertise is available. In accordance with international guidelines, the assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience. The persons assessing the application should be independent of the sponsor, the clinical trial site, and the investigators involved, as well as free from any other undue influence.\textquoteleft\textquoteleft

More specifically, Article 4 of the Clinical Trials Regulation mandates that a clinical trial shall be subject to scientific and ethical review, shall be authorised in accordance with the Clinical Trials Regulation and shall be performed by an ethics committee in

\textsuperscript{681} Fuchs, supra note 107, 132.

\textsuperscript{682} Pursuant to the Clinical Trials Regulation Ethics committee means “an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients’ organisations”.

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accordance with the law of the Member State concerned. Under Article 4, it is the responsibility of Member States to ensure that the timelines and procedures for the review by the ethics committees are compatible with those specified in the Clinical Trials Regulation for the assessment of the application for authorisation of a clinical trial. A Member State has a right refuse to authorise a clinical trial in certain circumstances under Article 8.4. Such circumstances include aspects relating to the characteristics of and knowledge about the investigational medicinal products; the risks and inconveniences for the subject, non-compliance with the requirements concerning the manufacture and import of investigational medicinal products and auxiliary medicinal products, non-compliance with the labelling requirements; insufficient completeness and adequacy of the investigator's brochure, non-compliance with the requirements for informed consent, non-compliance of the arrangements for rewarding or compensating subjects, non-compliance of the arrangements for recruitment of subjects, non-compliance with the applicable rules for the collection, storage and future use of biological samples of the subject; participation in the clinical trial leading to a subject receiving inferior treatment to normal clinical practice in the Member State concerned; infringement of its national law and considerations of subject safety and data reliability and robustness.

Hence, despite the centralised authorisation procedure, a significant margin of appreciation in ethical questions is left for the ethical committees of the Member States. In addition, Article 8.4 stipulates that if the reporting Member State finds that the clinical trial is not acceptable in relation to the characteristics of and knowledge about the investigational medicinal products; the risks and inconveniences for the subject, non-compliance with the requirements concerning the manufacturing and import of investigational medicinal products and auxiliary medicinal products, non-compliance with the labelling requirements; insufficient completeness and adequacy of the investigator's brochure, that conclusion shall be deemed to be the conclusion of all Member States concerned. As there is an “opt-out” possibility for a Member State under the Clinical Trials Regulation and the ethical positions of the EU Member States vary, for instance access to hESC as primary materials and opportunities to conduct clinical trials on hESCs is not equally granted in all jurisdictions.

683 Pursuant to Article 4 of the Clinical Trials Regulation “[t]he review by the ethics committee may encompass aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7 as appropriate for each Member State concerned. Member States shall ensure that the timelines and procedures for the review by the ethics committees are compatible with the timelines and procedures set out in this Regulation for the assessment of the application for authorisation of a clinical trial.”

684 According to Article 8.4. “[t]he Member State concerned shall refuse to authorise a clinical trial if it disagrees with the conclusion of the reporting Member State as regards Part I of the assessment report on any of the grounds referred to in the second subparagraph of paragraph 2, or if it finds, on duly justified grounds, that the aspects addressed in Part II of the assessment report are not complied with, or where an ethics committee has issued a negative opinion which in accordance with the law of the Member State concerned is valid for that entire Member State. That Member State shall provide for an appeal procedure in respect of such refusal.”
7.6.3 Risk-based approach in GMP and clinical trials to foster innovation whilst protecting public health

The risk to subject safety in a clinical trial on ATMPs originates from two primary sources: the ATMP and the trial. A central dilemma is this duality is the question how much of ATMP treatment is product-based and how much is it a treatment process that depends on the clinical and laboratory skills of manufacturers of ATMPs and clinicians administering the product at the bedside. In addition to the classification challenges addressed in Section 7.4 of this study, a further question of classification arises: should the ATMP classification procedure should have more weight in determining what is considered a medicinal product and what is considered medical procedure or practice across Europe? The risk-proportionate approach seems to suggest that risks associated with ATMPs at the early phases of development should be considered especially from a holistic process point of view (e.g., both at a system level and a trial level).

As a class of medical products, ATMPs are complex. Risks may substantially differ according to the type of ATMP being developed. The risks to the quality of the ATMP in the manufacturing process are higher when the process is multifaceted. It should be noted that the final product may also have a high level of variability stemming from the use of biological materials and complex manipulation steps (e.g., cultivation of cells). Special challenges arise when it comes to manufacture and testing of autologous ATMPs in particular. Hence, adequate risk management strategies and tools need to be in place to safeguard quality. These approaches must be tailored to accommodate restrictions on the ATMP manufacturing process. In the draft GMP Guidelines for ATMPs, the European Commission has deemed it is necessary to allow for some flexibility in the application of the GMP requirements so that the ATMP manufacturer can implement the procedures that are most appropriate for specific features of both the manufacturing process and the ATMP. If any such flexibility is applied, it should not in any circumstances compromise the need to ensure the high quality of the ATMP.

The production of IMP ATMPs entails some additional complexity (in comparison to commercial, licensed ATMPs). Special challenges in IMP ATMP manufacture originate among other things from incomplete information about the product as well as the absence of established routines. The European Commission notes in its draft GMP Guidelines for ATMPs that IMP ATMPs, which are also often developed in an academic or hospital environment, operate under quality systems which differ from those usually required for the manufacture of conventional medicinal products. It is particularly noted that additional flexibility is required in IMP ATMP manufacture for early phases of clinical trials. An acceptable level of quality must also be ensured for such trials, however.

687 Ibid.
As discussed in Section 7.5.3, the risk-based approach does not allow for derogations from the marketing authorisation or clinical trial requirements. By contrast, when ATMP-specific flexibility applies; it requires the manufacturer to ensure that additional measures are in place (in addition to those proposed in the GMP guidelines) if that is necessary given the particular risks of the ATMP. Therefore, in order to take all potential risks into consideration, the ATMP manufacturer is required to identify the risk control measures that are most appropriate in each case.688

The public consultation launched by DG SANTE seeks to get the perspectives of stakeholders and other interested parties on the document regarding "Risk proportionate approaches in clinical trials" which has been developed in preparation for the implementation of the Clinical Trials Regulation.689 Despite this consultation document not specifically addressing the risk aspects of ATMPs (further clarifications regarding risk management of ATMPs in clinical trials are needed), some general observations can be made. The approach adopted in the consultation document not only requires consideration of risks in clinical trials at the system level (e.g., facilities, standard operating procedures, computer systems, and personnel) but also at the trial level (e.g., in terms of investigational medical product, trial design, and data collection and recording). In addition to the risks relating to the IMP ATMP, risks may arise from intervention that may adversely affect the clinical trial subjects. Such risks may include failure to comply with the clinical procedures specified by the protocol, failure to obtain fully informed consent or to protect personal data, data integrity, the reliability of the results and their scientific use or validity. Pursuant to the European Commission’s proposal, a risk based quality management system should consist of the following consecutive steps: (1) risk identification; (2) risk evaluation; (3) risk control; (4) risk review; (5) risk communication and (6) risk reporting.690 Nevertheless, no ATMP specific clarifications have been provided regarding these elements of the quality control process in the consultation documents on risk based approaches in clinical trials. (Yet, some of these issues are addressed from the perspective of adaptations to GMP requirements in the draft GMP Guidelines as discussed in Section 7.5.3).

688 Ibid.
689 European Commission, supra note 425.
The proposed risk-based approach allows for some adaptations to low intervention clinical trials, such as those deemed to pose only a minimal additional risk to subject safety compared to normal clinical practice. Such trials, defined in Article 2(3) of the Clinical Trials Regulation must meet all of the following conditions: (a) the investigational medicinal products, excluding placebos, are authorised; (b) according to the protocol of the clinical trial, (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned. To safeguard the subject safety of low-intervention clinical trials, they are subject to the same evaluation process as any other clinical trial, but with adapted dossier requirements.\(^{691}\)

Given that most of the ATMPs are unauthorised and still in the early phases of clinical trials, very few of them may meet these criteria. In contrast, developers of ATMPs should take the particularities of each investigational product into account when developing a risk-based quality management system for a trial. Because of their complex nature, some products such as substantially manipulated ATMPs may indeed be considered as higher risk products that actually necessitate additional safeguards before they can be brought to clinical trials involving humans.

Risk identification and risk evaluation are crucial in managing and mitigating the risks when setting up a quality management system for a trial involving IMP ATMPs. Generally speaking, pursuant to EMA’s reflection paper on risk-based quality management of clinical trials, the risk evaluation assessment process covers following aspects i) the likelihood of potential hazards associated with the trial, ii) the impact, if

they could occur, of these hazards on the safety of subjects and data integrity and iii) the extent to which such hazards would be detectable.\(^{692}\) In a risk-based quality management system, a mitigation strategy (such as monitoring measures) for each identified risk must be implemented or alternatively a determination made that the risk can be accepted.\(^{693}\) The risk identification and risk evaluation should consider any and all risk factors for defining trial management and operations, including, but not limited to: informed consent requirements, adequacy of insurance coverage, safety reporting, monitoring, trial master file content, data management, computer systems, traceability requirements of investigational medicinal products, clinical sample management and analysis, data processing, analysis, and reporting.\(^{694}\) As for risk management system to address risks related to ATMPs, Recital 20 of the ATMP Regulation stipulates that

“Follow-up of efficacy and adverse reactions is a crucial aspect of the regulation of [ATMPs]. The applicant should therefore detail in its marketing authorisation application whether measures are envisaged to ensure such follow-up and, if so, what those measures are. Where justified on public health grounds, the holder of the marketing authorisation should also be required to put in place a suitable risk management system to address risks related to [ATMPs].”

In addition, Recital 22 states that “a system allowing complete traceability of the patient as well as of the product and its starting materials is essential to monitor the safety of [ATMPs]” and further requirements regarding traceability are specified in Article 15 of the ATMP Regulation.\(^{695}\) Under Article 15.1 of the ATMP Regulation the holder of a marketing authorisation for an ATMP is required to set up and maintain a system, which ensures that the individual ATMP and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced via the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is given to the patient.\(^{696}\) Furthermore,


\(^{693}\) European Commission, supra note 425, 6.

\(^{694}\) Ibid. See also European Medicines Agency. Reflection paper on risk-based quality management in clinical trials.

\(^{695}\) It is further specified in Recital 22 that ”[t]he establishment and maintenance of that system should be done in such a way as to ensure coherence and compatibility with traceability requirements laid down in Directive 2004/23/EC in respect of human tissues and cells, and in Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components. The traceability system should also respect the provisions laid down in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and the free movement of such data.”

\(^{696}\) In addition it is required under Article 15.4 that where an ATMP “contains human cells or tissues, the marketing authorisation holder, as well as the hospital, institution or private practice where the product is used, shall ensure that the traceability systems established in accordance with paragraphs 1 and 2 of this Article are complementary to, and compatible with, the requirements laid down in Articles 8 and 14 of Directive 2004/23/EC as regards human cells and tissues other than blood cells, and Articles 14 and 24 of Directive 2002/98/EC as regards human blood cells.”
under 15.3 of the ATMP Regulation is it required that the hospital, institution or private practice where the ATMP is administered shall set up and maintain a system for patient and product traceability. It must contain sufficient detail to allow linking of each product to the patient who received it and vice versa.

The risk evaluation measures should begin before the finalisation of the research protocol, because the risk assessment and evaluation affect the trial design and procedures. Risk evaluation measures may also have financial implications for the ATMP development project. Subsequent to a trial-specific risk identification and evaluation, a risk proportionate approach can be applied in a trial. The risk-proportionate approach necessitates description and implementation of measures to be taken. This description must include any specific required actions and allocation of responsibilities for such actions. For instance, in the case of risk identification and risk assessment of the safety reporting an ATMP described in the research protocol, the sponsor of the clinical trial should make sure that the investigators and trial staff are adequately trained. Tailored IMP ATMP-specific trainings should be arranged for them to deal with any potential adverse events that may occur due to the mechanisms of action of a particular IMP ATMP or the disease or condition to be treated.

ATMPs are a very heterogeneous class of medical product. Risk management approaches should also be tailored to accommodate the restrictions of the manufacturing process of the ATMP, as the risks to the quality of the ATMP are higher when the manufacturing process is complex. Safety and the high quality of the IMP ATMP should not be compromised when manufacturers of IMP ATMPs implement procedures that are most appropriate for the particular features of the manufacturing process and of the investigational medical product.

Risk assessment and evaluation should also take adequate measures to ensure the protection of privacy and integrity of the participants into consideration. It should be noted that, as mentioned in Section 7.3.3. of this study, the GDPR imposes a specific requirement, as well as imposing an obligation to appoint a data protection officer in certain circumstances, such as large-scale processing of sensitive data. It also requires controllers and processors to conduct a privacy impact assessment of the impact of the envisaged processing operations if the processing poses a high risk to the rights and freedoms of individuals. In the case of such a risk, consultation with a supervisory authority is mandatory.

Risk control aims at determining whether certain risks can be accepted and how such risks can be reduced to an acceptable level. The main elements of risk control involve mitigation, adaptations and risk acceptance actions. The Clinical Trials Regulation allows for risk adaptations in certain areas. The “Risk proportionate

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697 European Commission, supra note 425. 6.
698 European Commission, supra note 425. 7.
699 E.g., safety reporting (Article 41(2) regarding the safety profile of IMP and Annex III 2.5, 21 regarding the data integrity of safety information, IMP management (Article 51(1) regarding traceability
approaches in clinical trials” consultation document states that resources allocated for risk control should be “proportionate to the significance of the risk and the importance of the process or outcome exposed to the identified risk.” The control measures would typically involve personnel operating in multiple areas to cover the various aspects of the trial.  

A continuous, periodical risk review needs to be conducted to assess the new data arising in connection with the trial and the outcomes of trial management activities. This review must be updated continuously and must cover evaluation of the impact the new information has on the risk assessment and effectiveness and the need for measures taken.  

A risk communication process needs to be established to make sure that the risk assessment and mitigation plan and any updates thereto, as well as any amendments that may impact on the conduct of the trial, such as protocol updates, serious breaches, safety reporting, protocol deviations, etc., are communicated to the relevant clinical trial staff in time.  

The “Risk proportionate approaches in clinical trials” consultation document suggests that risk reporting should be conducted in accordance with the ICH guidelines E3- Structure and Content of Clinical Study Reports and E6- Good Clinical Practice. Hence, the sponsor should describe the risk adaptations implemented in the clinical study report.  

In addition to traceability requirements, post-authorisation follow-up of efficacy and adverse reactions, and risk management aspects constitute essential elements of a risk management system for ATMPs. Article 14.1 of the ATMP Regulation imposes reporting obligations to developers of ATMPs. It is required that besides other pharmacovigilance requirements, the applicant of marketing authorisation for an ATMPs shall specify in the marketing authorisation application, the planned measures to ensure the follow-up of efficacy of ATMPs and of adverse reactions thereto. In addition Article 14.2 of the ATMP Regulation states that in case of particular cause for concern, the applicant may be required to set up a risk management system designed to identify, characterise, prevent or minimise risks related to ATMPs, including an evaluation of the effectiveness of that system, or specific postmarketing studies be carried out by the holder of the marketing authorisation and submitted for review to the EMA. The EMA may also request submission of additional reports evaluating the


Ibid.  

Reference is made to Articles 21 to 29 of Regulation (EC) No 726/2004.
effectiveness of any risk management system and the results of any such studies performed.\textsuperscript{705}

The CAT has pointed out that the quality, safety, and efficacy of ATMPs are interlinked and lack of methodologies in one discipline can often be complemented by others.\textsuperscript{706} For instance, a lack of potency assays could be in some cases substituted by a sound process validation and consistent manufacturing, in conjunction with clinical trial data that demonstrate that this manufacturing process results in efficacious product. As safety and efficacy endpoints and the time of the patient’s follow up are very much dependent on the biological characteristics of the product, risk analysis allows the producer to adapt the product development (including the nonclinical and clinical investigations) to the characteristics of its medicine.\textsuperscript{707} Also combination of these therapies with conventional treatments may raise particular regulatory concerns.\textsuperscript{708}

Furthermore, the importance of possible surrogate endpoints of clinical efficacy has been addressed and platforms for defining and identifying categories of responding patients are under development. All in all, these questions may cause special regulatory concerns regarding approval of clinical protocols that need to be positively addressed to promote clinical trials in controlled and standardised conditions.\textsuperscript{709}

7.7 Burdensome centralised marketing authorisation procedure

The fact that only six ATMPs have succeeded in going through the ATMP Regulation funnel and successfully completed the mandatory centralised marketing authorisation procedure thus far implies a burdensome procedure under the ATMP Regulation. First, as presented above, clinical trials to generate evidence of positive risk-benefit balance are required for a grant of a marketing authorisation. Developers of ATMPs also encounter challenges with clinical trial authorisations and also with particularities of ATMPs that often require adaptations to clinical trial designs. Second, as discussed above, the GMP requirements to be agreed as a condition for the marketing authorisation constitute additional financial and administrative burden for developers of ATMPs. GMP manufacture of niche and tailor-made ATMPs also calls for ATMP-

\textsuperscript{705} Evaluation of the effectiveness of any risk management system and the results of any studies performed shall be included in the periodic safety update reports referred to in Article 24(3) of Regulation (EC) No 726/2004.


\textsuperscript{709} Op.cit., 74
specific adaptations to GMP standards. Third, hospital exemption constitutes negative incentives for developers of ATMPs, as it currently seems to accommodate the most of ATMPs. There is also a need to analyse whether the EMA’s current incentives for developers of ATMPs are sufficient to accelerate the market entry of these products.

7.7.1 The counterproductive and inconsistently used hospital exemption

The hospital exemption that is laid down in Article 28(2) of the ATMP Regulation (amending Article 3(7) of Directive 2001/83) allows hospitals to treat individual patients in the transitional period or in case of high-unmet medical need (i.e. no authorised ATMP available) with ATMPs on a non-routine basis in accordance with specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a physician, under an individual medical prescription for a custom-made product for an individual patient. Medicines falling within the scope of the ATMP definition and being covered by the hospital exemption are relieved from the mandatory centralised marketing authorisation procedure. Member States are required to set out for rules for authorising these medicines by national competent authorities whilst simultaneously safeguarding those relevant EU-wide requirements on applicable quality and safety standards are met. It is required that applicable pharmacovigilance, traceability and quality requirements for ATMPs provided under the hospital exemption should be comparable to those applicable for a mandatory centralised marketing authorisation procedure.

This ambiguous description has been subject to some significant debate and the inconsistent use of the hospital exemption has resulted in a lack of harmonisation across the Member States (as described in Table 5. in Appendix 3). Many of them have not implemented an adequate mechanism to issue hospital exemption production licences yet. Whilst in those who have done so, there are wide differences in how hospital exemption may be applied. Most Member States apply annual limits to the numbers of a specific product type that can be manufactured under a hospital exemption licence to comply with the requirement for “non-routine” production in the ATMP Regulation, whereas some do not apply any restrictions. It appears that rules including information on production process and environment and safety and efficacy data for applying hospital exemption are still under development in many Member States, which will necessitate major investments in improvement of manufacturing facilities.

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712 Pearce, et al., supra note 540, 295-296.
It is that apparent that the widely dissimilar interpretations of the hospital exemption by the national competent authorities conflict with the objective of approximation of laws and practices in the EU. Thus, there is a need for the European Commission to further clarify and streamline this definition. It has been argued by van Wilder that there is evidence that the hospital exemption rule is compromising the ATMP Regulation’s objective of guaranteeing the highest level of health protection for patients.\textsuperscript{715} Whilst Pirnay et al. have expressed that when production is only intermittent (e.g. less than 10 applications per year), it is very difficult obtain the experience and training necessary to guarantee the best quality of work.\textsuperscript{716} Limitations regarding the amount of individual ATMPs under the hospital exemption have been largely perceived as counterproductive.\textsuperscript{717} It could potentially result in patient migration to other Member States or non-EU countries only because the maximum number of patients has been treated in a single establishment during one year.

The ATMP Regulation prohibits the use of the hospital exemption for clinical trial product manufacture. However, some national competent authorities seem to allow the use of the hospital exemption to produce ATMPs for first-in-man cases. Some authorities permit the data arising from these cases to be utilised as part of the IMP ATMP dossier for later clinical trial applications.\textsuperscript{718} It has been observed that actually some national competent authorities refer to these first-in-man, compassionate-use cases as a novel “phase 0” type of clinical trial.\textsuperscript{719} Yet, systematic safety and efficacy trials are of paramount importance. Such evidence generation might be complemented, however not substituted by data arising from products used under hospital exemption.\textsuperscript{720}

In any case, it does not appear appropriate the hospital exemption rule is currently accommodating for the most of ATMPs, indeed.\textsuperscript{721} To avoid negative incentives it seems essential to ensure that these treatments should only be given when there are no


\textsuperscript{716} Pirnay, et al., \textit{ibid}. See also Mansnérus, \textit{ibid}.

\textsuperscript{717} Pearce, et al., \textit{supra} note 540, 295.


\textsuperscript{719} Pearce, et al., \textit{supra} note 540, 296.

\textsuperscript{720} See e.g. Mansnérus, \textit{supra} note 22, 444.

\textsuperscript{721} Pirnay, et al., \textit{supra} note 22, 549. See also Mansnérus, \textit{supra} note 22, 444.
approved ATMPs for a specific disease or it is impossible for a hospital to be involved in a clinical trial of a relevant medicine under development. This approach would minimise competition between licensed medicinal products and products manufactured under hospital exemption. It would also create incentives for the development of therapies with demonstrated quality and proved positive risk-benefit balance in clinical trials.

7.7.2 The EMA’s incentive mechanisms aiming at facilitating access to market

A regulatory study by Regnstrom et al. indicates that company size may be an independent predictor of success of a marketing authorisation application to the EMA: the smaller the company, the more probable a negative outcome.722 Their study also suggests that smaller companies are developing a larger proportion of orphan (and ultra orphan) medicines than larger ones. Whilst Maciulaitis et al. point out that regulators are well aware of idiosyncrasies of the ATMP field and there are a number of ways the EMA may provide guidance to developers of ATMPs.723 The particular needs of SMEs, hospitals and academia have been acknowledged by the EMA. The EMA provides pursuant to the ATMP Regulation incentives for product development tailored to them. The incentives, which focus on the main financial and administrative entry obstacles for SMEs in pre-marketing authorisation procedures are presented in Table 6 below. In addition, SMEs, academia and non-profit actors may take advantage of the EMA’s existing early access incentives and initiatives (such as PRIME scheme, adaptive pathways, Innovation Task Force meetings, health technology parallel scientific assessment and the certification procedure) to facilitate market entry of ATMPs.

Despite the incentives, SMEs still have had historically a lower success rate in the marketing authorisation procedure than larger companies.724 As possible explanations for this the EMA has acknowledged that the main problems relate to quality issues and clinical efficacy, in particular. Therefore, it is especially advisable for SMEs to seek scientific advice from the EMA early in development to ensure that the adequate trials are conducted to avoid that any major objections regarding the trial design are raised when the marketing authorisation application is assessed.725 Interestingly, a study by Regnstrom et al. indicates a strong association between a positive outcome of a marketing authorisation procedure and requests for and compliance with regulatory scientific advice. According to Regnstrom et al. direct interaction with regulators

723 Maciulaitis, *supra* note 559, 481-482.
724 Maciulaitis, *ibid*.
725 Maciulaitis, *op.cit.*, 482.
seems to be a key predictor of success.\textsuperscript{726} Therefore, to facilitate translation of research into authorised ATMPs and to deal with the regulatory and scientific challenges of ATMPs, the EMA recognises the need for increased and early interactions and open dialogue with the developers and producers of these innovative medicines. Figure 6. in Appendix 4 illustrates the EMA’s regulatory procedures for ATMPs. Figure 7. in Appendix 5 describes possibilities for interaction with the EMA during different stages of product development and the role of incentives in the regulatory path for ATMPs. As presented in Figure 7. certification system may facilitate early dialogue with the regulators. The certificate could support SMEs who wish to license out their technology or it could be used to attract venture capital allowing them to further develop their products.\textsuperscript{727} Yet, certification procedure is used very seldom as it relates to the pre-clinical data and it is not linked with the marketing authorisation procedure.\textsuperscript{728} The certification procedure would be more useful if it had a clear link with the marketing authorisation procedure.

\textbf{Table 6. The EMA’s pre-authorisation incentives for SMEs}\textsuperscript{729}.

<table>
<thead>
<tr>
<th>Service</th>
<th>Fee Reduction</th>
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<tbody>
<tr>
<td>Scientific advice</td>
<td>90% fee reduction for non-orphan products</td>
</tr>
<tr>
<td></td>
<td>100% fee reduction for designated orphan products</td>
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<tr>
<td></td>
<td>100% fee reduction for products granted eligibility to PRIME</td>
</tr>
<tr>
<td>Inspection (pre-authorisation)</td>
<td>90% fee reduction and deferral</td>
</tr>
<tr>
<td></td>
<td>100% fee reduction for designated orphan products</td>
</tr>
<tr>
<td>Application for marketing authorisation</td>
<td>Fee deferral until the outcome of marketing authorisation application</td>
</tr>
<tr>
<td></td>
<td>Conditional fee exemption, where EMA scientific advice is followed and a marketing authorisation application is not successful</td>
</tr>
<tr>
<td></td>
<td>100% fee reduction for designated orphan products</td>
</tr>
<tr>
<td>Scientific services (e.g. certification)</td>
<td>90% fee reduction for non-orphan products</td>
</tr>
<tr>
<td></td>
<td>100% fee reduction for designated orphan products</td>
</tr>
<tr>
<td>Translations</td>
<td>Assistance with translations of product information into all official European Union (EU) languages</td>
</tr>
</tbody>
</table>

Reference: The European Medicines Agency, \textit{supra} note 729. PRIME= piority access medicine.

\textsuperscript{726} Regnstrom, et al., \textit{supra} note 722.


\textsuperscript{728} European Commission, \textit{supra} note 6, 12.

Developers of ATMPs are also encouraged to take advantage of informal briefing meetings with the EMA’s Innovation Task Force that promotes early dialogue and interaction with the EMA experts on administrative and scientific issues, as well as interactions with the CAT in its stakeholder meetings, training sessions and workshops for industry, academia, and hospitals developing ATMPs.\textsuperscript{730} In 2015, 34 briefing meetings with Innovation Task Force took place, almost two-thirds of which were on methods, for instance to facilitate the development of medicines (e.g. biomarkers), or to improve the manufacturing of medicines, particularly in the context of certain advanced therapies that need to be produced at the patient’s bedside. According to the EMA nearly 40 percent of requests came from SMEs and 31 percent originated from academia.\textsuperscript{731}

The EMA has recently launched new incentives for developers of medicines for unmet medical need. Fee reductions on the EMA’s scientific advice have been recently extended to cover non-profit organisations, such as academic research establishments if they qualify for the EMA’s PRIME Scheme.\textsuperscript{732} This voluntary scheme is relies on improved interaction and early dialogue with developers of promising medicines for an unmet medical need, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.\textsuperscript{733} The recently launched PRIME scheme focuses on ‘priority medicines’ that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. To be accepted for PRIME, a medicine must show its potential to benefit patients with unmet medical needs based on early clinical data. By means of this new initiative the EMA aims at offering early and proactive support to developers of medicine so that they can to optimise the generation of robust data on a medicine’s benefits and risks and enable accelerated assessment of medicines applications. According to the EMA special benefits (beyond financial ones) for developers of priority access ATMPs include:

- appointment of a rapporteur from the CAT to provide constant support and assistance to generate knowledge before marketing-authorisation application;
- organisation of a kick-off meeting with the CAT rapporteur and a multidisciplinary group of experts, so that they provide guidance on the overall development plan and regulatory strategy;
- assignment of a dedicated contact point;

\textsuperscript{731} European Medicines Agency, supra note 70, 50.
• provision of scientific advice at main development milestones, involving additional stakeholders such as health-technology-assessment bodies, to facilitate accelerated access for patients to the new product;
• confirm potential for accelerated assessment at the time of an application for marketing authorisation (it may in some cases be reduced from 210 days to 150 days).

The EMA has also quite recently launched a pilot project on adaptive pathways that aims at accelerating the market entry of medicines in areas of high medical need where it is difficult to gather data through traditional means and where large clinical trials would unreasonably expose patients who are unlikely to benefit from the treatment. Benefits and limitations of this approach for developers of ATMPs will be discussed in further detail in Section 8.3. of this study.

7.8 Cost of ATMPs and reimbursement issues affecting access to therapies

As a starting point both the pricing and reimbursement of ATMPs fall under the responsibility and sole discretion of the Member States in accordance with the strong expression of the subsidiary principle in Article 168(7) TFEU, which states that:

“[u]nion action shall respect the responsibilities of the Member States for the definition of their health policy and for the organization and delivery of health services and medical care. The responsibilities of the Member States shall include the management of health services and medical care and the allocation of the resources assigned to them.”

Ensuring the financial sustainability of the healthcare system whilst encouraging the innovation and R&D of new advanced therapies to address unmet needs constitutes significant challenges for those responsible for allocation of limited resources within national health care systems. From the perspective of developers of ATMPs, besides IP protection reimbursability of medicines constitutes an incentive to innovate and cover remarkable development costs. The expenses of ATMPs are considerably higher than those of conventional medicines, as high R&D expenses of these innovative therapies need to be covered. Therefore, the developers of ATMPs must get payers early involved in the commercialisation process to inform them early on about the value of their

735 Hanna et, al., supra note 83,7
product. The developers should be also duly prepared to gather long-term evidence by means of post-launch studies (and possibly reimbursement coverage with evidence development with or without escrow arrangements). Yet, concerns have been expressed that not all pharmaceutical companies developing ATMPs have adequate market access strategies in place addressing reimbursement issues.

Whilst from the perspective of patients, a new ATMP may be available as a consequence of being granted a marketing authorisation, but not accessible within a given Member State’s health care system because a choice has been made not to reimburse it. Undeniably, reimbursement of ATMPs from public funds within the healthcare system of the Member States is a very problematic political topic. Report from EuropaBio’s Industry Hearing states that:

“[t]he regulatory framework is a necessary, but not sufficient, step to make tissue engineered treatments available to patients: [Member States] have to be prepared to pay to make them available to those in need.”

In practice access to these innovative therapies does not only depend on the availability of these treatments, but also on significantly their reimbursement status within the public health care system. The DG JRC-IPTS evaluation study also acknowledges the particularly important significance of reimbursement policies and it also concludes that:

“[h]TEPs are much more expensive than conventional treatment options and cost-effectiveness data are scarce. Product prices may rise initially as a result of higher regulatory compliance costs, but increased competition and economies of scale could eventually drive hTEP prices down”.

Pricing and reimbursement aspects are very critical for providers of ATMPs, since requirements of GMP compliance and mandatory centralised marketing authorisation requirements significantly increase the expenditure of these medicines. For instance, in Finland national health insurance is part of the Finnish social security system. Medical costs are partly reimbursed by a health insurance fund and the government fixes reimbursement rates. A medicine must be confirmed as reimbursable and as having a reasonable wholesale price set by the Pharmaceuticals Pricing Board, which operates in affiliation with the Finnish Ministry of Social Affairs and Health. This pricing scheme does not leave much discretion for unreasonable profits, as it was set to cover the real procurement and processing costs of the medical products.

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736 Hanna et, al., ibid.
737 See e.g., Jaroslawski, supra note 24. Jaroslawski seeks to explain why the market access strategy of Provenge failed.
738 EuropaBio Stakeholder Meeting Report, supra note 170, 4.
739 Bock, et al., supra note 77, 10.

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As an example of the impact of the regulatory compliance costs on pricing of medicines, in Belgium ChondroCelect, a TEP authorised for the treatment of symptomatic knee cartilage lesions, was granted national Belgian reimbursement in 2011.\textsuperscript{742} Pirnay et al. report that due to the high cost arising from regulatory compliance the reimbursement price is nearly ten times the price of non-ATMP autologous chondrocyte cultures, and reimbursement is limited to patients younger than 50 years (which is deemed by the authors to be in conflict with the equal access to health care that is one of the leitmotifs of the Belgian public healthcare system).\textsuperscript{743} Whilst in many Member States e.g. in Finland, ChondroCelect is not currently eligible for reimbursement from public funds.

Another example is alipogene tiparvovec (Glybera), the first gene therapy, whose manufacturer is seeking a price of EUR 53,000 per vial (amounting up to MEUR 1.1 per patient).\textsuperscript{744} Despite being an “ultra orphan drug” targeting a very small patient population, it may create a significant financial impact by adding it to the other expensive orphan drugs on the market. Currently, Glybera is not reimbursed in the EU, as following its assessment the Federal Joint Committee Der Gemeinsame Bundesausschuss could not confirm the benefits of the product due to the limited data provided by the manufacturer.\textsuperscript{745}

A third example of product encountering significant difficulties with reimbursement is Sipuleucel-T (Provenge), an ATMP used to treat metastatic castrate resistant prostate cancer. It was priced at USD 90,000 for three doses in the U.S.\textsuperscript{746} It was not granted reimbursement in the EU. (The National Institute for Health and Care Excellence concluded that Provenge did not demonstrate either additional benefit or cost effectiveness compared to the best standard treatment, and Federal Joint Committee Der Gemeinsame Bundesausschuss concluded there the added benefit could not be quantified.)\textsuperscript{747} The manufacturer Dendreon went bankrupt primarily, but not only due to difficulties with its market access strategy and pricing.\textsuperscript{748}

Given the high price of ATMPs, aging European population that increases spending in public health and the current EU-wide economic downturn, there is an evident need for establishing allocation criteria for reimbursement of medicines. It has been rightly questioned whether reimbursement schemes allowing for limited allocation are a viable alternative for SMEs that are already targeting a niche market.\textsuperscript{749} Already the Report from EuropaBio’s Industry Hearing stated that: ‘‘[s]ome level of harmonisation for reimbursement is needed, or at least agreement on the principles for evaluation and reimbursement.”\textsuperscript{750} Despite the EU lacks competence to legislate directly on pricing


\textsuperscript{743} Pirnay, et al., supra note 22, 550.


\textsuperscript{748} See e.g. Jaroslawski, supra note 24.

\textsuperscript{749} Pirnay, et al., supra note 22, 550.

\textsuperscript{750} EuropaBio Stakeholder Meeting Report, supra note 170, 21. See also Pirnay et al., supra note 22, 553.
and reimbursement of healthcare, harmonised reimbursement of authorised clinical indications of all ATMPs or at least a common view on the principles for evaluation of reimbursement criteria for these medicines, would be well suited in the Lisbon Strategy that pursues to promote equity and solidarity through improved social care systems in Member State. The recently implemented Cross Border Healthcare Directive that touches upon cross border health technology assessment (influencing pricing and reimbursement) represents a leap towards harmonisation in the field of medical devices.

Some diseases that can be treated with ATMPs in the market or some other diseases for which there are ATMPs under development may be classified as orphan diseases (condition affecting no more than five in 10 000 persons). In case of orphan diseases, the European Commission has described the Member States on decision-making pricing, reimbursement and health system coverage as a “bottleneck in access to orphan drugs”. Some strategies that have been proposed to alleviate this problem include improved collaboration at EU level on scientific assessment of the added therapeutic value of orphan drugs and establishment and implementation of plans, strategies, or other public health actions for the diseases at Member State level. The Cross Border Healthcare Directive addresses specific issues of constant problems of patients suffering from orphan diseases by stating that despite previous actions in the field “[s]ome patients affected by rare diseases face difficulties in their quest for diagnosis and treatment to improve their quality of life and to increase their life expectancy.” Article 12 of the Cross Border Healthcare Directive suggests development of reference networks at EU level in the orphan disease context. Such can be based on voluntary arrangements between health care providers and centres of expertise in the Member States that could

“[s]erve as research and knowledge centres, updating and contributing to the latest scientific findings, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary.”

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751 Pirnay, et al., supra note 22, 537. See also Mansnérus, supra note 22, 450.
753 Commission, Communication to the European Parliament, the Council and the European Economic and Social Committee and the Committee on the Regions on Rare Diseases: Europe’s Challenges. COM (2008)678 final, 3.
The Cross Border Healthcare Directive also seeks under its Article 13(b) to improve access to treatment of orphan diseases by pursuing to make patients and health care professionals aware of the referral possibility to another Member State where the treatment is available (e.g. in cases where a some particular ATMP has not successfully passed through the national health technology assessment process). However, it is still too early to predict what kind of effects the Cross Border Healthcare Directive may have.\(^{757}\) Notwithstanding the measures at EU level to pool expertise, the main financial obstacles still remain as EU lacks competence to legislate directly on pricing and reimbursement of medicines. Hence, the capacity of the EU to address reimbursement and pricing aspects of ATMPs is limited.

Yet, if widening access to orphan ATMPs is perceived as an important policy goal, there are some possible measures that could be taken. First of all, the more accurate information regarding the overall costs of an ATMP to the health care system could be acquired from standardised patient data bases coordinated via the European reference network system. This could facilitate more precise assessment of total costs within a health care system if access to an orphan ATMP is granted, instead of focusing upon the treatment costs of a single patient or conducting a single QALY assessment.\(^{758}\) Currently, the low number of authorised ATMPs and the fact that many of them are designated to treat orphan diseases currently implies a rather low impact of ATMPs to date on national health insurance budgets but also on patients’ health.\(^{759}\) Yet, it is predicted that in the budgetary impact of ATMPs is likely to grow if some cancer therapies in Phase III trials manage to enter the EU market as licensed ATMPs.\(^{760}\)

Furthermore, it has been argued that if costs remain as a significant obstacle to access to orphan ATMPs, there might be need for critically scrutinising the market exclusivity period of ten years.\(^{761}\) However, it should be noted that there is no evidence that the market exclusivity is the key driver of high prices of ATMPs. In addition, market exclusivity is an important form of IP protection and its reduction of market exclusivity period would constitute a negative incentive for developers of orphan ATMPs. It should be also noted that the concept of orphan similarity requires some

\(^{757}\) Syrett, supra note 754, 146.

\(^{758}\) A quality-adjusted life-year (QALY) takes into account both the quantity and quality of life generated by healthcare interventions. It is the arithmetic product of life expectancy and a measure of the quality of the remaining life-years.

\(^{759}\) Hanna, et al., supra note 83, 6.


\(^{761}\) Reference is made to Article 8.2 EC Regulation No. 141/2000 regarding orphan drugs.
further clarification in ATMPs context. It needs to be adapted for ATMPs and carefully considered in the context of new active status and changes to the active substance.\(^{762}\)

There are also some possible measures facilitating access to ATMPs that could be taken by the Member States, despite these measures still remain connected to the existing health technology assessment principles or methods. Among other things, it has been suggested that greater flexibility in the pricing and reimbursement regime of medical products may widen the access whilst sustaining a certain degree of control of expenses.\(^{763}\) For example, conditional pricing schemes allowing for rapid access to medicines subject to a possible later pricing adjustment based on further evidence generated by post-launch studies could be used. Some Member States have applied such a possible approach e.g. France applies an “Authorisation for Temporary Use”-system that is applicable for orphan medicines. Furthermore, Netherlands has regulation that conditionally reimburses orphan medicines used in teaching hospitals for a period of three years, during which the manufacturer is required to conduct post-effectiveness studies.\(^{764}\) In addition, related pricing practices, such as risk-sharing (the manufacturer bearing a part of the cost of the medicine to the health system) and value-based pricing (price of the product being determined by its value to patients and a health system, based upon criteria such as its ability to meet unmet medical need) could possibly be used to limit costs of ATMPs.\(^{765}\) The adaptive pathways approach of the EMA that also addresses the health technology assessment related issues will be discusses in Section 8.3 of this study.

Despite the choices regarding the scope of the health care system currently remains at the Member State level as reiterated by the Cross-Border Health Care Directive stating that “decisions about the basket of healthcare to which citizens are entitled... must be taken in the national context”\(^{766}\), industry (including SMEs) would benefit from harmonised rules and procedures regarding pricing and reimbursement of ATMPs. Pirnay et al. suggest that industry and reimbursement authorities should decide which types of ATMPs will be eligible for future reimbursement (for every patient in need) prior to development of the ATMP, as once an ATMP has been granted a marketing

\(^{762}\) European Medicines Agency. *Advanced therapy medicines: exploring solutions to foster development and expand patient access in Europe* Outcome of a multi-stakeholder meeting with experts and regulators held at EMA on Friday 27 May 2016, 6. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/06/WC500208080.pdf. Accessed 12 August 2016. The EMA has been actively involved in exploring ways to foster ATMP development and expand patient access. It convened a stakeholder meeting on 27 May 2016 attended by academia, university spin-offs, and consortium organisations, and representatives from patients and healthcare professionals, organisations, SMEs and big pharmaceutical companies, venture capitalists, health technology assessment bodies, national competent authorities and the European Commission. In particular following aspects were addressed in the meeting: facilitating R&D; optimising regulatory processes for ATMPs; moving from hospital exemption to marketing authorisation and improving funding, investment and patient access.

\(^{763}\) Syrett, * supra* note 754, 126.

\(^{764}\) Ibid. See also Commission, Pharmaceutical Forum, Pricing and Reimbursement Working Group, Risk-sharing practices and conditional pricing of pharmaceuticals, 2008.

\(^{765}\) Syrett, *ibid.*

\(^{766}\) Cross-Border Health Care Directive, para 5.
authorisation, the pressure on companies to get a positive reimbursement decision and authorities to grant it becomes high.\textsuperscript{767} It has been predicted a number of ATMPs being granted marketing authorisations (especially to treat various cancers) in the foreseeable future based on limited clinical data, yet with potential for very high benefit, rendering it extremely difficult for authorities to deny reimbursement.\textsuperscript{768} As a growing pipeline of innovative and expensive ATMPs is likely to enter the EU market in the coming decade, the regulators should increase transparency regarding different national reimbursement practices, coordinate actions in relation to reimbursement and agree at EU level different models for reimbursement and payment mechanisms, as well as for managed access schemes.


\textsuperscript{768} Hanna, et al., \textit{supra} note 83, 8.
8 Conclusions

Eight years after adoption of the ATMP Regulation, at least in terms of a number of ATMPs authorised via the mandatatory centralised procedure, at first glance its net outcome seems rather disappointing. Despite increasing number of companies and amount of investment in this field, requests for the optional ATMP classification procedure submitted to the CAT resulted in 15 marketing authorisation applications and only six marketing authorisations granted to ATMPs (four of which are currently still authorised). As of May 2016 the CAT has also completed seven certification and 211 classification procedures and has been involved in 197 scientific advice procedures for ATMPs.

At least in terms of the number of authorised ATMPs, it seems that the ATMP Regulation fails to meet one of its primary objectives — facilitation of the access of ATMPs to the internal market. Yet, the low number of ATMPs in the market can be only partly explained by reasons pertaining to the ATMP Regulation. It also appears questionable whether the ATMP Regulation has fostered the competitiveness of the European pharmaceutical industry. As for the objective of guaranteeing the highest level of public health protection, concerns have been voiced that creating an “ATMP hype” without consequent delivery risks creating a play-ground for providers of unsafe therapies (e.g., unverified stem cell therapies provided outside the regulated clinical trial system). However, no concrete evidence has been presented that the ATMP Regulation as such would jeopardise the safety of ATMP clinical trial participants or patients who have been prescribed ATMPs in the EU. When it comes to the implications of the higher level manufacturing requirements for ATMPs, in the absence of a comprehensive scientific evaluation of the quality and safety aspects of ATMPs, whether mandatory compliance with GMP guidelines really improve the quality and safety of ATMPs has been questioned. It is also questionable whether the conventional drug regulatory model that relies on a precautionary principle is well-suited for these innovative medicines that necessitate more flexible risk-proportionate assessment due to their complex nature and inherent characteristics that differ from conventional pharmaceutical products.

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772 Pirnay, et al., op. cit., 544.
However, despite the criticism common standards on market access of ATMPs and requirements on quality are needed to protection of public health. The most recent developments in the field indicate that there is an ongoing paradigm shift from the predominantly risk-averse approaches to more adaptive, risk-proportionate and facilitative approaches to clinical trials, GMP manufacture, and market access of ATMPs (see Sections 8.1.2, 8.2 and 8.3).

It should be also noted that the small number of authorised ATMPs on the market can only be partly explained by the impact of the ATMP Regulation. There are also a number of other factors that explain the paucity of these innovative products on the market. According to Pearce et al., ATMPs are a novel and developing domain where a high proportion of ATMP trials remain in the academic field and have not yet advanced to industrial development. Developers of ATMPs encounter a number of other roadblocks that impede their access to the internal market. As the early development phases of ATMPs are usually very experimental and predominantly investigator-led, ATMPs in early trials are not being developed with the ultimate objective of commercialisation. In addition, developers of ATMPs may encounter difficulty acquiring research funding; difficulty with access to materials or with IP protection. Furthermore, difficulty with getting clinical trial authorisations constitute a significant impediment for the market entry of ATMPs. Biomedical considerations preventing basic research findings from being tested in a clinical setting have been left outside the scope of this study. Whilst particularities of clinical trial design, human behaviour, organisational and research infrastructure related factors impeding market entry of ATMPs are beyond the scope of this study, some of these aspects will be briefly outlined in the epilogue.

8.1 Outcome of the ATMP Regulation

Upon emergence of human tissue engineering technologies in the late nineties, concerns about inadequate regulatory governance of this field were raised and a need for a harmonised EU-wide legislation was acknowledged. Industry representatives lobbied heavily on the EU policymakers to establish a favourable regulatory atmosphere to support and facilitate development of a robust internal market for ATMPs. Initially, it was assumed that enactment of EU legislation on ATMPs is necessary for safeguarding interests of public health. Actually, health care as a public service does not subordinate to the internal EU market. Therefore, “common safety concerns in public health in an area in which application of existing EU legislation and additional national measures have proven insufficient”, were actually the only route for the European Commission to launch regulatory initiatives in the ATMP field. It was argued by the industry that lack of EU-wide legislation on ATMPs would harm the patients, since they are denied the potential benefits of these regenerative medicines. Harmonised regulation was projected

773 Pearce, et al., supra note 540, 291.
to create predictability and help different industry actors to make informed investment choices, facilitating them to invest in R&D of ATMPs. It was also expected that harmonised regulation would also be more cost efficient, as it was anticipated to reduce the expenses of meeting diverse quality, safety, efficacy and marketing requirements in different Member States.

The drafting histories of the EUCTDs and the ATMP Regulation reveal that different stakeholders had divergent motives, objectives, values, incentives and resources in the ATMP domain. It appears at all levels of the legislative process (ranging from evaluation studies, public consultations and impact assessment process to creation of the draft legislative proposal) that the impact of the pharmaceutical industry was very significant. In terms of participation, representatives of academia and public tissue establishments were in practice paralysed, as they apparently had underestimated the significance, scope and extent, as well as practical implications of these important legislative initiatives. Very proficient lobbying by the industry resulted in a significant bias for the benefit of the actors representing big corporations in evaluation studies, public consultations and the impact assessment process regarding the ATMP field. That in turn led to the provision of inaccurate information to the EU decision makers regarding the potential economic, social or environmental influence of these draft legislative initiatives. As a consequence of the asymmetrical (and also partly distorted) information that was provided to law-makers, the industry’s view prevailed in the final legislative proposals and overruled the underrepresented voices of academia and public tissue establishments. As a conclusion of this regulatory review, it can be summarised that industry’s successful lobbying and had following consequences:

i. Due to the EU’s limited mandate to harmonise ethical aspects of ATMPs, some disputed social and ethical concerns were evaded (such as commercialisation of altruistically donated material of human origin from the scope of the EUCTDs and the ATMP Regulation). Whilst industry’s lobbying caused blurring the differences between non-profit and profitmaking activities of tissue establishments. Upon introduction of pharmaceutical industry standards, ethical issues were left to be dealt with by the Member State, as far as possible. This has resulted in disharmonised approaches to availability of certain types of raw materials or medicines based on such materials (such as hESCs). The current wording of Article 4 the Directive 2001/83/EC is drafted so ambiguityously that the Member States may deny access to a products based on cells or tissues on any grounds (not just ethical ones).

ii. Creation of a new concept of “tissue establishment” that allows commercial actors to perform cell and tissue banking activities. This amendment is not undesirable as such, but it should be noted that in some Member States it is still very difficult for SMEs and other commercial actors to carry out comprehensive biobanking activities despite the EUCTDs framework allows them to procure, store and process cells and tissues and to be qualified as tissue establishments (predominantly due to ethical
concerns relating to commercialisation of altruistically donated human tissue and cell primary material).

iii. Widening the initial scope of the EUCTDs to cover autologous cells to be used for medicinal products. Hence, distinction between regulation applicable for autologous and allogeneic tissue and cell based products was avoided. However, production of autologous products takes often place in hospital settings and in small batch sizes. For such niche and tailor-made production the conventional and costly industrial manufacture model is not well-suited.

iv. Adding ATMPs, as a subcategory of cell and tissue based products within the medicinal products regulatory regime. Consequently, any ATMPs shall be compliant with requirements for conventional pharmaceuticals (e.g. GMP and marketing authorisation requirements). It has been argued that rigorous technical requirements (which are not negative as such) risk becoming disproportionately costly for SMEs, research units in the academia, public tissue establishments, consequently impeding innovation. In practise, the EUCTDs framework was designed to ensure that large public tissue establishments would be able and willing to provide high quality cells and tissues to meet the needs of the emerging tissue engineering industry. However, subsequent to adaption of the ATMP Regulation, it appears that in practise their role actually became limited to that, as they would not be due to resource consuming industry-adapted GMP and marketing authorisation requirements able to compete with commercial tissue engineering companies.

v. Attaining such a level playing field, in which conditions for applying hospital exemption are kept as narrow as possible, so that hospitals are not able to compete with commercial actors manufacturing ATMPs. This has resulted in some valuable established therapies are risking to become unavailable for patients in need of them. However, the hospital exemption should be kept narrow for avoidance of negative incentives. Other flexibilities should be applied to facilitate R&D and manufacture of ATMPs.

vi. Creating an incentive system that addresses particular needs of SMEs by providing incentives for product development tailored to them. These incentives focus on the main financial and administrative entry obstacles for SMEs in pre-marketing authorisation procedures. Recently, some of the incentives have been extended to cover the academia and non-profit organisations. Despite these incentives, other obstacles (especially financial hurdles relating to GMP compliance) make it hard for SMEs to enter the EU market. Yet, GMP standards play an important role in quality management of ATMPs and protection of public health.
8.1.1 Benefits and shortcomings of the ATMP Regulation

The ATMP Regulation was created to ensure the free movement of ATMPs within the EU to facilitate their access to the internal market, and to foster the competitiveness of European pharmaceutical companies, while guaranteeing the highest level of health protection for patients. Initially, the predicted benefits for public health of a mandatory marketing authorisation appeared evident: a risk v. benefit analysis conducted by independent experts based on quality, nonclinical, and clinical data was presumed to provide confidence to patients and health care professionals in new medicinal products. Both industry and patients were assumed to benefit from a facilitated access to the EU market via a single procedure.774 In addition, manufacturers were seen to be provided with regulatory certainty for the development of their products and are ensured free movement of those products within the EU. Furthermore, patients and health care professionals were predicted to benefit from timely access to innovative treatments.775 It should be noted the impact assessment report of the ATMP Regulation anticipated that the contemplated legislative initiative would confer merely indirect consequences to the health care systems of the Member States.776 A predicted direct impact would have constituted a breach of the subsidiarity principle. It seems unlikely that the ATMP Regulation would have been implemented as such, if its actual direct consequences were known. The ATMP legislative framework, which was purported to improve public health protection, is in its current form both indirectly (in terms of high cost of ATMPs and limited reimbursement of ATMPs) and directly (in a form of the loss of some established advanced therapies) adversely affecting patients’ access to such therapies within the national health care systems of the Member States.777 Yet, when it comes to new ATMPs, as discussed in Chapter 7 the reason for low number of authorised ATMPs in the market cannot be only attributed to the ATMP Regulation.

In 2013 the European Commission organised a public consultation regarding the experience gained from the application of the ATMP Regulation. According to the European Commission it is not possible to determine whether the ATMP Regulation has given rise to a larger number of ATMPs in the EU because the Member States have insufficient data about the ATMPs which were already available before the ATMP Regulation came into force.778 It has also been very difficult to obtain precise figures about the number of ATMPs that were on the EU market prior to the entry into force of the ATMP Regulation. It is noted in the report issued by the European Commission that this may be partially explained by the intrinsic difficulties associated with the

774 Klug, et al., supra note 730, 338.
777 De Corte, et al., supra note 5. See also Pirnay, et al., supra note 22, 555. See also Mansnérs, supra note 22, 460
application of the definition of ATMP. However, according to pooled data from surveys conducted by the EMA in 2007 and 2009, the Member States have reported 31 ATMPs as being legally on the EU market prior to the entry into force of the ATMP Regulation. It has been emphasised by the European Commission that this figure may not be accurate as, on the one hand, the same product may have been reported by more than one Member State and, on the other hand, not all Member States have been able to report. The low number of marketing authorisation applications for ATMPs received by the EMA has been interpreted to demonstrate that many of the developers of ATMPs that were on the market prior to the entry into force of the ATMP Regulation did not apply for a marketing authorisation. It has been reported by the Member States that approximately 60 derogations from the obligation to obtain a marketing authorisation prior to the marketing of ATMPs had been granted until April 2012. Such derogations were granted under the hospital exemption. Hence, many of the existing ATMPs continue to be used in the absence of a marketing authorisation under derogations granted by Member States. As a conclusion of benefits and shortcomings of the ATMP Regulation following remarks are presented:

Hospital exemption should not become the normal route to market. The inconsistent application of the hospital exemption is conducive to create uncertainty amongst national competent authorities and biobanks and it does not promote harmonisation of practices in the European tissue engineering field. The European Commission appears very sceptical when it comes to the use of hospital exemptions. It notes that they allow patients fast access to ATMPs. However, they may result in a failure to apply for the mandatory EU-wide authorisation for ATMPs. Especially a concern has been expressed that there is a risk of too frequent use of the hospital exemption discouraging the submission of marketing authorisation applications, as ATMPs that have been granted a marketing authorisation via the centralised procedure face much higher developmental and maintenance costs than ATMPs that have been produced under the hospital exemption. Hence, developers of ATMPs applying for a marketing authorisation via the centralised procedure are put in a significant competitive disadvantage in comparison to those manufacturing ATMPs under the hospital exemption. Also, products under hospital exemptions then do not enter the

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779 European Commission, supra note 6, 13.
780 According to the European Commission, the reported figures may be incomplete as some products may have been put on the market as tissues/cells or medical devices despite having the potential to fall under the definition of ATMP. Furthermore, the European Commission points out that a number of Member States have indicated that no ATMP was available in their territory prior to the entry into force of the ATMP Regulation, the non-availability of these products being more common in the smaller Member States.
781 According to the report issued by the European Commission ten marketing authorisation applications for ATMPs had been submitted to the EMA by 30 June 2013. Five of them concerned products that were previously on the EU market.
782 According to the European Commission, nearly half of the ATMPs that have been reported by the Member States as being marketed in their territories before the ATMP Regulation entered into force were chondrocyte-containing products (16 out of 31).
internal market and can only be used within the scope of the exemption, i.e. only for other domestic patients.\textsuperscript{783} In addition, the European Commission also acknowledges that there have only been authorisation applications very few ATMPs on the market due to the fact that the Member States have approved hospital exemptions for other ATMPs.

There is a concern that if the hospital exemption became the normal route to market, there would be detrimental consequences for public health. As clinical trials constitute primary means for obtaining information about the efficacy and safety of ATMPs, the lack of appropriate clinical trials could compromise the safety of the patients. In addition, the gathering efficacy and safety data would risk to be undermined as each production site would only generate information on a small number of patients and there would be no efficient transmission of information between the national competent authorities of the Member States. Moreover, the treatment would not be available to all patients across the EU. Hence, it is necessary to strike a balance between the need to ensure that ATMPs are made available to patients only after adequate demonstration of the quality, efficacy and safety of the product, and the need to facilitate early access for new treatments in case of unmet medical needs.\textsuperscript{784}

\textbf{Voluntary certification procedure is used infrequently by the developers of ATMPs.} The European Commission has found it disappointing that the voluntary certification procedure has been used very seldom. There are possibly three main reasons for this: First, the fee reductions do not apply to non-profit organisations (i.e. academia). Second, the value of certification is too low because the procedure only applies to the preclinical sector and is not linked to the marketing authorisation procedure.\textsuperscript{785} Third, some SMEs have expressed concerns about certification procedure triggering a GMP inspection.\textsuperscript{786} Yet, regulators have clarified that the procedures do not in fact lead to GMP inspections but rather to informal site visits by experts to assist developers overcome early problems.

\textbf{Classification procedure needs to be improved.} The European Commission gives a positive assessment to the ATMP classification procedure. Yet, there is an evident need for improvements. Positive aspects of the ATMP classification procedure are that the procedure is carried out centrally for the entire EU and is free of charge.\textsuperscript{787} However,

\textsuperscript{783} Sohn, supra note 778, 2. European Commission, supra note 6, 7.
\textsuperscript{784} Mansnérus, supra note 22, 442-444.
\textsuperscript{785} Sohn, supra note 778, 2. The European Commission has reported that only three certification requests had been submitted to the Agency by 30 June 2013. Two of the requests concerned exclusively quality data, while the third request related to quality and non-clinical data. The CAT granted the certification in all three cases.
\textsuperscript{786} European Medicines Agency, supra note 762, 6.
\textsuperscript{787} Sohn supra note 778, 2. The European Commission has reported that the CAT had received 87 requests and it had issued 81 classification recommendations by 30 June 2013. According to the European Commission almost half of all classification requests received originated from SMEs and an additional 15% of the requests came from the non-for-profit sector. Furthermore, it is noted by the European Commission that classification requests from large pharmaceutical companies represented approximately 5% of all submissions.
the deficiency is that the national competent authorities cannot use it when they are confronted with difficulties of classification.\textsuperscript{788}

\textbf{The coverage of the fee reductions on scientific advice has been extended.} The European Commission sees the scientific advice in a positive light.\textsuperscript{789} The fee reductions on the EMA’s scientific advice have been recently (on 27 May 2016) extended to cover academia and non-profit organisations if the applicant qualifies for the EMA’s PRIME scheme.\textsuperscript{790}

\textbf{Risk-averse regulatory environment hampering market entry of ATMPs.} Introduction of pharmaceutical industry standards (such as GMP and marketing authorisation requirements) to cover ATMPs resulted in a risk-averse EU regulatory environment that in its current form does not seem to benefit or facilitate the actual actors (i.e. SMEs, academia and hospitals) providing tailor-made or niche advanced therapies. The current heavy requirements for the developers of ATMP must be limited to what is necessary as they appear to impede development and commercialisation of ATMPs. However this should not compromise patient safety.\textsuperscript{791} It also appears that the high cost of GMP compliance seems to be underestimated by research funding bodies.\textsuperscript{792} This is detrimental to development of new ATMPs and commercialisation of these medicines.

Despite, the EUCTDs and the ATMP Regulation were applauded by the pharmaceutical industry; it now appears that big pharmaceutical companies have a limited interest in this field. However, SMEs specialising in tailor-made, niche advanced therapies are facing great difficulties when trying to get their products through the mandatory centralised ATMP approval process. The actual suppliers of advanced therapies, research units in hospitals and public tissue establishments, are discouraged by the industrial scale GMP and marketing authorisation requirements. As predicted in the second DG JRC-IPTS evaluation study, providers of equipment or GMP grade ancillary reagents may benefit from the ATMP Regulation as their short term sales may increase as ATMP suppliers are adapting to meet the standards.\textsuperscript{793} Also, pharmaceutical companies in need of invaluable research tissues of human origin are benefitting, as it has been difficult for commercial actors to obtain of human tissues due

\textsuperscript{788} Sohn, \textit{op.cit.}, 3.
\textsuperscript{789} Sohn, \textit{ibid}. The European Commission has reported that by 30 June 2013, the CAT had provided scientific advice regarding ATMPs on 93 occasions; the advice referring to 65 different products. According to the European Commission over 60% of the requests for scientific advice had been submitted by SMEs and an additional 6% was from academia. Requests from big pharmaceutical companies represented less than 10% of all requests. Additionally, it is noted by the European Commission that seven out of the ten applicants for marketing authorisation had previously requested scientific advice.
\textsuperscript{790} European Medicines Agency. \textit{Decision of the Executive Director on fee reductions for scientific advice requests on PRIME products for SMEs and applicants from the academic sector}, 27 May 2015, \textit{supra note} 732.
\textsuperscript{791} European Commission, \textit{supra} note 6, 7.
\textsuperscript{792} Pearce, et al., \textit{supra note} 540, 289.
\textsuperscript{793} Bock, et al. \textit{supra note} 74, 11.
to ethical and/or donor consent related reasons.\textsuperscript{794} However, industry’s access to primary material is not equally guaranteed in all Member States.

**High cost of ATMPs impedes access to advanced therapies.** In addition to the above described implications to SMEs and research units in hospitals and public tissue establishments, it appears that the ATMP legislative framework, which was purported to improve public health protection, is both indirectly (in terms of pricing and reimbursement) and directly (in a form of the possible loss of significant advanced therapies) adversely affecting patients’ access to therapies within Member States’ health care systems.\textsuperscript{795} Despite reimbursement issues are at discretion of the Member States, there is also a need for harmonisation for ATMP reimbursement or at least an agreement on the principles for evaluation and reimbursement.

**Inconsistencies in the Member States’ approaches despite the ATMP Regulation exists.** Furthermore, the current inconsistencies in the implementation of the ATMP Regulation are a considerable barrier to development of ATMPs across the EU. This is due to many differences in national pharmaceutical laws and practices underpinning the ATMP Regulation. Amendments to the ATMP Regulation and related practices are of paramount importance. Both SMEs and academic GMP practitioners developing ATMPs should improve their political visibility and contribute more actively to the creation of functional and effective harmonised European Union legislation in the ATMP field.\textsuperscript{796} The main benefits and shortcomings of the ATMP Regulation are summarised in Table 7. below.

\textsuperscript{794} Pirnay, et al., supra note 22, 546.
\textsuperscript{795} Pirnay, et al., supra note 22, 550, 555.
\textsuperscript{796} Pearce, et al., supra note 540, 289.
Table 7. Summary of the benefits and shortcomings of the ATMP Regulation

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Shortcomings</th>
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<tbody>
<tr>
<td>+ regulatory and administrative assistance from the EMA’s SME Office</td>
<td>- the number of licenced ATMPs in the internal market remains low (Yet, reasons for this can be only partly attributed to the ATMP Regulation)</td>
</tr>
<tr>
<td>+ 90 percent fee reductions for scientific advice and inspections for SMEs (65 percent fee reduction for others)</td>
<td>- interest of big pharma in development of ATMPs remains limited and pharmaceutical industry standards constitute significant financial impediments for the actual developers of ATMPs (i.e. SMEs, academia and hospitals) providing tailor-made or niche advanced therapies</td>
</tr>
<tr>
<td>+ fee reduction for the marketing authorisation application for SMEs developing ATMPs or orphan drugs</td>
<td>- introduction of pharmaceutical industry standards (such as GMP and marketing authorisation requirements) to cover ATMPs resulting in a predominantly risk-averse regulatory environment (Yet, it is positive that draft GMP Guidelines recently issued by the European Commission suggest ATMP-specific adaptations and flexibilities)</td>
</tr>
<tr>
<td>+ fee reductions on the EMA’s scientific advice have been recently extended to cover academia and non-profit organisations if the applicant qualifies for PRIME scheme</td>
<td>- the inconsistent application of the hospital exemption is conducive to create uncertainty amongst national competent authorities and developers of ATMPs as it does not promote harmonisation of practices</td>
</tr>
<tr>
<td>+ postponement of the fee payable for the marketing authorisation application or related inspection until after the grant of the marketing authorisation for SMEs</td>
<td>- the significant administrative burden and high cost of GMP compliance has been underestimated by research funding bodies</td>
</tr>
<tr>
<td>+ conditional fee exemption where scientific advice is followed and the marketing authorisation is unsuccessful for SMEs</td>
<td>- inconsistencies in the implementation of the ATMP Regulation, in particular the lack of harmonised ATMP classifications constitute a barrier to development of ATMPs across the EU, as national competent authorities cannot use the classification procedure when they face difficulties with classification of ATMPs</td>
</tr>
<tr>
<td>+ certification of quality/nonclinical data for ATMPs for SMEs</td>
<td>- certification procedure is used very seldom, it needs to be linked with the marketing authorisation procedure and fee reductions should be extended to cover non-profit organisations (i.e. academia)</td>
</tr>
<tr>
<td>+ providers of equipment or GMP grade ancillary reagents may benefit from the ATMP Regulation as their short term sales may increase as ATMP suppliers are adapting to meet the standards</td>
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</table>
8.1.2 Possible amendments to the ATMP Regulation and other measures to foster innovation

ATMPs are inherently complex modern biotechnology products originated from different biological primary materials, (including e.g., cells, tissues or viral vectors), and their unique characteristics necessitate adapted approaches in R&D as well as GMP manufacture of these products. Developers of ATMPs are facing challenges when ensuring the homogeneity of cell starting material and maintaining continuous supply of raw materials. Furthermore, as discussed in Section 7.5.3 certain manufacturing requirements may be not be appropriate for all types of ATMPs. Also the complexity of upgrading immature developmental production technologies to commercial GMP manufacture, process validation and product characterisation constitute challenges for those involved in GMP manufacture. As presented in Chapter 7 the pre-clinical and clinical phases of ATMP development involve special challenges, ranging from identification of relevant animal models to particularities of clinical trial design able to address small populations, inter-individual inconsistency and complex methods of administration of ATMPs. It is also apparent that SMEs and spin-offs from academia need support with the complex regulatory framework. In addition, such companies would benefit from improved access to capital investments and other funding.

Subsequent to the public consultation regarding the experience gained from the application of the ATMP Regulation the European Commission has raised a concern that the marketing authorisation procedure of ATMPs and the ATMP Regulation are in their current form too complex and need to be streamlined. From a process perspective, the scientific evaluation a marketing authorisation for ATMPs may involve up to five committees. However, the Commission does not make any concrete amendment proposals to the ATMP Regulation or related processes, even if it has discussed some specific features of autologous products. Yet, different stakeholders have expressed to the European Commission that additional flexibility should be applied (especially regarding quality of ATMPs under development) to ensure that the marketing authorisation application requirements take adequately the scientific progress and

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797 European Medicines Agency, supra note 762, 2.
798 See also op.cit., 3.
799 European Commission, supra note 6, 11-12. The application procedure is complex: (i) the CAT assesses the marketing authorisation application and gives its opinion to the Committee for Medicinal Products for Human Use ("CHMP"); (ii) the CHMP adopts an opinion which is transmitted to the Commission; (iii) the Pharmacovigilance Risk Assessment Committee ("PRAC") provides recommendations to the CHMP on pharmacovigilance matters; (iv) the Paediatric Committee ("PDCO") intervenes on aspects related with the obligations imposed under Regulation (EC) No 1901/2006 of the European Parliament and of the Council; and (v) the Committee on Orphan Medicinal Products ("COMP") provides scientific opinions to the Commission on aspects related to the application of the orphan incentives (this committee is only involved therefore if the applicant seeks orphan status).
800 In case of such ATMPs, the patient's own cells are taken, treated or expanded and finally reintroduced. As the starting material is different for each patient, the manufacturing process has specific characteristics not applicable to other medicinal products.
specific characteristics of ATMPs into account. Alternative approaches to reduce regulatory costs are currently being explored, as many stakeholders involved in the public consultation had proposed the introduction of a marketing authorisation granted on the basis of limited data to be used in a restricted setting (especially, in case of an unmet medical need). According to the proposal of some stakeholders the data generated on the uses in the restrictive settings could then be used to expand the marketing authorisation up to the point of becoming a standard authorisation. This proposed approach is actually possible in certain specific circumstances under the current regulatory framework (such as the EMA’s adaptive pathways initiative, as discussed in Section 8.3).

To improve translation of research into commercialised ATMPs, the European Commission has identified the following five concrete amendment proposals: (1) conditions for non-profit organisations should be improved; (2) certification procedure should be extended to cover non-commercial organisations and it should be amended to ensure a better link with the marketing authorisation procedure; (3) the current definitions of ATMPs to cover all ATMPs should be streamlined to prevent disparities in national classifications; (4) the marketing authorisation requirements should be adapted for special products, particularly autologous ATMPs; and (5) the hospital exemption should be revised to avoid negative incentives. This Section 8.1.2 discusses the proposed amendments and makes some further proposals to accelerate market entry of ATMPs.

Conditions for non-profit organisations should be improved. There is an evident need for adapting a clear ethical approach to deal with commercialisation aspects of material of human origin. Commercialisation of human bodily material could be perceived more acceptable when tissue establishments are acting bona fides and not for profit to supply human cell and tissue products for application in meaningful therapies. Especially, the good faith of public biobanks could be reflected in a reasonable price of the product, which only attributes to the additional biotechnological production process. The EMA has recently taken some measures to improve conditions for such non-profit actors, as fee reductions on the EMA’s scientific advice have been extended to cover non-profit organisations, such as academic research establishments if they qualify for the EMA’s PRIME scheme. Whilst the certification procedure still remains to be extended to cover academia and non-commercial organisations and amended to ensure a better link with the marketing authorisation procedure. Yet, as discussed in Section 7.7.2, the new PRIME scheme introduced a range of other measures are provided to support generation knowledge needed for marketing authorisation application.

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801 European Commission, supra note 6, 9-10.
803 Pirnay, et al., supra note 22, 556. See also Mansnérus, supra note 22, 446.
The current definitions of ATMPs to cover all ATMPs should be streamlined to prevent disparities in national classifications. When it comes to the need of streamlining the ATMP classification, the EMA has quite recently organised a public consultation and issued a new reflection paper address the challenges of the classifications. Yet, the great majority of the comments were not accepted as they concerned amendments to legal definition that cannot be amended by a recommendation. It was especially noted that the legislation does not allow for differential treatment of individualised therapies. As divergent classifications of ATMP subcategories by national competent authorities may have far-reaching consequences to commercialisation prospects of ATMPs, a mechanism should be established to improve consistency of classifications e.g. national competent authorities should have access to use the EMA’s classification procedure when they encounter difficulties with classification of ATMPs. Also a national competent authority should be required to provide scientifically justifiable grounds for deviation of the EMA’s initial classification if such has been issued (for instance amendments made to the ATMP require re-classification of the product).

The marketing authorisation requirements should be adapted for special products, particularly autologous ATMPs. The European Commission’s initiative regarding adaptation of the marketing authorisation requirements for special products (autologous ATMPs, in particular) is very important. The recently issued draft GMP Guidelines on ATMPs represents a significant leap forward in the right direction. These guidelines provide some feasible adaptations to facilitate production of smaller-scale, tailor-made and niche IMP ATMPs in early clinical trials. Despite the high standards on safety and quality must be ensured, the draft GMP Guidelines on ATMPs suggest some flexibilities for early developmental phases. In particular, adaptations are needed for non-substantially manipulated products, as these may be seen to fall on the borderline between transplants and ATMPs. The draft GMP Guidelines on ATMPs also allow for a more pragmatic approach to process validation.

Furthermore, these draft GMP Guidelines for ATMPs support risk-based approach in ATMP manufacture. Yet, as discussed risk-proportionate approach does not allow for derogations from the clinical trial authorisation or marketing authorisation requirements. In contrast, manufacturer is required to ensure that additional measures are in place (in addition to those proposed in the GMP guidelines) if that is necessary considering specific risks of the ATMP. Therefore, in order to take all potential risks into consideration, the ATMP manufacturer is required to identify the risk control measures that are most appropriate case by case. In addition, when it comes to risk management of ATMP manufacturing and administrations of ATMPs in clinical trials, efficient mechanism for enforcement of safety standards should be established (i.e.

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805 European Medicines Agency, supra note 762,4.
inspections, adequate training of inspectors and unified assessment criteria are needed when pursuing similar quality and safety standards for cells and tissues that used for therapeutic purposes across the EU).

Hence, to accelerate market entry of ATMPs, the marketing authorisation requirements must negotiated with the regulators to take into consideration the particularities of ATMP manufacture. For instance, sometimes ATMP manufacture can take place at multiple manufacturing sites and some products may need to be manufactured close to the bedside due to short shelf-lives. Consequently, all manufacturing sites involved (including hospitals) need to have a manufacturing licence.\textsuperscript{806} According to the EMA some Member States allow hospitals to hold a manufacturing licence while others do not. There is also a need for improved transparency regarding manufacturing authorisation requirements across Europe. The regulators should also investigate whether some new approaches to GMP manufacture could be promoted (such as, closed systems and bedside manufacturing or manufacturing as a service).

\textbf{The hospital exemption should be revised to avoid negative incentives.} The hospital exemption needs be urgently revised to avoid negative incentives. As there are that widely different interpretations of the hospital exemption by the national competent authorities, there is a need for the European Commission to further clarify and streamline the definition of “non-routine production”. It should be also ensured that treatments should only be given under hospital exemption when there are no approved ATMPs for a specific disease or it is impossible for a hospital to be involved in a clinical trial of a relevant medicine under development. In addition, the reporting of results (particularly negative ones), should be improved so that patients are not unnecessarily exposed to unsafe or ineffective treatments.\textsuperscript{807} (In this respect the Clinical Trial Regulation establishing a data base of clinical trials is likely to improve transparency.) Other issues that could benefit from additional clarification include: the role of derogatory provisions of Directive 2001/83/EC other than the hospital exemption (especially Article 5.1 of the Directive) in the context of ATMPs, and the role of data generated from the use of a product under the hospital exemption in the context of an application for a marketing authorisation.\textsuperscript{808}

\textbf{Access to primary materials should be improved.} To improve transparency and harmonisation regarding tissues and cells used as primary materials for ATMPs, regulators could set up a database for EU cell and tissue authorities to disseminate information regarding their additional requirements for testing cells and tissues at national level.\textsuperscript{809} Such harmonisation measure could possibly facilitate the movement of

\textsuperscript{806} European Medicines Agency, \textit{supra} note 762, 4.
\textsuperscript{807} European Commission, \textit{supra} note 6,8.
\textsuperscript{808} Article 5(1) of Directive 2001/83 provides that a Member State may exclude from the provisions of the Directive medicinal products supplied in response to a \textit{bona fide} unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.
\textsuperscript{809} European Medicines Agency, \textit{supra} note 762, 4-5.
materials between Member States (and also outside the EU) applying different requirements. It could also possibly serve to ease the burden of having to re-test the cells and tissues prior to the ATMP manufacture.\textsuperscript{810} Furthermore, as scientific advancements take place in the global scale, the EU regulators could for instance consider cooperating with U.S. and Japanese regulators to harmonise aspects of regulation on ATMPs internationally. Such harmonisation could possibly accelerate international research and facilitate exchange of primary or intermediate materials as well as final licensing of products.\textsuperscript{811}

Despite the numerous challenges the ATMP developers face with the existing ATMP Regulation (and some related regulatory instruments), it still represents a significant leap forward in creating a facilitating environment for ATMPs within the EU. The European Commission has acknowledged that the ATMP Regulation should be adapted to rapid scientific progress.\textsuperscript{812} The practical implications of the legislation clearly illustrate some of the challenges regulators meet when dealing with nascent technologies to accommodate scientific progress and to give investors an acceptable level of certainty and predictability in a rapidly evolving field. There is an evident need for regulators to engage in new and innovative legislative approaches as they are expected to create facilitating and proactive legislation in cooperation with all stakeholders. To recapitulate findings of this study Table 8. below identifies in light of market, risk and human rights/ethics frames major legal and ethical roadblocks to market entry of ATMPs (also covering some particularities regarding hESC-based ATMPs) and it proposes some measures to accelerate innovation whilst protecting public health. Yet, it should be noted that the division of competences between the EU and its Member States in the field of public health may limit the possibilities to use some of the proposed measures.

\textsuperscript{810} Ibid.
\textsuperscript{812} Sohn, supra note 778, 3.
### Table 8. Summary of the potential factors accelerating market entry of ATMPs and proposals for other measures to foster innovation

<table>
<thead>
<tr>
<th>Frame(s)</th>
<th>Challenge</th>
<th>Comment</th>
<th>Measures</th>
</tr>
</thead>
</table>
| **Market**             | **Complexity of the EU legislation on ATMPs**                              | Despite its complexity, the ‘umbrella approach’ to regulation of ATMPs allows for some flexibility, as e.g. the proposed ATMP-specific GMP standards can be quite smoothly updated to reflect particularities of ATMPs and most recent scientific advancements.                                                                 | Regulators to:  
  – consider whether ATMPs could be covered by a single efficient legislation instead of many separate pieces of legislation;  
  – provide more ATMP specific guidance to SMEs and academia (e.g., workshops and training); and  
  in particular the EMA – to streamline internal regulatory processes for ATMPs. The EMA could for instance consider setting up a dedicated office for academia with expertise in ATMPs, and dedicate one contact person for each ATMP that guides developers through the regulatory process.  
  
  **SMEs/Academia to:**  
  – promote early interaction with the regulatory authorities; and  
  – educate interdisciplinary teams (such as scientists with legal/regulatory skills). |
| **Scope: R&D, education** |                                                                          |                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                         |
| **Human rights/Ethics** | **Wider ethical aspects evaded in the ATMP Regulation**                   | Yet, the ATMP Regulation is a very technical piece of legislation; ethical aspects are more aptly covered by other legislative instruments or ethical standards. The EU policies should however allow for a wide margin of appreciation in ethical questions for the Member States.                                                                 | Regulators: For avoidance of paternalistic legislation, when feasible flexible soft law approaches (e.g. non-coercive, self-regulatory measures such as recommendations, guidelines as well as incentives and risk management tools) should be promoted to facilitate adaptations to present day conditions.  
  
  *(Yet, in this very technical field, it may be difficult to avoid casuistic legislation or ethical standards. Even soft law instruments such as GMP standards may become quickly obsolete in course of rapid scientific advancements.)* |
| **Scope: R&D**         |                                                                          |                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                         |
### Market/Risk

**The high cost of adaptation to GMP standards**

Pharmaceutical industry standards (e.g. GMP and marketing authorisation requirements) constitute significant financial impediments and administrative burden for the SMEs and academia providing tailor-made or niche advanced therapies.

GMP standards and an adequate level of evidence of benefits outweighing the risks required for market access are essential for safeguarding public health.

**Regulators** to adopt more pragmatic approach with licensing requirements for ATMPs by means of:
- applying GMP standards more flexibly, especially in early development phases
- promoting ATMP-specific, risk-proportionate adaptations to GMP standards
- increasing transparency of manufacturing authorisation requirements across Europe
- promoting innovative manufacturing technologies (e.g. bedside manufacturing, closed systems) and innovative manufacturing models (e.g. decentralised manufacturing) and encouraging development of manufacturing sites, as a service
- promoting the EMA’s early access schemes (such as PRIME, adaptive pathways, Innovation Task Force, parallel scientific assessment and the certification procedure).

**SMEs/ Academia** to promote early interaction with the regulators and to consider possibilities of pursuing market access via the EMA’s early access schemes.

### Benefit-risk balance of products in development

**Focuses mainly on risks**

Yet, the recent developments indicate a shift from predominantly risk-averse approaches to more adaptive, risk-proportionate and facilitative approaches to clinical trials, GMP manufacture, and market access of ATMPs.

**Regulators** to reconsider risk-based approach, placing additional emphasis on expected, realistic benefits especially in areas of unmet medical need.
### Market/Risk

**Scope:** financial, market access

**Risk-proportionate flexibilities needed to accommodate autologous products**

The authorisation requirements of the ATMP Regulation are not well adapted to specific characteristics of autologous products. Some have argued that autologous ATMPs should not be regulated as medicines. Yet, an adequate level of public health protection should prevail over economic interests.

1. There are autologous products where the patient’s cells/tissues are transported to a company and the final medicinal product is delivered back to the hospital for administration in the same patient.

2. Whilst sometimes patient’s cells/tissues are manipulated in the hospital prior to re-administration to the same patient.

*Regulators to revise the requirements for the authorisation of ATMPs to ensure that applicable requirements are proportionate and well-adapted to the specific characteristics of autologous products.*

*SMEs/Academia to participate actively in stakeholder consultations to promote risk proportionate approaches to GMP manufacture of autologous ATMPs.*

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### Market/Risk

**Scope:** marketing authorisation

**Hospital exemption may create negative incentives.**

The inconsistently applied hospital exemption is conducive to create uncertainty amongst national competent authorities and developers of ATMPs as it does not promote harmonisation of practices. It may also create negative incentives. Hospital exemption should not replace systematical and controlled clinical trials.

1. no approved ATMPs for a specific disease or ongoing clinical trials; or

2. it is otherwise impossible for a hospital to be involved in a clinical trial of a relevant medicine under development.

*Regulators to streamline hospital exemption. It is essential to limit the use of hospital exemption to exceptional circumstances. It is important to ensure that treatments under hospital exemption should only be given when there are:*

*Regulators could also improve transparency making details of hospital exemption products in each Member State publicly available. Developers of ATMPs could also benefit from systematical collection of clinical data generated by means of hospital exemption (yet hospital exemption should not replace clinical trials).*
<table>
<thead>
<tr>
<th>Market Scope: R&amp;D, marketing authorisation</th>
<th>Disharmonised ATMP classifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>National competent authorities cannot use the classification procedure when they face difficulties with classification of ATMPs.</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Market Scope: R&amp;D, financial, marketing authorisation</th>
<th>Certification is used very seldom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certification procedure is used very seldom and it does not link with the marketing authorisation procedure. It does no cover non-profit organisations.</td>
<td>It is associated with early research (quality/preclinical data). Conditions for non-profit organisations need to be improved.</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Market/ Ethics Scope: R&amp;D, manufacture</th>
<th>Cell, tissue, blood and GMO-related requirements are disharmonised across the EU</th>
</tr>
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<tbody>
<tr>
<td>Despite the EUCTDs and the GMO Directive (Directive 2001/18/EC) requirements are disharmonised. Hence, access to primary materials is not equally granted in all Member States of the EU. Possibilities to conduct research vary from a jurisdiction to another as ethical considerations of trials remain within competence of Member States.</td>
<td>For instance there are widely different practices regarding hESC research in the Members States of the EU. In addition, some Members States do not allow companies to register as tissue establishments. Greater harmonisation could possibly facilitate the movement of materials between Member States (and also outside the EU).</td>
</tr>
</tbody>
</table>

| Regulators | to streamline the current definitions of ATMPs to reflect latest scientific developments and to prevent disparities in national classifications. The national authorities should have access to the CAT’s classification procedure when they face difficulties with classification of ATMPs. |

| SMEs/Academia | to participate in stakeholder consultations to ensure that the classifications are flexible enough to cover latest advancements in science. |

| Regulators to: | − ensure a better link with the marketing authorisation procedure; and − consider extending certification procedure to cover non-commercial organisations (such as academia) to strengthen its value. |

| SMEs/Academia may also otherwise promote early interaction with regulators to agree on appropriate trial designs, measures to ensure safety of the patients and the acceptable evidence of risk-benefit balance needed for market access. | Regulators could harmonise cell, tissue, and blood requirements across EU by means of increased transparency and creation of a public portal for EU cell and tissue authorities and approved establishments as a resource for stakeholders. Also publishing an overview of national requirements for GMOs could create greater uniformity. Regulations could also investigate possibilities for harmonisation of global requirements by cooperating with regulatory authorithies. |
applying different requirements. It could also possibly serve to ease the burden of having to re-test the cells and tissues prior to the ATMP manufacture.

outside the EU (for instance U.S. and Japan).

**SMEs/ Academia:** ethical considerations render “full” harmonisations of rules governing the use of materials of human origin impossible. However, SMEs and academia could benefit from increased transparency, as they could more efficiently choose a jurisdiction with a favourable regulatory environment depending on the intended research activity.

<table>
<thead>
<tr>
<th>Market Scope: IP</th>
<th><strong>The concept of orphan similarity requires further clarification in ATMPs context</strong></th>
<th>It needs to be adapted for ATMPs and carefully considered in the context of new active status and changes to the active substance.</th>
<th><strong>Regulators</strong> to adapt concept of orphan similarity to ATMPs.</th>
</tr>
</thead>
</table>

| Market Scope: financial | **High prices and limited, non-harmonised reimbursement** | Pricing and reimbursement remain within the competence of the EU Member States. | **Health technology assessment** bodies and **payers** to:  
- get involved earlier in development process;  
- provide a platform for informal dialogue;  
- issue ATMP guidance and increase uptake of parallel advice;  
- coordinate actions in relation to reimbursement; and  
- design and agree at EU level different models for reimbursement and payment mechanisms (for instance investigate possibility of risk sharing arrangements) for managed access schemes.  

**SMEs/Academia** to consider the possibility to pursue market access via **PRIME scheme** or **adaptive pathways** or otherwise involve health technology assessment bodies and payers early in discussions. |
<table>
<thead>
<tr>
<th>Risk</th>
<th>Scope: R&amp;D</th>
<th>Pre-clinical data provided for IMP ATMP dossier resulting in use of contrived animal models</th>
<th>Limitation regarding the use of animal models of disease must be acknowledged.</th>
<th>Regulators should also investigate benefits and limitations of novel development tools complementing animal models and their feasibility as an alternative for animal models (e.g., organoids, modelling/simulation, biomarkers, etc.) to address non-clinical requirements. Trainings and further guidance regarding such new tools should be organised for developers of ATMPs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMEs/Academia: The choice of the most relevant animal model should be determined by the specific safety aspect to be evaluated. The selection of animal models and the duration of animal studies should be adequate for evaluation of long-term effects taking into account the persistence and functionality of the cells. Academia to cooperate early with the regulators to reach a common understanding of benefits and limitations of new analytical models and development tools.</td>
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<tr>
<th>Risk</th>
<th>Scope: risk management</th>
<th>Lack of efficient mechanisms for enforcement of safety standards.</th>
<th>Despite the recent positive reforms that improved the EU pharmacovigilance framework, there is a need for establishing ATMP specific measures to improve enforcement of safety standards.</th>
<th>Regulators: Efficient mechanism for enforcement of safety standards should be established. Inspections, adequate training of qualified persons as well as inspectors and unified assessment criteria are needed when pursuing similar quality and safety standards for cells and tissues that used for therapeutic purposes across the EU.</th>
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<tr>
<td>Market/Ethics</td>
<td><strong>Incoherence between the patent system and the regulatory system in ethical considerations create uncertainty and may hamper commercialisation of certain types of biotechnological inventions (such as hESC-based inventions).</strong></td>
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<tr>
<td><strong>Scope:</strong> IP</td>
<td>Risk management is not a primary duty of patent authorities. As presented in this study risk management aspects pertaining to ATMPs are usually complex and the pharmaceutical regulatory authorities are better vested with resources to conduct risk assessments than patent authorities. Regulatory stakeholder consultations provide a well-functioning forum of expression for risk related issues.</td>
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<table>
<thead>
<tr>
<th>Human rights/Ethics</th>
<th><strong>Patentability restrictions impose challenges for commercialisation of hESC-based inventions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope:</strong> IP</td>
<td>The developers may adjust the use of the primary materials to meet the funding requirements under Horizon2020 e.g. non-destructive sources of hESCs.</td>
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</table>

<table>
<thead>
<tr>
<th>Human rights/Ethics/Market</th>
<th><strong>SMEs and academia would benefit from further access to funding, capital investment and incentives</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Scope:</strong> financial</td>
<td>The significant administrative burden and high cost of GMP compliance has been underestimated by research funding bodies. Also the EU research funding policies discriminate certain types of hESC research due to ethical considerations. Yet, research on human stem cells, both adult and embryonic, may be financed, depending both on the contents of the scientific proposal and the legal framework of the Member States involved.” Non fundable activities include: research intended to create human embryos solely for the purpose of</td>
</tr>
</tbody>
</table>

| Regulators: | Moral limitations on patents need to be aligned with pharmaceutical regulatory standards to avoid unpredictability. Patent authorities should take the practice of pharmaceutical regulatory authorities into consideration in ethical moral questions to avoid harmful fragmentation the field. Morality clause should be kept strictly within the limits of the patent system, viz. commercial exploitation. |

| SMEs/Academia: | If possible, developers can make use of non-destructive sources of hESCs or use iPSCs alternatively to improve patentability prospects (e.g. hPSCreg operates in line with the European policy, no cell lines that fall within the non-fundable activities can be registered). |

| Venture capitalists to: | Prioritise funding based on realistic expected patient benefit – coordinate funding more effectively, with multi-stakeholder participation and monitoring |

| Regulators to: | increase awareness of financial incentives – provide a functioning process for SMEs and academia to seek early parallel regulatory/health technology assessment advice – foster collaboration between private investors and European Commission to provide continuity and complementary funding; and – fund registries to support comparative evaluation and collection of post-marketing data |
research or for the purpose of stem cell procurement, including by means of SCNT)

- consider regulatory, GMP and manufacturing costs and plan for extending funding longer term

SMEs/Academia to:
- take advantage of the EMA’s existing incentives and possibilities to seek early parallel regulatory/health technology assessment advice;
- explain costs relating to GMP compliance to research funding bodies when applying for funding; and
- ensure that the research does not fall within the scope of non-fundable activities under Horizon2020 in case of funding being applied from the European Commission.
8.2 Risk-proportionate approaches to GMP and clinical trials addressing the problematic precautionary principle in the age of evidence-based medicine

Contemporary liberal regulatory approaches are intended to promote scientific and medical development from the outset that is beneficial to humanity. In addition to societal matters, the liberal approach intends to regulate the interest of the **patient** and **public health**. Since the emergence of environmental law in the 1960s, the precautionary principle and risk management have been used as typical justifications for restricting the freedom of science. The precautionary principle has been acknowledged as an important general principle of EU law and policy. This principle is specifically stated in Article 191.2 TFEU as an environmental protection principle; and Article 11 of TFEU requires environmental protection to be integrated into all EU policies. Yet there is no consensus on how the precautionary principle should be applied in healthcare and health technology regulation and policy.

As a starting-point, in terms of the precautionary principle, there are two possible ways ATMPs may adversely influence the environment or public health; 1) via the **ATMP production process** and/or 2) via the **use** of ATMPs. It was noted in the first DG JRC-IPTS evaluation study that emissions of potentially hazardous substances into the environment may occur in course of normal ATMP production, as a result of accidents or production waste disposal. Various ingredients are frequently used in the production of ATMPs: **cells of human origin**, **scaffolds** and **biomolecules**. It was noted that “low risk” human cells that do not involve genetic modification are usually used in ATMP development. **Ancillary reagents** are also used (e.g., growth media, growth factors, hormones, and antibiotics may be applied). In addition, **substances resulting from the conversion, degradation, contamination or other reactions** may be produced. **Contamination with higher risk organisms** than the human cells used may also occur in course of the production process. Notwithstanding the potential environmental risks, it was noted in the DG JRC-IPTS evaluation study that such risks are relatively low because of the low production volume, the biodegradable substances, the very restricted survival of human cells outside the controlled laboratory environment, and rigorous production facilities. It was also noted that regulatory framework for prevention, control and treatment of emissions already exists. In general, the understanding of the

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816 Ashcroft, *supra* note 21, 312.
818 Ibid.
environmental impact of pharmaceutical substances still seems quite narrow and there is no data on the potential hazards of ATMPs to the environment (and the ecosystem). Pursuant to the precautionary principle however, the emission of pharmaceutical substances should be prevented and an environmental risk assessment carried out prior to marketing authorisation.820 Given the low production volumes and the mode of action of ATMPs, environmental risk is assumed to be rather low.

The environmental risks of ATMPs need however to be adequately assessed on a case-by-case basis, especially if they include genetically modified cells.821 Yet, it should be noted that the GMO Directive (Directive 2001/18/EC) is not specifically designed for medicinal products and according to the EMA its deficiencies in this respect appear in disharmonised implementation across the EU.822 The regulators should investigate whether changes to the GMO Directive itself are needed or whether other measures could be sufficient to address these aspects in context of clinical trials on genetically modified cells. The EMA has noted that as requirements differ among Member States, the integration of assessment in clinical trials authorisation poses a challenge, especially in the context of multicentre clinical trials on ATMPs. Timelines of such assessment should be aligned with those of clinical trial authorisation. Setting up of a central repository listing the requirements and timelines for GMO assessment in every Member State could possibly be the first step to facilitate harmonisation in the field.823

The rationale behind the idea that the freedom to conduct scientific research is restricted is the notion that new experiments will cause novel risks whose unpredictability requires societal control. Yet, as to on freedom of science it may be difficult to justify the application of the precautionary principle as a restriction in pre-clinical research that take place in a controlled laboratory environment, as in research conducted on human embryos. Laura Walin has pointed out that:

"[w]hen research takes place under very controlled conditions in a laboratory environment, it is difficult to see any risk to the environment. However, the protection of human health can be justified as a principle for limiting research if clinical trials are conducted on patients (i.e. hESC based products are tested as medicines). 824

In such a case, the research protocol must comply with the generally accepted principles for clinical trials. Hence, the scope of the precautionary principle is not well-suited to accommodating pre-clinical research, unless risks to public health arise in the

821 A genetically modified product that can be implanted in a patient is considered as a genetically modified organism that is released into the environment and thus falls under Directive 2001/18/EC, whilst the patient, is not considered a genetically modified organism as long as the germ line cells are not modified,. In the case of experimental releases as well as putting genetically modified organisms on the market subjected to an environmental risk assessment according to Directive 2001/18/EC.
822 European Medicines Agency, supra note 762, 4-5.
823 Ibid.
context of such research (which seems unlikely given the readily biodegradable nature of primary materials, the very restricted survival of human cells outside laboratory conditions, and controlled laboratory conditions and measures in place to deal with disposal of such biological risk waste). In contrast, the protection of human health is more justifiable as a principle for limiting research if clinical trials are conducted on patients and if research involves risks to human health.

Finding the appropriate approach to uncertainties and potential risks to public health is challenging for policy-makers and regulators alike, as they need to pursue a balance between conflicting interests such as innovation, safety, free movement of goods, etc. Some scepticism has also been expressed regarding the status of the precautionary principle as an ethical principle. First of all, in the context of EU law it is evidently perceived as a risk management principle. Despite ethics and risk management intersecting, as shown in the framing approach of Section 3.4.1, they are not the same. Furthermore, there are some significant conceptual and normative problems in interpreting and applying the precautionary principle, as no definitive consensus on the meaning, scope and application of that principle exists in law and ethics. Although the precautionary principle is constantly being developed by the EU policy conversation, it still lacks a commonly understood meaning, and it is still less a commonly accepted normative force. The precautionary principle has nonetheless guided law-makers in creating a regulatory regime for ATMPs. Some content and scope of the precautionary principle has been established by the ECJ practice that defines some specific triggering factors for the precautionary principle as follows: a risk of serious and irreversible damage to health and the environment deemed unacceptable to society, supported by solid and objective scientific reasons, even if uncertain.

Upon introduction of the supplementary GMP requirements for ATMPs, they were taken to be necessary for safeguarding public health. However, it should be noted that without efficient enforcement in the form of inspections and effectiveness measures, EU directives and regulations as such are inadequate to protect patients from unsafe ATMPs. Article 78 of the Clinical Trials Regulation mandates Member States to appoint inspectors who shall supervise compliance with the Clinical Trials Regulation. It still remains the responsibility of the Member States to ensure that inspectors are adequately qualified and trained. No unified ATMP inspection training or assessment criteria have been established either. It should also be noted that GMP compliance as such does not automatically guarantee the quality, safety and efficacy of a medicine. Inspections and unified assessment criteria are needed when similar quality and safety standards for ATMPs are pursued in the Member States. There is also a concern that

825 See also Munthe, C. The Price of Precaution and the Ethics of Risk (Springer), 2011.
826 Ashcroft, supra note 21, 313.
829 Pirnay, et al, supra note 22, 545. See also Mansnérus, supra note 22, 461.
the current risk-based approach puts major pressure on qualified persons, as they may release products according to different interpretations in different Member States. Qualified persons would benefit from more guidance and training in risk-proportionate approaches.  

Quality and safety standards used to be predominantly evidence-based, meaning that they were scientifically justified and clinically proved. Criticism has been directed towards the regulators’ reliance on the precautionary principle, Pirnay et al. stating that:

“[i]t is odd that in an age of evidence based medicine, regulators increasingly rely on the precautionary principle — i.e. the prevention of harm to human health by removing the requirement for scientific proof of risk in advance of legislative intervention, thus evading liability (umbrella policy) and shifting the burden of proof to the researchers and manufacturers.”  

The precautionary principle has been perceived as a double-edged sword by Kirkland who has asserted that we should try to balance the risk avoidance principles with the broader risks to the community that can result from overzealous or inappropriate application of regulatory standards. Furthermore, EuropaBio’s industry hearing report declares that: “technical requirements must be risk based and fully proportionate, to reflect the characteristics of the individual product”. Pirnay et al. have criticised the requirements following from ATMP Regulation compromising patient care and safety, by disabling valuable established therapies or delaying the development of new technologies in the field of transplantation of human keratinocyte grafts, as in their view donor skin products used for severely burnt wound patients e.g., do not need to be sterile and do not need to be processed in a clean room facility as required by the GMP standards. (Yet, as discussed in Section 7.5.3. ATMP specific adaptations to GMP requirements regarding clean room facilities have been recently proposed to take the specific characteristics of ATMPs into consideration).

Costs associated with GMP compliance have been seen to constitute a major bottleneck for translation of research into advanced therapies. It has been argued that rigorous technical requirements (which are not negative as such) risk becoming disproportionately costly for SMEs and consequently impeding innovation. The DG Sanco provided an amended version for Annex 2 of the GMP Guidelines to more adequately cover ATMPs. It appears that in some cases marketing authorisation or clinical trial authorisation, instead of sterility requirements, provides for an acceptable

830 European Medicines Agency, supra note 762.4.
831 Pirnay, et. al., supra note 22, 544.
833 EuropaBio Stakeholder Meeting Report, supra note 170, 11.
835 Belardelli, et al., supra note 708, 74.
type and level of bioburden.\textsuperscript{837} Despite the criticism regarding the regulatory “umbrella approach”, it appears that the revision of Annex 2 of the GMP Guidelines is actually a good example of the benefits of this regulatory pathway: technical provisions of the ATMP Regulation can be updated and revised flexibly and rapidly to adapt legislation to scientific progress in a timely manner. More recently, as we saw in Section 7.5.3., further additional ATMP-specific adaptations to GMP requirements have been proposed to take the specific characteristics of ATMPs into consideration. These potential adaptations are anticipated to decrease the costs related to compliance with GMP Guidelines. The draft GMP Guidelines on ATMPs also allow for a risk-based approach in GMP manufacture.

This regulatory umbrella approach is a determining characteristic of the ATMP Regulation, explaining the complexity of the resulting regulatory structure which combines several pieces of existing legislation with new provisions and rules.\textsuperscript{838} Notwithstanding the criticism of the regulatory pathway of ATMPs that still significantly relies on the precautionary principle, it should be noted that also the revised Annex 1 of the Medical Products Directive actually allows for a more flexible, risk-based approach. Pursuant to this prominent approach, risk analyses are conducted to define the extent of quality, nonclinical, and clinical data to be included in the marketing authorisation application.\textsuperscript{839} It is especially well-suited for ATMPs as it relies on identifying risk factors inherent to the nature of the specific ATMP and related to its quality, safety, and efficacy.\textsuperscript{840} In addition to the proposed risk-based approach in the draft GMP Guidelines, a proportionate approach to the design and conduct of clinical trials is supported by the Clinical Trials Regulation. This approach allows for adaptation of the risk to the subject of the research conducted.\textsuperscript{841} However, further clarification of how the risk-based approach could be applied to manufacture and trials on ATMPs is needed.

The need for a multidisciplinary science-based approach and flexibility in accepting new development models and adapting trial designs has been acknowledged.\textsuperscript{842} The CAT has stated that the quality, safety, and efficacy of ATMPs are interlinked and a lack of methodologies in one discipline can often be


\textsuperscript{839} Klug, et. al., supra note 730, 340.


\textsuperscript{841} European Commission, supra note 425.

complemented by others. Safety and efficacy endpoints and the time of a patient’s follow up depend largely on the biological features of the product. A risk-proportionate approach could allow the manufacturer to adapt the product development (including the nonclinical and clinical investigations) to the characteristics of its product. In addition, further clarification of the risk-proportionate approach to combination of ATMPs with conventional treatments is required. Since these issues may cause special regulatory hurdles, the need for risk-proportionate adaptations in clinical protocols must be positively addressed to encourage clinical trials in controlled and standardised conditions.

Regulatory authorities in some Member States seem to have already adapted this pragmatic approach, allowing for risk-based assessment of manufacturing procedures. It has been reported that despite the risk-based approach to ATMP development in fact being generally accepted by the EMA, it is infrequently used by companies. The proposed adaptations to the ATMP-specific GMP requirements together with the risk-proportionate adaptations to clinical trials represent positive developments that may facilitate the market entry of ATMPs.

Despite the Clinical Trials Regulation intended to streamline the clinical trial application processes by establishing an EU-wide portal for clinical trials, ethical approvals of clinical trials remain within the competence of the Member State. Hence, the opportunity to conduct a particular trial may depend on the ethical position adopted by the ethical boards of the Member States. In so far as classification of medicines as ATMPs is applied differently by different national competent authorities, this will also persist as a real hurdle for ATMP development. This is particularly challenging in the case of orphan diseases, as research must be conducted across many jurisdictions to obtain adequate recruitment rates.

There is a concern that benefit-risk balance of products in development focuses mainly on risks. Reasonable arguments have been presented that additional emphasis should be placed on expected but realistic benefits, particularly in case of unmet medical need. It remains to be seen whether the proposed risk-based approach in GMP manufacture and clinical trials may gain wider general acceptance among the national regulatory authorities and whether these adaptations are sufficient to foster the ATMP field and improve the availability of valuable therapies for those needing them. In any case a careful consideration of benefit-risk balance should included the early development strategy and discussed with regulators (including health technology

843 Committee for Advanced Therapies, supra note 706,195-201. For instance, a lack of potency assays could in some cases be replaced by a sound process validation and consistent manufacturing, in conjunction with clinical trial data that demonstrate that this manufacturing process results in an efficacious product.
844 Pearce, et al., supra note 540, 294.
846 Pearce, et al., supra note 540, 295.
847 European Medicines Agency, supra note 762, 4.
assessment bodies) as early as possible to allow GMP and marketing authorisation requirements to be adapted accordingly. Both informal interactions (such as Innovation Task Force meetings) and more formal scientific advice are needed.  

8.3 Evidence v. access in the adaptive pathways approach

In addition to the potential to adapt the risk-proportionate approach in GMP manufacture and clinical trials on ATMPs, the adaptive pathways approach may be applied in some cases to improve accelerated access for patients to new ATMPs. The adaptive pathways approach currently being piloted by the EMA is a scientific concept for medicine development and data generation enabling early and progressive patient access to a medicine. In particular, it addresses the “evidence v. access” balance and it aims at consistently, with a staged approach collecting evidence, resulting in consequent marketing authorisation adaptations. The opportunities arising out of the existing EU regulatory framework for medicines are used in this prospectively-planned lifespan approach. The adapted pathways approach is built on three main principles:

1. iterative development, which either means:

   a. a stagewise marketing approval, beginning with a restricted patient population then expanding to larger patient populations; or

   b. confirmation of the benefit-risk balance of a medicine, following conditional approval based on early data (using surrogate endpoints) considered predictive of important clinical outcomes;

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848 Ibid. Yet, not all SMEs or academic spin-offs have the resources to seek scientific advice.

849 European Medicines Agency. Adaptive pathways. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WCOB01ae05807d58ce. Accessed 21 June 2016. See also European Medicines Agency. Adaptive pathways to patients: report on the initial experience of the pilot project. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500179560.pdf. Accessed 21 June 2016. The EMA launched a pilot project in March 2014 to investigate how the adaptive pathways approach might work in the existing regulatory framework with real medicines in development. According to the EMA, 34 applications for the pilot project had been received as of the beginning of December 2014 (6 of them concerned ATMPs, 12 orphan products, 11 came from SMEs and 14 were anti-cancer medicinal products). Ten candidate products fulfilling the criteria for adaptive pathways were selected for a Stage I discussion (an initial teleconference). According to the EMA, a broad array of therapeutic areas were represented by the indications of the 10 selected products, together with large and small patient populations: 5 were orphans, 2 ATMPs, and 4 originated from SMEs. Of these, 6 products have been selected for further discussions with the participation of all stakeholders (Stage II) with the aim of offering companies the elements to inform the design of parallel safety/health technology assessments about the next steps in development. The EMA is still accepting applications and more recently, it has received some additional applications, amounting to 60, 20 of which have been selected to proceed to further initial discussions.
2. collection of statistical evidence from “real-life use” to supplement clinical trial data; and

3. early involvement of patients and health-technology-assessment bodies in discussions on a medicine’s development.\textsuperscript{850}

Developers of ATMPs may pursue this approach in areas of high medical need where it is difficult to gather data through traditional means and where larger clinical trials would unreasonably expose patients who are unlikely to benefit from the treatment. The adaptive pathways approach does not aim at introducing new regulatory tools, but does seek increasing awareness and optimising the use of all tools and flexibilities within the existing EU regulatory framework. It relies on the following regulatory processes:

1. \textit{Scientific advice} and \textit{protocol assistance} may be requested from the EMA. For human medicines, scientific advice and protocol assistance are given by the Committee for Medicinal Products for Human Use on the recommendation of the Scientific Advice Working Party. (Protocol assistance is a form of scientific advice available for companies developing orphan medicines.)\textsuperscript{851}

2. \textit{Compassionate use} allows the use of an unauthorised medicine as a treatment for life-threatening, long-lasting or seriously debilitating illnesses which cannot be treated satisfactorily with any currently authorised medicine. Under compassionate use programmes, subject to strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials. The medicine must be undergoing clinical trials or have entered the marketing-authorisation application process. The early studies will generally have been completed, although its safety profile and dosage guidelines may not be fully established.\textsuperscript{852}

3. \textit{A conditional approval} can be granted in the interest of public health for such medicines where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required, based on the scope and criteria defined in the legislation and guidelines. Medicines for human use are eligible if they belong to at least one of these categories:

   a) designed to treat, prevent or diagnose seriously debilitating or life-threatening diseases;

\textsuperscript{850} Op. cit.

b) intended for use in emergency situations (less comprehensive pharmaceutical and non-clinical data may also be accepted for such products); and/or

c) designated as orphan medicines.

Conditional marketing authorisations may be granted if all of the following requirements are met:

i. the benefit-risk balance of the product is positive;

ii. it is likely that the applicant will be able to provide comprehensive data;

iii. unmet medical needs will be fulfilled; and

iv. the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks arising from the need for further data.

Conditional marketing authorisations are valid for one year and will be subject to annual review. The marketing authorisation holder will be required to complete specific obligations (ongoing or new studies, or collection of pharmacovigilance data) with a view to providing comprehensive data confirming that the benefit-risk balance is positive. As soon as the comprehensive data on the product has been obtained, the marketing authorisation may be converted into a standard marketing authorisation. The EMA also encourages applicants with products deemed suitable for a conditional marketing authorisation to early interaction and to consider requesting accelerated assessment that may reduce the assessment timeframe from 210 to 150 days; 853 and

4. patient registries and other pharmacovigilance tools that allow collection of real-life data and development of the risk-management plan for each medicine. The EMA has set up an initiative to make better use of existing registries and facilitate the establishment of high-quality new registries to provide an adequate source of post-authorisation data for regulatory decision-making. 854

The use of adaptive pathways does not however alter the evaluation criteria of the benefits and risks involved. Hence, a positive benefit-risks balance is required to obtain a marketing authorisation, pursuant to the adaptive pathways approach. The marketing authorisation granted under the adaptive pathways (full or conditional under exceptional
circumstances), including any potential restrictions or conditions, will be determined case-by-case depending on the level of evidence finally obtained.\textsuperscript{855}

Pursuant to the adaptive pathways approach, two scenarios have been suggested to allow for earlier market access to medicines. Under the first approach, a stagewise marketing approval may be granted in a well-defined, high medical need subgroup, and the indication is subsequently extended to a larger patient population (please refer to Figure 8. in Appendix 6).\textsuperscript{856} In the second approach, confirmation of the benefit-risk balance of a medicine, early (possibly conditional) marketing approval is prospectively planned, based for instance on surrogate endpoints, and uncertainty is planned to be reduced by means of obligations to collect post-approval data. Upon accumulation of the further data, marketing authorisation may convert into “full” approval (please refer to Figure 9. in Appendix 6).\textsuperscript{857} Under both scenarios, there is potential for earlier access to market via an early first approval, and also via streamlined health economic appraisal, provided that the health technology assessment bodies have been involved and they have shared their view on their specific requirements for evidence generation during the development process.\textsuperscript{858}

While this pilot project on adaptive pathways launched by the EMA has been perceived to have great potential benefits for society, it has also provoked some critical perspectives within academia, in response to which the EMA has provided further clarifications of the concept of adaptive pathways.\textsuperscript{859} To streamline the adaptive pathways concept, some further perspectives have been presented including:

1. It has been acknowledged by the EMA that medicines to be submitted to the adaptive pathway must be selected on clear and shared criteria based on the impact of the target disease or health problem.\textsuperscript{860}

2. The EMA has also noted that before the use of an adaptive pathway leads to authorisation, any subsequent plan to generate evidence must be agreed, following an agreed protocol.\textsuperscript{861} Academic stakeholders have asserted that “[t]his is because of the need to ensure accountability for the considerable sums of public money which have been invested and will be invested in the process and because of the role that patients will play in the emergence of

\textsuperscript{855} European Medicines Agency. Adaptive pathways to patients: report on the initial experience of the pilot project, supra note 849, 2.

\textsuperscript{856} Op. cit., 2.


\textsuperscript{858} Op. cit., 2.


\textsuperscript{860} European Medicines Agency. The EMA’s response letter, op. cit., 3

\textsuperscript{861} Ibid.
evidence on drugs that are still being evaluated. This is a form of co-
development with great potential benefits, but there is a need for
communication of the uncertainty involved to those who will be receiving the
treatment, who occupy an intermediary position between patients and research
subjects.\footnote{The letter dated 13 May 2016 by nine professors and scientists, \textit{supra} note 859.} The EMA has agreed on this in all respects. However, it has
pointed out that under the current EU legal framework post-authorisation
obligations are only legally binding on those who hold the marketing
authorisation.\footnote{European Medicines Agency. The EMA’s letter in response, \textit{op. cit.}, 3.}

3. Criticisms has been directed towards use of the term “real world evidence” (as
it has been deemed to be open to misinterpretation) that the EMA has used to
describe healthcare-related data collected outside of randomised clinical trials. The EMA has further clarified that “real-world evidence” is used by the EMA
to mean evidence originating from registries, electronic health records, and
insurance data either in specific observational studies or via continued
monitoring of use, benefits and risks.\footnote{European Medicines Agency. The EMA’s letter in response, \textit{ibid.}}

4. Furthermore, the EMA has acknowledged that “\textit{any adaptive pathways
registration should have an initial roll-out plan clearly describing the potential
beneficiary population(s) and the factual information on the uncertainty of the
pathway to be conveyed to users.}”\footnote{European Medicines Agency. The EMA’s letter in response, \textit{ibid.}, 4.}

5. The EMA has also agreed that all documents relating to adaptive pathways
need to be made public promptly, as the adaptive pathways paradigm relies on
interpretation of current problems and their proposed solutions. The
confidential nature of the individual preliminary discussions must nevertheless
be respected.\footnote{The letter dated 13 May 2016 by nine professors and scientists, \textit{supra} note 859, 4.}

Furthermore, the paradigm of \textit{adaptive pathways} has triggered concerns in
academia that need to be addressed. The EMA has provided clarifications and further
perspectives on a range of issues. The misinterpretation has been made that pursuant to
the \textit{adapted pathways} approach it is assumed that “\textit{new drugs and biologics are more
effective and safer than existing ones.} It has also been understood that “\textit{new}” and
“\textit{innovative}” are synonymous.\footnote{Ibid.} The specific concern has also been expressed that
these alleged principles are not based on any solid evidence and the definition of
“\textit{innovative}” is unclear.\footnote{The letter dated 13 May 2016 by nine professors and scientists, \textit{supra} note 859, 4.} In response to these concerns, the EMA has clarified that
under the \textit{adaptive pathways} approach “\textit{innovative}” means no more than “\textit{new}”. The
EMA’s clarification of the term is that “\textit{innovative}” is meant to be neutral with respect
to whether an assumed product to be “\textit{innovative}” is more (or less) effective and/or safe
than existing medicines. Many new products entail improvements to existing treatments but others do not. As the adaptive pathways approach aims at bringing potentially beneficial therapies to the right patient group as early as appropriate, “the likely benefit over existing treatment options” must precede a decision to follow adaptive pathways instead of “newness”. Furthermore, concerns have been expressed that “fast track registration processes are being applied to drugs that are not first in class and potentially less innovative”. As a response to this criticism, the EMA notes that the existing “drug development and authorisation pathways are less than ideal for some novel products, and patients with a range of serious diseases express a desire for earlier access to beneficial new treatments. Not adapting the current research, authorisation and access path would indeed be bad for those patients who are in urgent need of better treatments.”

The EMA further clarifies that the promise of added benefit is the key factor, whilst “innovative” and “novelty” are not. It also appears from the EMA’s most recent Annual Reports (2014 and 2015) and the European Public Assessment Reports of individual products that the EMA has applied sufficient early evidence of relevant patient benefit to justify fast-tracking as a decision criterion when selecting products for fast-tracking procedures.

A concern about the risk of premature market approvals has also been raised, as early marketing authorisations have sometimes been assumed to be linked with a greater occurrence of post marketing safety warnings. In addition, the risk of potential conflicts of interest has been voiced (i.a., due to the inclination of authors to interpret findings in an excessively positive light). The EMA’s starting-point is that the adapted pathways early market entry is beneficial to patients in need as long as products demonstrate sufficient early evidence of benefit. A retrospective cohort study of products authorised in the EU by Arnardóttir et al. actually does not support the view that early drug approval increases the risk of serious safety issues emerging after market approval. Yet, when adaptive pathways are applied robust pharmacovigilance must be in place in any case, as it is vital to learn about the benefits

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870 The letter dated 13 May 2016 by nine professors and scientists, supra note 859, 4.
871 European Medicines Agency. The EMA’s response letter, supra note 859, 5.
872 Ibid.
874 The letter dated 13 May 2016 by nine professors and scientists, supra note 859, 5.
875 European Medicines Agency. The EMA’s letter in response, supra note 859, 5.
and risks associated with a new product during the post-authorisation period. The EU pharmacovigilance system was revised in 2010 to strengthen and rationalise the system for monitoring the safety of medicines in the EU. Under the new system, patient safety and public health is improved via better prevention, detection and assessment of adverse reactions to medicines. Patients are also allowed to report adverse events directly to the competent authorities and such reporting has been extended to cover such matters as medication errors and overdosing. The main elements of this new legislation are proactive and proportionate risk management; higher quality of safety data; a stronger link between safety assessments and regulatory action; strengthened transparency, communication and patient involvement; clear tasks and responsibilities for all stakeholders; improved EU decision-making procedures (harmonised decisions and efficient use of resources), and establishment of a new scientific committee, the Pharmacovigilance Risk Assessment Committee at the EMA. In the case of ATMPs however, a more efficient safety standards enforcement mechanism should be established (i.e., inspections, adequate training of inspectors and unified assessment criteria are needed when pursuing similar quality and safety standards for cells and tissues that are used for therapeutic purposes across the EU).

In addition, there is a concern that subsequent to the grant of a marketing authorisation based on preliminary evidence, it may be difficult to control demand, despite the medicine having been demonstrated to be less effective or more unsafe than initially expected. The EMA acknowledges the problem that physicians have not always acted on post-marketing warnings on harm and restrictions of use. The EMA however seems confident that restrictions and/or warnings can be successful when prospectively designed risk management plans are implemented appropriately. To mitigate the reversibility issue, the EMA needs to place particular emphasis on aligning prescription/utilisation with the state of understanding of the benefits and risks of medicines released under adaptive pathways.

Concerns have also been voiced regarding the use of surrogate endpoints. Fears have been expressed that the current system may be approving many costly, toxic drugs that do not improve overall survival. The EMA notes that the problem with the use of surrogate endpoints is well-known. However, it is not deemed to be peculiar to adaptive pathways. As a central principle of adaptive pathways is to repeat cycles of evidence generation and assessment, a pre-agreed plan needs to be in place, creating a connection

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878 The letter dated 13 May 2016 by nine professors and scientists, supra note 859, 5.

879 European Medicines Agency. The EMA’s letter in response, supra note 859, 6.

880 The letter dated 13 May 2016 by nine professors and scientists, supra note 859, 5.

881 European Medicines Agency. The EMA’s letter in response, supra note 859, 7.
with the clinical outcome when a product is initially authorised based on an endpoint that is not clinically directly relevant to patients.

In addition, there is concern that the current system is slow to react when the use of the medicine is related to increased mortality and when post-marketing commitments are not duly followed;\textsuperscript{882} yet the EMA appears confident with the current EU pharmacovigilance legislation that in the EMA’s view has signified major improvements in the regulators’ ability to monitor medicines on the market and to react promptly when needed. Indeed, all launches of a new medicine (as well as those under\textit{ adaptive pathways}) are accompanied by a legally binding risk management plan agreed between the sponsor and the regulator.\textsuperscript{883}

There is also a concern that sufficient information on the performance of a medication will not be provided, and it may be both unethical and misleading.\textsuperscript{884} According to the EMA, it would be unethical and incompatible with the role of regulators to “\textit{sell hope instead of help}”.\textsuperscript{885} Therefore, when applying the \textit{adaptive pathways} approach, there must be sufficient early evidence of relevant patient benefit and adequate monitoring subsequent to the marketing authorisation. The EMA considers that the \textit{adaptive pathways} concept as such is neutral as regards placebo- or active-controlled studies and it generally agrees that many randomised trials have been misleading and are not an impeccable approach.

Concerns have also been expressed regarding the reliability of observational data to test hypotheses.\textsuperscript{886} The EMA notes that observational studies may produce non-reproducible or contradictory results, and so may other approaches such as randomised clinical trials.\textsuperscript{887} The EMA justifies the use of observational data by stating that:

\begin{quote}
“\textit{The adaptive pathways concept therefore emphasises the need for planned collection of observational data where evidence from trials may need to be complemented. This collection is based on expert methodological advice and multi-stakeholder input. Furthermore, repeat cycles of evidence generation are emphasized to quickly refine or correct past decisions where needed. The adaptive pathways concept holds that the full spectrum of knowledge generation tools should be used to inform decision-making, including [randomised clinical trials] and observational data. When considering the totality of evidence, inferences based on observational studies may need to be more circumspect, in light of the non-randomised nature of study findings.”}\textsuperscript{888}
\end{quote}

All in all, \textit{adaptive pathways} is an emerging concept – not an impeccable one (as appears from the criticism it has faced and the EMA’s responses addressing some of its

\begin{flushleft}
\textsuperscript{882} The letter dated 13 May 2016 by nine professors and scientists, \textit{supra note} 859, 6.
\textsuperscript{884} The letter dated 13 May 2016 by nine professors and scientists, \textit{supra note} 859, 7.
\textsuperscript{886} The letter dated 13 May 2016 by nine professors and scientists, \textit{supra note} 859, 7.
\textsuperscript{887} European Medicines Agency. The EMA’s letter in response, \textit{supra note} 859, 7-8.
\textsuperscript{888} \textit{Ibid.}
\end{flushleft}
limitations). After all, it is an important initiative with great potential benefits for public health. It also addresses a number of obstacles the developers of ATMPs, particularly niche/orphan, face, ranging from data generation difficulty for the marketing authorisation dossier to reimbursement and cost related considerations. It promotes awareness of the existing, flexible regulatory approaches to first-time market entry of medicines. It also represents a novel approach to stakeholder engagement involving a wide range of stakeholders (including patients) as early as possible in a commercialisation process and providing facilitation for low threshold interactions with the regulatory authorities and health technology assessment bodies in a “safe harbour” environment. As it also aims at aligning health technology assessment parties early in the development process it may, if successful, facilitate commercialisation of medicines and improve access to health. Table 9. below lists out some of the initial benefits and shortcomings for developers of ATMPs with the adaptive pathways approach.

**Table 9. Summary of the potential benefits and shortcomings of the adaptive pathways approach**

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Shortcomings</th>
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<tr>
<td>+ potential to accelerate the market entry of ATMPs in areas of great medical need where it is difficult to gather data through traditional means and where large clinical trials would unreasonably expose patients who are unlikely to benefit from the treatment</td>
<td>- potential difficulty in defining “the likely benefit over existing treatment options” when the evidence base is limited (it may be difficult to define the level of initial evidence required for the initial market access)</td>
</tr>
<tr>
<td>+ provides a low threshold avenue for early interaction with regulatory authorities and health technology assessment bodies and a prominent site for stakeholder engagement</td>
<td>- lack of clear and shared criteria based on the impact of the target disease or health problem when medicines are submitted to the adaptive pathway</td>
</tr>
<tr>
<td>+ allows for a flexible and adaptive collection of evidence for the regulatory dossier for a “full” marketing authorisation</td>
<td>- a risk of premature market entry (a failure in assessment of an adequate level of evidence may lead to post-marketing safety concerns)</td>
</tr>
<tr>
<td>+ does not require institution of new legislative instruments for approval mechanisms</td>
<td>- surrogate endpoints may fail to predict the actual outcomes (although this problem is not peculiar to adaptive pathways)</td>
</tr>
<tr>
<td></td>
<td>- observational studies may produce non-reproducible or contradictory results (so may other approaches such as randomised clinical trials)</td>
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<td></td>
<td>- reversibility issues need to be addressed to ensure that physicians act promptly on post-marketing warnings on harm and restrictions of use</td>
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<tr>
<td></td>
<td>- more efficient mechanism for enforcement of safety standards should be established for ATMPs (unified assessment criteria for inspections, training of inspectors, etc.)</td>
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9 Epilogue

There are three major types of obstacle that impede translation of research into advanced therapies. The first of these, translational block (T1), prevents basic research findings from being tested in a clinical setting. Such impediments include biological and biotechnological issues, problems relating to clinical trial recruitment, and some regulatory concerns, whilst the second translational block (T2) prevents proven interventions from becoming standard practice. It struggles with human behaviour and organisational indolence, as well as research infrastructure and limited resources. The third translational block (T3) identified in this study, the legal and bioethical constraints, tend to prevent efficient translation of research and access to therapies and commercialisation of novel therapeutics. This study has investigated such legal and ethical crossing points of translational research in the contexts of development and commercialisation of ATMPs. A conclusion of this study is that a number of legal and ethical considerations addressed in Chapter 7 pertaining to fragmented legislative landscape covering the ATMP Regulation, EUCTDs, clinical trials legislation, and intellectual property rights constitute essential, albeit not the only obstacles to the streamlined market entry of ATMPs. Despite specific issues relating to first and second translational blocks being left outside the primary scope of this study, it should be noted that a number of other factors beyond legal or bioethical considerations affect the market entry of ATMPs. To provide a more balanced and comprehensive overview of factors affecting ATMP commercialisation prospects, some perspectives need to be mentioned.

To begin with, development of ATMPs is lengthy and costly. As discussed, the traditional sequential trial (ranging from the Phase I-III sequence of clinical drug testing) may seem inherently inefficient in the development of niche and tailor-made ATMPs. Hanna et al. point out that the complexity specificity of ATMPs means that new clinical trial methodologies are expected to be considered. The problems and strategies to address the challenges ATMPs encounter with trial design resemble those of oncology products and orphan drugs (e.g., small sample size, nonrandomised trials, single-arm trials, surrogate end points, integrated protocols, combined Phase II/III, and adaptive designs etc.). Trials on ATMPs are often small-scale, which risks giving misleading signs of efficacy. There is a concern that this sequential trial paradigm puts major emphasis on Phase II studies, because they typically generate information on whether or not it is advisable to proceed to a Phase III study. Hence, the risk of false negative or false positives outcome of a Phase II constitutes a relevant scientific

889 Woolf, supra note 132.
891 Hanna et al., supra note 83, 7.
concern. To overcome pitfalls caused by heterogeneous patient populations, lack of control groups, selection bias, and choice of endpoints, some strategies for streamlining trial design may be adapted. As ATMPs are a very heterogeneous class of medicines, these enhancement proposals may not fit a particular development product. However, after careful consideration of the characteristics of the ATMP in question and the particular condition to be treated, the following approaches could in some cases be used to improve ATMP trial design: larger Phase II trials (if possible), inclusion of controls (preferably randomised ones, if randomisation is possible), consideration of integrated Phase 2/3 trials, taking into account patient heterogeneity even in small-scale randomised trials, provision of information about the number of patients available for study vs. those who were actually provided with treatment, and avoidance of unvalidated surrogate endpoints and premature publication to avoid publication bias. It should be noted however that randomisation of a trial that sometimes involves a surgical procedure (as most TEPs do) may not be possible or could at least raise some significant ethical concerns. Also, as discussed it may not be possible to increase participation rate in clinical trials to generate larger sets of evidence due to particularities of ATMPs and conditions treated. In any case physician and patient education about clinical trials on ATMPs should be improved and collaboration between academic centres and other stakeholders strengthened. Yet, adapted pathways may in some cases be pursued as described in Section 8.3. In such cases a well-adapted risk management plan and related processes must be in place, as evidence generation after market entry will become unavoidable to get further confirmation on positive risk v. benefit balance.

Some further measures to improve safety and efficiency of clinical trials could also be taken. Biomarkers could be used in clinical trials to improve decision-making in the development process of a medicine. Biomarkers predicting therapeutic response enable the selection of patients most likely to respond positively to a particular advanced therapy. Implementation of predictive pharmacogenomic biomarkers allowing for elective treatment is becoming increasingly common. Biomarkers predicting the safety of a compound or an investigational medicine may be valuable for preclinical testing, or early clinical studies. Furthermore, microdosing studies (so-called Phase 0 trials with a very small number of patients and administration of sub-therapeutic doses) could be used to improve safety when assessing ATMP candidates at the early stages of development. Flexible, adaptive trial designs could be implemented to improve safety and efficacy by providing opportunities to make changes to a study in response to

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894 Ibid.
acquiring data whilst maintaining the integrity and validity of the trial. However, as discussed further guidance is needed regarding adaptive trial designs, especially in case of first-in-human trials.

The concept of adaptive trial designs also raises questions about comparability. Further clarification is needed on the concept of comparability as it applies to ATMPs. Comparability studies seek to confirm that the quality attributes of the product, including biological activity, are maintained subsequent to amendments in pharmaceutical development process. This is of particularly relevant in case of new manufacturing models (such as decentralised manufacturing). Regulators need to reconsider the existing principles of comparability and issue specific guidance and training on both standard and decentralised ATMP manufacturing in this context.

Furthermore, fostering interdisciplinary research on ATMPs from “bench to bedside and back” should be accelerated. Interdisciplinary approaches may result in new discoveries to address complex questions via the interfaces and frontiers of the disciplines involved. A number of barriers may still constitute impediments for effective integration across disciplines. Integrative approaches and structures can be used to bridge the gaps between disciplines. Efficient integration, however, requires commitment from all stakeholders and integrative interdisciplinary teamwork and leadership skills. The main categories of barriers to interdisciplinary research and commercialisation of ATMPs are: attitudinal resistance, communicational problems, inflexible academic and career structures and difficulty in obtaining funding. In addition, the heterogeneity of research institutions, organisational structures, and values embedded in both private and public systems may complicate these impediments even further.

Attitudinal barriers to translation. Notwithstanding interdisciplinary research being recognised by most researchers for decades, many researchers still remain reluctant to reconsider the focus of their own research. Some researchers have expressed the concern that the quality of interdisciplinary research may be poor because of the lack of depth. Yet the major benefit of the interdisciplinary problem-based approach is its ability to address broader sets of problems across boundaries between disciplines. This may raise concerns about the “purity” of one’s own research or the perception of interdisciplinary research as “high risk research,” or concerns about the “potential loss their professional identity or status.” Some researchers also find approaches in their

897 Faduola et. al., supra note 893, 12.
898 European Medicines Agency, supra note 762, 6.
900 These barriers may also apply to the development of conventional medicines, not only ATMPs.
902 See e.g. Pellmar, et al., op.cit.
own field of science too “incomplete” or “too immature” to be combined with another. It has been argued that these latter considerations may in fact be a good reason to pursue an interdisciplinary approach. All in all, attitudinal barriers to efficient interdisciplinary cooperation represent a natural fear of change and individual perception of the unknown. As a starting-point, humility and acknowledging limitations are required to mitigate attitudinal barriers to translation. Both limitations and the value of one’s own and others’ approaches in “soft and hard sciences” must be acknowledged to foster interdisciplinary cooperation.

**Communicational barriers to translation.** Researchers trained in a specific discipline learn a particular terminology and adopt the analytical and methodological concepts of that discipline. Terminology specific to one discipline has an important role in so-called “professional socialisation”. It may also strengthen the consistency and integrity of a discipline. In the interdisciplinary setting, however, lack of a common “language” may constitute a barrier to research. Two major communicational problems may arise: First, lack of understanding of the professional language of the other disciplines. Second, misinterpretation of the same terms used in different disciplines, which may have a very different meaning in each. Efficient teamwork also requires confidence in another’s expertise, as well as facilitating, flexible, and inclusive managerial approaches to promoting relationship-building. Performance assessments in an interdisciplinary setting may constitute challenges. Members of an interdisciplinary team must be able to adjust, compromise, and cooperate. Particular efforts to overcome communicational barriers include learning to speak a common language, setting clear expectations, allocating responsibilities and roles in sharing of data and resources. When it comes to interaction with regulatory authorities, Maciulaitis et al. point out that the increasing number of academics and SMEs developing ATMPs will necessitate that regulators more clearly communicate their

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903 See also e.g., Sigma, supra note 901. See e.g. Bechtel, W. The nature of scientific integration. Integrating Scientific Disciplines. (Boston: Martinus Nijhoff Publishers), 1996, 3-52.
904 Faduola et al., supra note 899,2.
906 Faduola, et al., supra note 901. See also Faduola, et al., supra note 899,2-3.
907 Pellmar, et al., supra note 901. See also Faduola et al., supra note 901, See also Faduola et al., ibid.
requirements and expectations in order to help academics and SMEs become more familiar with the “language” and approach to regulation.\footnote{Maciulaitis, supra note 559, 481.}

*Academic and funding barriers to translation.* Fostering interdisciplinary research and more efficient industry collaboration requires a commitment from academia. Scientific education needs to be broad enough to generate researchers who can understand critical components of other disciplines whilst getting a solid foundation in one or more fields. To promote interdisciplinary research on ATMPs, academic institutions should allocate appropriate funds for interdisciplinary efforts and strive to facilitate collaboration with the industry, establish tenure policies that promote interdisciplinary research and education, and facilitate interaction among researchers via shared facilities and interdisciplinary research centres and programmes.\footnote{Faduola, supra note 899, 3.}

In conclusion, fostering innovation in the ATMP field requires both the tools and structures for bridging the interdisciplinary knowledge, commitment from all stakeholders involved, and integrative interdisciplinary skills. Successful commercialisation of ATMPs not only requires the translation of biotechnological innovations into novel therapeutic opportunities and understanding of legal and ethical roadblocks to innovation, but it also necessitates greater interdisciplinary collaboration, promotion of transparency, and facilitated cooperation between academia, industry, regulatory authorities, health technology assessment bodies and payers alike. It is evident that stakeholders need more support from regulators, especially SMEs and academic spin-offs with less experience traversing the regulatory system.\footnote{European Medicines Agency, supra note 762, 4.} Also evidence generation after launch of an advanced therapy is likely to become unavoidable to deal with uncertainties.\footnote{See for instance, Hanna et al., supra note 83, 7.} Further post-launch evidence of the risk-benefit balance may need to be presented to address payers’ expectations. Better interdisciplinary training of stakeholder groups (including also clinicians) and the creation of a dedicated EMA office for academia with expertise in ATMPs could possibly facilitate translation of research into advanced therapies and provide an avenue for multistakeholder engagement.
Appendices
Appendix 1. Table 1. ATMPs authorised via the centralised marketing authorisation procedure as of 23 August 2016.915

<table>
<thead>
<tr>
<th>Name of the product</th>
<th>ATMP subcategory</th>
<th>Indication</th>
<th>Marketing authorisations holder</th>
<th>Date of the grant of the marketing authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChondroCelect</td>
<td>TEP</td>
<td>Used in adults to repair damage to the cartilage in the knee.</td>
<td>TiGenix NV, Belgien</td>
<td>5 October 2009</td>
</tr>
<tr>
<td>Glybera</td>
<td>GTMP</td>
<td>Authorised for treating adults with lipoprotein lipase deficiency who have severe or multiple attacks of pancreatitis.</td>
<td>uniQuere biopharma B.V., Niederlande</td>
<td>25 October 2012</td>
</tr>
<tr>
<td>Imlygic</td>
<td>GTMP</td>
<td>Imlygic is an oncolytic immunotherapy used to treat adults with melanoma.</td>
<td>Amgen Europe B.V.</td>
<td>16 December 2015</td>
</tr>
<tr>
<td>Maci</td>
<td>TEP</td>
<td>An implant used to repair cartilage defects at the ends of the bones of the knee joint.</td>
<td>Genzyme Europe B.V., NL-1411 DD Naarden</td>
<td>27 June 2013, (Maci is currently suspended for the use in the EU)916</td>
</tr>
</tbody>
</table>


916 In the absence of an authorised manufacturing site for the active substance, finished product and batch release, the requirements laid down in Article 41 of Directive 2001/83/EC are no longer met.
## Appendix 2: Table 2. Examples of hESC and iPSC-based ATMPs in clinical trials

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Company</th>
<th>Jurisdiction</th>
<th>Indication</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>hESC-derived RPE (MA09-hRPE)</td>
<td>Ocata Therapeutics</td>
<td>U.S.</td>
<td>Dry AMD</td>
<td>Phase I/II</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>hESC-derived RPE (MA09-hRPE)</td>
<td>Ocata Therapeutics</td>
<td>U.S.</td>
<td>Stargardt</td>
<td>Phase I/II</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>hESC-derived RPE (MA09-hRPE)</td>
<td>Ocata Therapeutics</td>
<td>U.K.</td>
<td>Stargardt</td>
<td>Phase I/II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>hESC-derived RPE (MA09-hRPE)</td>
<td>CHABiotech (licensed from Ocata)</td>
<td>Korea</td>
<td>Dry AMD</td>
<td>Phase I/II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>hESC-derived RPE (MA09-hRPE)</td>
<td>CHABiotech (licensed from Ocata)</td>
<td>Korea</td>
<td>Stargardt</td>
<td>Phase I</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>hESC-derived RPE (MA09-hRPE)</td>
<td>University of California, Los Angeles (with Ocata’s cells)</td>
<td>U.S.</td>
<td>MMD</td>
<td>Phase I/II</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>iPSC-derived RPE (autologous)</td>
<td>Rikagaku Kenkyūsho (RIKEN) Institute</td>
<td>Japan</td>
<td>Wet AMD</td>
<td>Phase I</td>
<td>On hold</td>
</tr>
<tr>
<td>hESC-derived RPE (PF-05206388)</td>
<td>Pfizer</td>
<td>U.K.</td>
<td>Wet AMD</td>
<td>Phase I</td>
<td>Recruiting</td>
</tr>
<tr>
<td>hESC-derived RPE (Opregen)</td>
<td>Cell Cure Neuroscience</td>
<td>Israel</td>
<td>Dry AMD</td>
<td>Phase I/II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>hESC-derived CD15 ISL-1 cardiac progenitors</td>
<td>Assistance publique, Hôpitaux de Paris</td>
<td>France</td>
<td>Severe heart failure</td>
<td>Phase I</td>
<td>Recruiting</td>
</tr>
<tr>
<td>hESC-derived pancreatic endoderm (VC-01)</td>
<td>ViaCyte</td>
<td>U.S.</td>
<td>Type diabetes</td>
<td>Phase I/II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>hESC-derived oligodendrocyte progenitors (AST-OPC1)</td>
<td>Asterias Biotherapeutics</td>
<td>U.S.</td>
<td>Spinal cord injury</td>
<td>Phase I</td>
<td>Completed</td>
</tr>
<tr>
<td>hESC-derived oligodendrocyte progenitors (AST-OPC1)</td>
<td>Asterias Biotherapeutics</td>
<td>U.S.</td>
<td>Spinal cord injury</td>
<td>Phase I/II</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

Adapted from Ilic, D., Devito, L., Miere, C., Codognotto, S. Human embryonic and induced pluripotent stem cells in clinical trials. *Br Med Bull.* 2015;116:19-27. Abbreviations: AMD=age-related macular degeneration; hESC=human embryonic stem cell; iPSC=induced pluripotent stem cell; MMD=myopic macular degeneration; RPE=retinal pigment epithelium
### Table 5: Hospital exemption rule across the EU

<table>
<thead>
<tr>
<th>Member State</th>
<th>Status of the hospital exemption implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Rules are still under development. Manufacturing license needed for production under the exemption. 918</td>
</tr>
<tr>
<td>Belgium</td>
<td>Rules are still under development. GMP principles will generally apply for ATMPs and only very minor deviations will be accepted on a case-by-case basis. 919 According to the Belgian authorities, some cell and tissue banks have received temporary authorisation until further examination of their activities has been performed (on the basis of a dossier), with the purpose to identify products that would fall under the hospital exemption. 920</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Hospital exemption necessitates the ATMP being tailored for a specific patient. The overall number of a particular product prepared, as well as the regularity and frequency of production, and the time frame for preparation of that product, together with the progression of the rate of manufacturing should be taken into account. 921</td>
</tr>
<tr>
<td>Finland</td>
<td>The main criterion for a hospital exemption is an initial phase of drug development before entering into a clinical. Oncolytic viruses have been used under hospital exemption for single patients having different diagnosis of cancer and no option for conventional therapies. The treatment has been offered individually in a private hospital under the responsibility of a treating physician. Also TEPs have been prepared for individual patients in a non-routine basis for experimental treatment of facial defects. The aim of these experimental treatments has been find the most suitable combination of stem cells and biomaterial to be taken into the future clinical trial. A centrally authorised product ChondroCelect, is in the Finnish market. It has been reported that Finnish university hospitals, orthopaedic clinics have used autologous chondrocyte preparations, for which patient biopsies are collected in Finland, exported for processing to a Swedish cell laboratory in Gothenburg and imported back to Finland for the clinical use. Such activities require a license for tissue establishment. The number of patients treated by using this optional method is approximately 10-20 per year. 923</td>
</tr>
</tbody>
</table>

917 Adapted from Pirnay, et al., supra note 22, 548-9; Kent, supra note 383; Pearce, et al., supra note 540; Lowdell, supra note 662; and Mush, supra note 604, and European Union European Commission Health and Consumers Directorate General. Hospital exemption for ATMPs, supra note 662 (in which the most of the content is based upon information provided by the national competent authorities of the Member States of the EU and the accuracy thereof cannot be guaranteed). Developers of ATMPs could benefit from systematical collection of clinical data generated by means of hospital exemption.


<table>
<thead>
<tr>
<th>Country</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Hospital exemption has been implemented by an amendment of the ‘German Medicinal Products Act’. In addition to the criteria specified in the ATMP Regulation, for hospital exemptions an authorisation of the product by the higher federal authority is necessary. The hospital exemption procedure is performed by the Paul-Ehrlich-Institute. Definition of “prepared on a non-routine basis” is further defined in Section 2 of Article 4b the German Medicinal Products Act. Accordingly, a product should be manufactured in small quantities and, if based on a routine manufacturing process, variations in the process, medically justified for an individual patient, are carried out. Alternatively, the product has not yet been manufactured in sufficient quantities so that the necessary data to enable a comprehensive assessment are not yet available (e.g. that data with respect to product quality, clinical efficacy, and safety are available, but not to the extent required for marketing authorisation via the centralised procedure). Thus, manufacturing on a non-routine basis is not merely associated with an exact maximal quantity.</td>
</tr>
<tr>
<td>Greece</td>
<td>Rules are still under development.</td>
</tr>
<tr>
<td>Hungary</td>
<td>Since 1 January of 2011 hospital exemption has been defined in a national act stating that the human medicines national competent authority shall licence the ‘manufacturing site’ of such products in the in-patient institutions.</td>
</tr>
<tr>
<td>Lithuania</td>
<td>The rules on manufacture of ATMPs for individual patients were approved by the Minister of Health in 2010. An entity is allowed to manufacture ATMPs on non-routine basis for individual patients if it possesses a permit issued by the State Medicine Control Agency at the Ministry of Health. ATMPs must be prepared on non-routine basis, when different (modified) manufacturing processes are applied for every product or when the same ATMP is manufactured with the frequency that may not be attributed to the routine manufacture. An entity is eligible to get a permit if it possesses a health care licence and meets manufacturing and control requirements approved by the Minister of Health.</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Hospital exemption may be granted for maximum 10 applications per annum. In the Netherlands a request for a hospital exemption must be submitted at the Health Care Inspectorate.</td>
</tr>
</tbody>
</table>

924 Committee for Advanced Therapies, supra note 706.
928 Ibid.
929 Ibid., 10.
<table>
<thead>
<tr>
<th>Region</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>Rules are still under development.932 The centrally authorised ChondroCelect has entered the Spanish market. There are also other products in hospital use, belonging to one of the following three categories: corneal limbal stem cells, chondrocytes and skin keratinocytes. These products are manufactured by a non-industrial process and have a “historical”, consolidated use prior to the ATMP Regulation, and will be regulated under the hospital exemption clause that is still under development.933</td>
</tr>
<tr>
<td>Sweden</td>
<td>From 1 May 2012 the manufacturers have been required to apply for a manufacturing licence for ‘hospital exemption products’ in accordance with the specific standards required by the Medical Products Agency.934</td>
</tr>
<tr>
<td>The UK</td>
<td>The UK Medicines and Healthcare Product Regulatory Agency (the “MHRA”) did not deem necessary to apply a simple numerical rule to draw a line between routine production and production on a “non-routine” basis.935 Instead, a special scheme was created pursuant to Article 5 (1) of the Medicinal Products Directive that allows a Member State “in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.”936 This derogation is in principle allowable for any classes of medicinal products, including ATMPs. However, the MHRA applies a ‘special needs test’ which implies that unlicensed ATMPs may authorised in the absence of a pharmaceutically equivalent and available licensed product.937</td>
</tr>
</tbody>
</table>

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934 Ibid.
936 Kent, supra note 383.
Appendix 4: Figure 6. The EMA’s regulatory procedures for ATMPs.\textsuperscript{938}

Appendix 5: Figure 7. Interaction with the EMA and incentives mechanism

Based on processed described in the website of the EMA, supra note 938. Abbreviations: MA= marketing authorisation, SME= micro, small or medium sized enterprise, CTA= clinical trial application.
Appendix 6

Figure 8. The EMA’s adaptive pathways approach: widening the indication scenario

Widening of the indication Scenario

(Final target indication in blue and red)


Figure 9. The EMA’s adaptive pathways approach: prospectively planned reduction of uncertainty scenario

Prospectively planned Reduction of uncertainty Scenario

Advanced therapy medical product, ATMP

According to Article 2.1.a of the ATMP Regulation, an ATMP means any of the following medicinal products for human use: a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, as amended; a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, as amended; or a tissue engineered product as defined in Article 2.1.b of the ATMP Regulation. In addition, Article 2.1.c. of the ATMP Regulation defines ATMPs as products that contain or consist of cells or tissues that “have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved” or “the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor”.

References:

Allogenic transplantation

Situation in which the transplant is taken from different individuals of the same species.

EATB, supra note 28.

Alternative nuclear transfer, ANT

In ANT-technique the donor cells are genetically altered to disrupt the expression of gene that is necessary for the formation of a functional trophoblast. The resulting “ANTities” form inner cell mass from which embryonic stem cell can be procured.


Antisense technology

Technology utilising RNA to interrupt a cells ordinary function, i.e. a technology that interrupts the production of proteins, but cannot e.g. result in the production of a different protein.

See Section 7.4 for further details.

Autologous transplantation

Situation in which the donor and recipient are the same person. For instance, an autologous graft is a graft (such as a graft of skin) that is provided for oneself.

EATB, supra note 28.

Batch

“[D]efined quantity of tissue produced according to a single processing cycle during the same processing cycle which is intended to have uniform character and quality within specific limits, precluding mixing of cells and/or tissue from two or more donors.”

EATB, supra note 28.

Blastomere

A totipotent cell resulting from the cleavage of a fertilised ovum during early embryonic development.

See Research Article I for further details.
Bioburden “[P]opulation of viable micro-organisms found on a given amount of material (EATB 2003).”

Cell therapy medical product, CTMP CTMP means a biological medicinal product which has the following characteristics: 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. It 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.

Clean (non-sterile) “[U]se of methods and techniques that keep microbial contamination of the tissues collected at a minimum level (EATB 2003).”

Combined ATMPs These are medicines that contain one or more medical devices as an integral part of the medicine. An example of this is cells embedded in a biodegradable matrix or scaffold.

Diploid Diploid’ refers to a cell that contains two copies of each chromosome. Almost all the cells of human origin have two homologous, copies of each chromosome. The only exception is germ cells, which produce gametes. Haploid germ cells contain a single set of chromosomes. In diploid cells, one set of chromosomes carries maternal DNA, while the second is inherited from the father. Humans have 46 chromosomes in each diploid cell. Those include two sex-determining chromosomes, and 22 pairs of autosomal chromosomes.

Ectopic engraftment Cell engraftment at an abnormal, non-target tissue location.

Epigenetic Relates to changes in the way genes are expressed by a cell or an organism; changing the phenotype without changing the genotype.

Gene therapy medical product, GTMP GTMP means a biological medicinal product which has the following characteristics: it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. Its
therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Haploid

Haploid germ cells contain a single set of chromosomes.

Human embryonic stem cell, hESC

A self-replicating, undifferentiated human cell of embryonic origin that has depending on its potency a capacity to develop into different kinds of cells or tissues in a human body.

Induced pluripotent stem cell, iPSC

iPSCs are somatic cells by reprogramming via forced expression of a specific set of transcription factors that can revert the cell towards a pluripotent stage similar to embryonic stem cells.

Lentivirus

Lentiviruses can deliver a significant amount of viral RNA into the DNA of the host cell. They are one of the most efficient methods of a gene delivery vector, which have the unique ability to infect non-dividing cells.

Morula

Morula is an early stage embryo (3-4 days post fertilization) consisting of blastomeres.

Multipotent hESC

Multipotent stem cells (e.g. hematopoietic or neuronal stem cells) have a potential to generate a limited range of terminally differentiated cell types.

Orphan disease

Condition affecting no more than five in 10 000 persons.

Parthenogenesis

In parthenogenesis an ovum is subjected to an electrical or chemical stimulus that causes it to behave as if it had been fertilized.

also the European Medicines Agency: Reflection paper on classification of advanced therapy medicinal products, supra note 70.


<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Reference/Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parthenote</td>
<td>Parthenotes are created via process of parthenogenesis, in which a uniparental embryo-like entity is developed directly from oocyte without fertilization by sperm. Parthenotes contain a single or double set of maternally derived chromosomes but do not contain any paternal DNA.</td>
<td>See Research Article III for further details.</td>
</tr>
<tr>
<td>Pluripotent hESC</td>
<td>A hESC possessing a capacity to generate all cell types in an organism but being unable to develop into a complete organism. To qualify as a pluripotent, stem cells are required to meet following criteria: unlimited proliferation \textit{in vitro} while maintaining their normal diploid karyotype, differentiation potential into cell of all three germ layers: ectoderm, mesoderm and endoderm.</td>
<td>See e.g. Rossbach, M., Hadenfield, M., Brüstle, O. “Industrial Application of Stem Cells in” in Hug, K., Hermerén, G. (eds.) \textit{Translational Stem Cell Research}. (New York, Dordrecht, Heidelberg, London: Springer), 2011.</td>
</tr>
<tr>
<td>Primordial germ cell</td>
<td>A germ cell prior to its maturation into a haploid gamete.</td>
<td>Wagner, C.R. Germ Cells and Epigenetics. \textit{Nature Education} 2010:3(9) :64</td>
</tr>
<tr>
<td>Retrovirus</td>
<td>Retrovirus is a enveloped virus that replicates in a host cell by means of reverse transcription. It is a single-stranded positive-sense RNA virus with a DNA intermediate and, as an obligate parasite, targets a host cell.</td>
<td>NCBI.\textit{Retroviruses}. Available at: <a href="http://www.ncbi.nlm.nih.gov/genome/viruses/retroviruses/">http://www.ncbi.nlm.nih.gov/genome/viruses/retroviruses/</a>. Accessed 21 June 2016.</td>
</tr>
<tr>
<td>Somatic gene therapy</td>
<td>Therapy utilising DNA to genetically alter normal function of an adult cell.</td>
<td>See Section 7.4 for further details.</td>
</tr>
</tbody>
</table>
Stem cell
An undifferentiated cell that gives rise to specialised cells.

See Research Article I for further details.

Stem cell technology
Technology utilising a stem cell that divides and can be reprogrammed to a specific cellular function.

See Section 7.4 for further details.

Sterilisation
“[A] validated physical or chemical process to destroy, inactivate or reduce microorganisms to a sterility assurance level of 10^-6.”

EATB, supra note 28.

Teratoma
A teratoma is a monodermal or polydermal tumor with tissue or organ mechanisms reminiscent of normal derivatives of more than one germ layer. The tissues of a teratoma may be quite different from surrounding tissues and they also may be very different.


Tissue establishment
“A tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells (2004/23/EC).”

EATB, supra note 28.

Tissue engineered medical product, TEP
TEP means a biological medicinal product containing /consisting of engineered cells/tissues. It 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.

Tissue engineered product has been defined in Article 2.1.b of Regulation (EC) No. 1394/2007. See also the European Medicines Agency: Reflection paper on classification of advanced therapy medicinal products, supra note 70.
<table>
<thead>
<tr>
<th><strong>Totipotent hESC</strong></th>
<th>The totipotent hESC possesses the potential to develop into a full human including all somatic-, germline-, and extraembryonic tissues. Zygotes and early blastomers of mammalians are examples of totipotent cells.</th>
<th>See e.g. Rossbach, M., Hadenfield, M., Brüstle O. “Industrial Application of Stem Cells in” in Hug, K., Hermerén, G. (eds.) Translational Stem Cell Research. (New York, Dordrecht, Heidelberg, London: Springer), 2011.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traceability</strong></td>
<td>“[T]he ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells (2006/86/EC)”.</td>
<td>EATB, supra note 28.</td>
</tr>
<tr>
<td><strong>Transgene</strong></td>
<td>Transgene refers to a segment of DNA containing a gene sequence that has been isolated from one organism and is introduced into a different organism. It has the potential to alter the phenotype of an organism.</td>
<td>See Research Article I for further details.</td>
</tr>
<tr>
<td><strong>Unipotent hESC</strong></td>
<td>Unipotent hESCs can only give rise to one cell type.</td>
<td>See e.g., Smith, A.G. Embryo-derived stem cells: of mice and men. Annu Rev Cell Dev Biol. 2001;17:435-62.</td>
</tr>
<tr>
<td><strong>Validation</strong></td>
<td>“[E]stablishing documented evidence that provides a high degree of assurance that a specific process, piece of equipment or environment will consistently produce a product meeting its predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use (2006/86/EC).”</td>
<td>EATB, supra note 28.</td>
</tr>
<tr>
<td><strong>Zygote</strong></td>
<td>A totipotent cell produced by the union of two gametes, before it undergoes cleavage.</td>
<td>See Research Article I for further details.</td>
</tr>
</tbody>
</table>
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