Creating European Markets through Regulation: The Case of the Regulation on Advanced Therapy Medicinal Products

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Abstract

This article analyses the EU regulatory efforts to create a European market for advanced therapy medicinal products. It focuses on the pitfalls of European regulatory intervention in a difficult market which is characterised by multiple, often contradictory stakeholder expectations, rapid scientific and technological change, and ethical diversity. It contends that while the Regulation on Advanced Therapy Medicinal Products was, in principle, equipped to address these challenges, its fundamental paradigms and choices, and its treatment of some of the dilemmas of the emerging technology market, undermined its ability to establish the balanced and sustainable market desired by the EU legislator.

Introduction

By means of legal regulation, the EU has contributed significantly to the creation of integrated European markets for traditional chemical-based medicinal products and for medicinal products which are based on advanced biomedical technologies. Its involvement is driven fundamentally by twin aims: to make medicinal products available to patients through the market and to ensure that these products are safe, effective and of sufficient quality. The market creation and market integration intentions of the Union have, however, been hindered by the difficulties of regulatory intervention in these domains. The markets regulated are characterised by uncertainty because of rapid scientific and technological change; their regulation has to realise competing, potentially contradictory objectives; the products involved and their commercialisation and use may be ethically controversial; and the regulation of these markets is expected to address their diversity as a matter of stakeholder expectations, modes and scales of production, or of the applicable value considerations. In such an environment, regulation, especially at the European level, must establish a careful balance between the different aspects and pressures of the market, failing which the objectives of EU intervention could be jeopardised.

* The research leading to this article was supported by the Seventh Framework Programme of the European Commission through the EUCelLEX Project (Cell-based regenerative medicine: new challenges for EU legislation and governance) (Grant number: 601806).

This article—prompted among others by the 2014 comprehensive review of the Commission[1]—examines the Regulation on advanced therapy medicinal products (the Regulation) which was enacted to create a new European market for gene and cell therapy and tissue engineering products.[2] It explores, specifically, how the Regulation managed to meet its multiple objectives and also whether the ultimate aim of creating a European advanced therapy medicinal product (ATMP) market has been achieved. It is far from clear that the market paradigm followed by the Regulation was capable of delivering the expected results and that the balances created between the different objectives, expectations and other imperatives of regulatory intervention were satisfactory. The treatment of the ethics of ATMPs was particularly problematic as it showed how EU regulation may opt for the politically and practically feasible instead of addressing the dilemmas and the potential conflicts which may arise from the ethical dimension of the market. The article begins with an overview of the general challenges of regulating new technologies and their markets. This is then followed by an examination of the Regulation's main provisions, which paves the way to the ensuing analysis of the experiences and the potential problem areas of applying the Regulation.

Creating and integrating technology markets in the EU

The creation of integrated markets is a core objective of the EU as stated originally in arts 2 and 3 EEC. This objective has been fulfilled following a variety of regulatory approaches and strategies. There were and there are European markets based on detailed regulation and a centralised administration (e.g. formerly, coal and steel),[3] markets which are governed in a predominantly decentralised structure and which place emphasis on regulatory competition and horizontal co-operation (e.g. the market for services),[4] and there are markets which were newly created through European instruments deregulating and re-regulating the marketplace (e.g. energy).[5] The virtually continuous reform of European agricultural market regulation,[6] or the keeping of policies for integrated markets dormant for decades, as in the case of transportation,[7] both indicate that the EU's involvement is heavily context-dependent and that regulatory success depends on a right alignment of politics, economic circumstances and stakeholder expectations. In the case of technology markets, rapid changes in technology, unforeseeable technological developments, or the ethical dilemmas affecting the source materials, human innovative activity and the final products make EU regulatory intervention a similarly fragile exercise which may ultimately struggle with finding the adequate linkages with the technology and the market regulated.

Regulating new technologies and their market is burdened, first, by the known hard dilemmas of technology regulation.[8] Secondly, the sheer complexity of issues raised by technology markets demands

[1] *Commission Report in accordance with art.25 of Regulation 1394/2007 on advanced therapy medicinal products* COM(2014) 188 final (Report).

[2] Regulation 1394/2007 on advanced therapy medicinal products [2007] OJ L324/121. The category "advanced therapies"—as created by the Regulation—refers to therapies which belong to an emerging area of biomedicine, commonly called as regenerative medicine. Advanced therapies include, for example, cartilage tissue reparation using scaffolds, somatic cell implantation, or gene transfer to regenerate tissue or to treat disease.

[3] See ECSC High Authority, *The ECSC: Basis of a Wider European Community* (Luxembourg: 1967).

[4] See Directive 2006/123 on services in the internal market [2006] OJ L376/36.

[5] See, for example, E. Szyszczak, *The Regulation of the State in Competitive Markets in the EU* (Oxford: Hart Publishing, 2007), pp.139–176.

[6] See generally J. Usher, *EC Agricultural Law* (Oxford: Oxford University Press, 2002).

[7] L. Ortiz Blanco and B. van Houtte, *EC Competition Law in the Transport Sector* (Oxford: Oxford University Press, 1996), p.30.

[8] See L. Brévignon-Dodin, "Regulation as an enabler for emerging industries: literature review", CIG Working Paper 2009/2, pp.6–10, available at *http://www.ifm.eng.cam.ac.uk/uploads/Research/CIG/0902cig_working_paper.pdf* [Accessed 6 January 2016], which highlighted three main dilemmas from the literature: the challenge of maintaining "regulatory connection" with the new technology (Brownsword); the "pacing problem", referring to the struggle of regulation to keep up with technological change (Bennet Moses); and the "Collingridge dilemma", meaning that

regulatory intervention which establishes appropriate and proportionate balances among its different objectives and which develops a framework in which the contradictions among its competing objectives can be adequately resolved. It needs to ensure, for example, that its market creation agenda is reconciled with the moral issues of that market, and this needs to be achieved without the regulatory technique selected to achieve one objective undermining the other. Furthermore, regulatory intervention must avoid creating new problems for stakeholders while addressing those originally faced by them. It is a common challenge that while clear, predictable and scientifically sound legal rules are expected to be introduced so as to incentivise innovation and stimulate the emergence of new markets,[9] the enactment and application of those rules—in cases where they are excessive or badly targeted, or when they become obsolete rapidly—may in fact supress innovation and knowledge creation.[10] Finally, when in diverse and rapidly developing fields regulatory intervention is expected to pursue multiple regulatory targets,[11] there is a danger that meeting demands for open, flexible and adaptable regulation will erode the original intention of putting in place a clear and predictable regulatory framework, and an overly complex and at the same time gap-ridden regulatory instrument will emerge.[12]

At the European level, these fundamental questions of technology regulation are coupled with further difficulties linked to EU regulatory intervention.[13] First, there is the question of competence. The EU may not have sufficient competences to regulate the different aspects of a given technology: it may address product safety and quality, but may lack the powers to deal with the ethics of that technology, especially when the relevant ethical standards diverge from one Member State to another. There are certain sensitive areas, such as public health regulated under art.168 TFEU, where policy competences are jealously safeguarded by the Member States, and European intervention proposing centralised or other common regulatory frameworks needs to overcome Member State resistance.[14] Secondly, a decision needs to be reached on the territorial allocation of functions for administering the market and its different segments. The EU instrument must have regard to the requirement of subsidiarity under art.5(3) TEU in defining the appropriate territorial level of regulatory intervention, and it must observe the principle of proportionality under art.5(4) TEU in deciding how far uniform rules are implemented in what is potentially an economically and ethically diverse market. It is also necessary to determine which aspects of the technology can be regulated effectively at the European level, which also involves assessing how the new domain can be integrated into existing EU regulatory frameworks. Fourthly, the political reality of EU

regulators face a twin hurdle in regulating new technology—it is either too early, and they suffocate innovation, or too late, making it too expensive to challenge technological entrenchment (Collingridge).

[9] Inter alia, L. Firth and D. Mellor, "The Impact of Regulation on Innovation" (1999) 8 *European Journal of Law & Economics* 199; J. Kent et al., "Towards Governance of Human Tissue Engineered Technologies in Europe: Framing the Case for a New Regulatory Regime" (2006) 73 *Technological Forecasting and Social Change* 41. This is also recognised by the EU policy-maker in Commission, "Innovation in a knowledge-driven economy" COM(2000) 567 final.

[10] For a discussion on the traditional understanding of the relationship between law and science as constraint on and obstacle for scientific activity, and as not being available to respond to the demands of rapid scientific progress, see E. Vergès, "Scientific and Technological Evolution through the Legal Prism: Visions of a Multi-faceted Relationship through the Lens of French and EU Law" (2014) 6 *Law, Innovation and Technology* 77, 76–77.

[11] See L. Bennet Moses, "How to Think about Law, Regulation and Technology: Problems with 'Technology' as a Regulatory Target" (2013) 5 *Law, Innovation and Technology* 1, 5–6.

[12] Observed in connection with the Regulation in Brévignon-Dodin, "Regulation as an enabler for emerging industries", CIG Working Paper 2009/2, p.11, available at *http://www.ifm.eng.cam.ac.uk/uploads/Research/CIG /0902cig_working_paper.pdf* [Accessed 6 January 2016].

[13] See, in general, on the complex and contradictory rationales of legislative harmonisation at the European level, S. Weatherill, "Why harmonise?" in T. Tridimas and P. Nebbia (eds), *European Union Law for the 21st Century*, Vol.2 (Oxford: Hart Publishing, 2004), pp.11–32.

[14] See *Germany v Parliament and Council (Tobacco advertising)* (C-376/98) [2000] E.C.R. I-8419; [2000] 3 C.M.L.R. 1175.

decision-making may have an impact on regulatory design, permitting only the adoption of a framework instrument through the normal political process and leaving the detailed regulation of technology to a more confined delegated process.[15] Finally, because the regulatory intervention takes place at the European level, it may be impossible to develop common regulatory categories and distinctions of the desired precision which then would be available to cover the entirety of a complex and fluid technological domain.[16]

In the regulation of new biomedical technologies and their markets, although risk and the related public health objectives provide the focus of its involvement,[17] the EU—in an attempt to create synergies with its policies in parallel areas—has always pursued complex agendas.[18] EU instruments balance the aim of controlling the quality, safety and efficacy of technologies against the objectives of incentivising innovation and commercialisation. Rapid scientific and technological change in these markets means that EU instruments recognise the value of regulatory clarity, certainty and predictability, and of regulatory flexibility and adaptability. Securing the access of new technologies to the market is promoted in parallel with the aim of creating a certain and predictable environment for developers and investors. The different interests of different stakeholders are also taken into account, such as the special needs of small and medium-sized enterprises (SMEs). The protection of consumers is part of the agenda, as well as raising their interest and their confidence in new markets. In case the source materials of products are affected by ethical complications, for instance, because they are of human origin, the ethical and the potential related human rights benchmarks of their use and of their commercialisation are considered. While this broad engagement makes EU regulatory intervention appropriately considered, the overloading of instruments with multiple, potentially contradictory objectives may hold considerable risks for when they are eventually applied.

The Regulation

Aims and objectives

The aim of the Regulation was to create a European marketplace for ATMPs where the fragmented and heterogeneous national regulatory frameworks are replaced by a single and uniform legal framework establishing a centralised system of marketing authorisation in which the quality, safety and efficacy of products are adequately supervised and monitored. This was expected to offer stakeholders—the industry, mainly—a clear and predicable pathway for product development and also for obtaining a marketing authorisation for their products, which would enable—ultimately—the availability of ATMPs to all patients

[15] As shown by the example of the Regulation.

[16] See the discussion on the "mangled" ATMP field, A. Mahalatchimy et al., "The Legal Landscape for Advanced Therapies: Material and Institutional Implementation of European Union Rules in France and the United Kingdom" (2012) 39 *Journal of Law and Society* 131, 144–145, and at 146 the enlightening discussion on the difficulties of developing adequate regulatory categorisations at EU level.

[17] See A.-M. Farrel, "The Politics of Risk and EU Governance of Human Material" (2009) 16 *Maastricht Journal of European and Comparative Law* 41.

[18] A. Faulkner, "Regulatory Policy as Innovation: Constructing Rules of Engagement for a Technological Zone of Tissue Engineering in the European Union" (2009) 38 *Research Policy* 637, 638. The EU's interest is not restricted to public health issues as its regulatory agenda also extends to enterprise and industrial policies: A. Faulkner, "Commensuration and Proliferation: Similarity and Divergence in Law's Shaping of Medical Technology" (2012) 4 *Law, Innovation and Technology* 165, 175. See the discussion on the different "frames" of EU new health technologies regulation in I. Bache et al., "The Defining Features of the European Union's Approach to Regulating New Health Technologies" in M. Flear et al. (eds), *European Law and New Health Technologies* (Oxford: Oxford University Press, 2013), pp.7–45 at pp.20–41.

in Europe through the market.[19] The new pathway for ATMP development and authorisation had to be distinguishable from other pathways in the European medicinal products market.[20] For this purpose, the Regulation explicitly located ATMPs in the existing European regulatory framework.[21] A key element of this was the coining of the distinct product category "ATMP".[22] Their separate regulation was justified foremost by the EU legislator holding that ATMPs are novel, complex and technically specific products which require "specially tailored and harmonised rules"[23] distinct from those applicable to standard chemical-based medicinal products.[24] Using this new term, the Regulation was also able to take the relevant products out of the scope of national regulation.

The market waiting to be regulated was thoroughly researched by the European Commission. In its preliminary reports, it identified the main stakeholders,[25] the expectation that market integration will increase the level of activity in the market, the disappointing pre-regulation state of the market, and the problems requiring EU intervention, such as the uncertainties faced by stakeholders, the failures in development and commercialisation, the unbalanced market expectations, and the geographical fragmentation of the market.[26] The Commission emphasised that the national regulatory frameworks, which were either fragmented or non-existent, were not benefiting the emerging ATMP industry, and that European regulatory intervention was needed, first, to incentivise developers and, secondly, to increase the acceptance of ATMPs by patients, practitioners and by potential investors. Expert analyses of the sector also suggested that the uncertainties of the market were inhibiting innovation and commercial activity, and that EU regulation—by incentivising stakeholders and by clarifying which measures were applicable to which medicinal product, how quality, safety and efficacy standards should be met, and how to address the relevant ethical challenges[27]—could bring the necessary change.[28] Developing an

[19] L. Brévignon-Dodin and P. Singh, "ATMP in Practice: Towards a New Industry Landscape in Tissue Engineering" (2009) 15 *Journal of Commercial Biotechnology* 59, 60 and 62. The Regulation has brought a degree of ordering to what was a confused, internationally variegated marketplace with widely differing regulatory regimes, or indeed in some cases, no clear national regulatory regime at all: see Faulkner, "Commensuration and Proliferation" (2012) 4 *Law, Innovation and Technology* 165, 177.

[20] N. Chowdhury, "Common Market but Divergent Regulatory Practices: Exploring European Regulation and the Effect on Regulatory Uncertainty in the Marketing Authorization of Medical Products" (2013) 35 *Journal of European Integration* 635, 641.

[21] There was considerable pressure on the EU to keep ATMPs under the existing regulatory frameworks, which would have enabled the development of products without meeting the heightened standards and other burdens of a sector-specific regulatory instrument: see Faulkner, "Regulatory Policy as Innovation" (2009) 38 *Research Policy* 637, 643.

[22] This was determined in long negotiations among stakeholders: see Faulkner, "Regulatory Policy as Innovation" (2009) 38 *Research Policy* 637, 643; and Mahalatchimy et al., "The Legal Landscape for Advanced Therapies" (2012) 39 *Journal of Law and Society* 131, 133–134.

[23] Regulation 1394/2007, Recital 5 of the Preamble.

[24] *Commission Report* COM(2014) 188 final, para.4.4.1. The regulation of these therapies together under the ATMP label emerged, therefore, as an autonomous agenda, which characterises specifically EU regulatory intervention in this domain.

[25] See also Regulation 1394/2007, Recital 25 of the Preamble. Stakeholders are mainly academia, non-for-profit entities and SMEs, with limited access to market-based financing and limited capacity to adhere to complex regulatory structures: see *Commission Report* COM(2014) 188 final, para.4.4.1.

[26] Commission, *Human Tissue-engineered Products: Today's markets and future prospects* (Brussels: 2003) and Commission, *Human Tissue-engineered Products: Potential socio-economic impacts of a new European regulatory framework for authorisation, supervision and vigilance* (Brussels: 2005).

[27] ATMP developers must be provided a clear and identifiable development and commercialisation pathway: Brévignon-Dodin and Singh, "ATMP in Practice" (2009) 15 *Journal of Commercial Biotechnology* 59, 60.

[28] Faulkner, "Regulatory Policy as Innovation" (2009) 38 *Research Policy* 637, 640.

ATMP-specific European regulatory framework was also supported by the possibility that these products might fall into a "regulatory vacuum" under the EU rules existing at that time.[29]

The main features of the Regulation

As it indicated by its general regulatory aim, the Regulation pursued twin public health policy objectives. It was introduced to ensure, on the one hand, that ATMPs are available to meet unmet medical needs in Europe through the creation of an integrated product market, and, on the other, that patients are protected from the failures of that market. The main instrument available to realise these objectives was the setting up of a centralised marketing authorisation system before the European Medicines Agency (EMA), which offers access to the market through a single process of product assessment under uniform European standards and which also ensures that the quality, safety and efficacy of medicinal products are controlled before they are allowed to enter the market. It was expected that the new marketing authorisation system would be able to achieve both objectives in parallel without compromising the overall applicability of the Regulation.[30]

Beyond the centralised marketing authorisation system, the Regulation was furnished with further administrative and regulatory tools. Its system for post-marketing controls is available to assess the quality, safety and efficacy of products which have been authorised to enter the market. For the pre- and the post-marketing controls of ATMPs a special body, the Committee for Advanced Therapies (CAT), was created within the EMA. The CAT, which brings together the best expertise in regenerative medicine available in Europe, assesses the scientific data submitted by developers, and it is supposed to ensure that product assessments keep up with scientific and technological changes in the domain.[31] The technological rules applicable in the marketing authorisation procedure were not included in the Regulation. Faithful to the Regulation's "two-staged regulatory strategy",[32] they were ordered to be enacted with a delay under its provisions delegating legislative powers for this particular purpose. The development of the applicable good manufacturing and good clinical practice rules was also regulated by means of delegating powers for legislation for these purposes. As an alternative to its centralised marketing authorisation system, the Regulation acknowledged through the so-called "hospital exemption" the possibility of obtaining marketing authorisation at the national level when ATMPs are produced instead of large-scale industrial processes in a small-scale clinical environment. The Regulation also contained a number of incentivising elements urging developers to place their products—sooner, rather than later—on the market. The integration of the distinct marketing authorisation pathway for ATMPs into the pre-existing EU medicinal products regulatory framework was achieved by the Regulation including cross-references to the relevant pieces of EU legislation and/or amending them to the necessary extent.[33] The ethical implications of producing, marketing and using ATMPs and the compatibility of the marketing authorisation system with the relevant

[29] A. Faulkner et al., "Human Tissue Engineered Products—Drugs or Devices?" (2003) 326 *British Medical Journal* 1159.

[30] Commission: DG Enterprise, "Consultation Document on the need for a Legislative Framework for Human Tissue Engineering and Tissue Engineered Products" (Brussels: 2002).

[31] See also the powers given to the Commission to adopt any necessary changes—following scientific and technical developments—regarding the applicable technical requirements: Regulation 1394/2007, Recital 25 of the Preamble and art.24 (power to amend the Annexes to the Regulation). The different incentives for stakeholders to seek advice from the EMA are also available to tackle—as early as possible—the rapid evolution of science and discoveries in the field: Recitals 23 and 24 of the Preamble.

[32] Brévignon-Dodin and Singh, "ATMP in practice" (2009) 15 *Journal of Commercial Biotechnology* 59, 60–61.

[33] These cross-references are also important for ensuring that no gaps are allowed for products in the "patchwork" European regulation of medicinal products and medical devices: see Faulkner, "Regulatory Policy as Innovation" (2009) 38 *Research Policy* 637, 643.

ethical standards were addressed by way of the Regulation deferring to the national legal measures regulating these matters.[34]

The main features of the Regulation are summarised in Table 1.

Table 1: The main regulatory components of the Regulation

Instrument	Purpose	Explanation
Marketing authorisation	Market access/availability of therapies	Centralised procedure before EMA for large-scale production
Marketing authorisation	Product quality, safety and efficacy	Centralised procedure before EMA for large-scale production
Hospital exemption	Market access/availability of therapies at local level to meet individual therapeutic needs	Authorisation of ATMPs produced in small-scale procedures at the national level
Technological regulation (including good manufacturing and good clinical practice)	Product quality, safety and efficacy	Delayed and reserved for delegated legislation
Incentives	Availability of therapies/navigate in regulatory framework	Linking the EMA and ATMP developers
Post-marketing control	Product quality, safety and efficacy	Throughout the lifespan of the product in the market
CAT assessment	Product quality, safety and efficacy	Gather the scientific expertise available in Europe
CAT assessment	Flexibility to keep up with technological change	Best scientific knowledge in Europe
Cross-references	Integrate into existing regulatory framework	Managing regulatory overlaps and distinctions
Deference	Address ethical issues and ethical diversity	Locus of regulation at the national level

Piggybacking on the structure made available under Regulation 726/2004,[35] arts 8 and 9 laid down the fundamental rules of the centralised system for the marketing authorisation of ATMPs in Europe.[36] These provisions promise the assessment of products on the basis of "the best available expertise" in the science of advanced therapies in Europe, which will be carried out with a view to ensuring scientific consistency and efficiency in the operation of the different authorisation pathways within the EMA system.[37]

[34] Regulation 1394/2007 art.28 states that the Regulation "must 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 relevant instruments of EU law. This list also includes human embryonic stem cells: see Recital 7 of the Preamble. In a cross-reference to the Tissues and Cells Directive (Directive 2004/23), the Regulation also recognised the applicability of the ethical principles governing the donation and procurement of human tissues and cells for ATMPs.

[35] Regulation 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [2004] OJ L136/1.

[36] Regulation 1394/2007 art.9 deals with the specific complications of authorising combined ATMPs containing medical devices, having regard to the fact that the Medical Device Directives (Directives 93/42 and 90/358) have set up a decentralised system for the authorisation of medical devices at the national level. The quality, safety and efficacy requirements for medical devices are lower than those applicable to ATMPs including combined ATMPs. Despite the complications combined ATMPs represent for regulation, maintaining this category is vital as increasing technological complexity and combination in the ATMP market is a desirable development.

[37] Regulation 1394/2007, Recitals 11–12 of the Preamble. Members of the CAT should cover the relevant scientific areas, "including gene therapy, cell therapy, tissue engineering, medical devices, pharmacovigilance and ethics. Patient associations and clinicians with scientific experience of advance therapy medicinal products should also be represented".

Centralisation was a preferred choice not only because the EMA was available as a marketing authorisation agency with jurisdiction for the entire EU, which had administered before the adoption of the Regulation some of the products now recognised as ATMPs, but also because it promised overcoming the fragmentation and the diversity of previously adopted national practices. Centralisation was also a necessity as the limited expertise in Europe on advanced therapies had to be pooled at the European level in the CAT so as to ensure that product assessments are carried out at the highest quality in light of the scientific state of the art.[38] Centralised product assessment through the CAT also makes sure that in a highly uncertain and changeable market uniform and transparent administrative practices can be developed.[39]

Stakeholder compliance with the new provisions is expected to be enhanced by the Regulation's incentivising instruments. In parallel, they are available to nudge developers to exploit the opportunities offered by the new marketing authorisation framework.[40] Under art.16, applicants and holders of a marketing authorisation are entitled to request scientific advice from the EMA "on the design and conduct of pharmacovigilance and of the risk management system", which instruments are regulated in the Regulation as part of the complex system of post-authorisation follow-ups and risk management.[41] The second incentive provided is the possibility of requesting a "scientific recommendation" from the EMA for the purpose of determining whether the product in question falls "on scientific grounds, within the definition of an advanced therapy medicinal product".[42] This preliminary product classification by the EMA informs stakeholders whether they should follow the development and authorisation pathway offered by the Regulation or the other pathways available under EU medicinal products law.[43] The third incentivising element enables SMEs specifically to submit to the EMA their relevant quality and non-clinical data for scientific evaluation and certification. These are the data which will be requested from them when they submit a product for authorisation.[44] With this, art.18 gives SMEs the opportunity to obtain a legally non-binding certification which they can rely on when they conduct studies on the quality and non-clinical safety of their products, and which could facilitate the evaluation of future applications for clinical trials and for marketing authorisations based on the same data.[45] Finally, the Regulation offers to hospitals and SMEs specifically a reduction by 50 per cent of the marketing authorisation fee on the condition that they

[38] Chowdhury, "Common Market but Divergent Regulatory Practices" (2013) 35 *Journal of European Integration* 635, 638. Regulation 1394/2007, Recital 9 of the Preamble emphasises that the *single* scientific evaluation of ATMPs before the EMA following the highest possible standards necessary "in order to overcome the scarcity of expertise in the Community, ensure a high level of scientific evaluation of these medical products in the Community, preserve the confidence of patients and medical professions in the evaluation and facilitate Community market access for these innovative technologies".

[39] The uncertainties of ATMPs as marketable products are indicated in Regulation 1394/2007 art.8(1) demanding that the CAT "shall endeavour to reach a scientific consensus", or when that is not possible, a majority position must be developed regarding the scientific justifiability of the ATMP in question, with divergent scientific positions and their justification also made visible in the draft opinion of the CAT.

[40] An implied incentive is that by placing the Regulation within the framework of existing EU pharmaceutical regulation the beneficial arrangements of that regime will also be available to ATMP developers: see Brévignon-Dodin and Singh, "ATMP in practice" (2009) 15 *Journal of Commercial Biotechnology* 59, 63.

[41] This is further incentivised by a compulsory reduction of the fees payable to the EMA for scientific advice in case the advice is given in respect of ATMPs: a 90 per cent decrease for small and medium-sized enterprises and a 65 per cent decrease for all other applicants.

[42] Regulation 1394/2007 art.17.

[43] *Commission Report* COM(2014) 188 final, para.4.3.2.

[44] Under Annex I to Directive 2001/83.

[45] Regulation 1394/2007, Recital 25 of the Preamble. This is aimed especially at SMEs involved in the first stages of developing ATMPs but needing further resources (capital) to conduct clinical trials and "to facilitate the transfer of research activities to entities with the capacity to market medicinal products": *Commission Report* COM(2014) 188 final, para.2.

are able to prove that "there is a particular public health interest in the Community in the advanced therapy medicinal product concerned".[46]

The "hospital exemption" rule introduced in art.28[47] follows from the recognition by the EU legislator that the development of ATMPs may be driven by the need to provide therapies to individual patients in a clinical setting, and, for this purpose, a separate decentralised authorisation pathway needs to be kept open in this segment of the European market.[48] These are essentially small-scale development processes, the oversight of which could be trusted with the responsible authorities of the Member States. According to the Regulation, the ATMPs covered are products which are "prepared on a non-routine basis according to specific quality standards" and which are used within the same Member State "in a hospital under the exclusive professional responsibility of a medical practitioner".[49] Authorisation may be granted when the use of the product is necessary to "comply with an individual medical prescription for a custom-made product for an individual patient". In order to avoid the "hospital exemption" undermining the objectives of the Regulation, its application comes with the condition that the Member States must ensure that the relevant national product standards and that their application are equivalent to those applicable at the European level.

As indicated earlier, establishing a distinct authorisation pathway for ATMPs and integrating it into the EMA framework required the use of cross-references in the Regulation to the parallel sources of EU medicinal products law. The cross-references also informed developers of the applicable legal requirements contained in other pieces of EU legislation.[50] The "new" European ATMP market thus emerged from existing medicinal products markets, as governed by Regulation 726/2004, Directive 2001/83 and Directive 2004/23.[51] The regulatory framework for this European "super-market" also includes the Clinical Trials Directive, the GMP Directive, the Directives on medical devices (93/42 and 90/385), and the directive on investigational medicinal products (2005/28).[52] Regulation 726/2004 is of particular importance as it lays

[46] Regulation 1394/2007 art.19. The same rule also applies to fees charged by the EMA for post-authorisation activities in the first year following the granting of the marketing authorisation.

[47] Before the adoption of the Regulation, there were claims for a decentralised system of authorisation for autologous products: see Faulkner, "Regulatory Policy as Innovation" (2009) 38 *Research Policy* 637, 643. There is little biological evidence supporting the separate regulatory treatment of autologous and allogeneic products, and the interest of avoiding the mushrooming of unauthorised (unsafe, ineffective or low quality) autologous cell therapies in Europe could support the strict regulatory stance of regulating them together.

[48] It was also expected that non-profit stakeholders will be incentivised to engage in research and development and to produce valuable information on an ATMP before a centralised marketing authorisation before the EMA is made: see *Commission Report* COM(2014) 188 final, para.4.2.

[49] As now regulated in art.3(7) of Directive 2001/83.

[50] Regulation 1394/2007, Recital 6 of the Preamble states that the Regulation is *lex specialis* to the existing EU medicines market regulatory framework, which should be duly applied to ATMPs.

[51] Regulation 726/2004; Directive 2001/83 on the Community code relating to medicinal products for human use [2001] OJ L311/97; Directive 2004/23 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells [2004] OJ L102/48. Cell therapy and gene therapy had already been regulated before the adoption of the Regulation; only tissue engineering needed new regulatory recognition: see Faulkner, "Commensuration and Proliferation" (2012) 4 *Law, Innovation and Technology* 165, 174–175.

[52] Directive 2001/20 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [2001] OJ L121/34; Directive 2003/94 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use [2003] OJ L262/22; Directive 93/42 concerning medical devices [1993] OJ L169/1; Directive 90/385 on the approximation of the laws of the Member States relating to active implantable medical devices [1990] OJ L189/17; Directive 2005/28 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products [2005] OJ L91/13.

down the general rules on the authorisation, supervision and pharmacovigilance of medicinal products, as administered by the EMA. These rules also apply to ATMPs. Directive 2001/83 contains the substantive and procedural rules for obtaining a marketing authorisation for medicinal products for human use. Directive 2004/23 incorporates the standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, which are key source materials for ATMPs. Its provisions apply to ATMPs with the reservation that only the donation, procurement and testing of human cells and tissues are governed by its rules and the remaining aspects of securing source materials for ATMPs are regulated by the specific provisions of the Regulation.[53]

The central regulatory paradigm of the Regulation, which enabled its integration into the existing EU medicinal products regulatory framework, is that a market created for ATMPs—the entry to which is subject to controls in a centralised system of marketing supervision—will deliver the expected scientific, commercial and public health benefits.[54] The EU legislator relied on previous experiences which seem to have confirmed that it is sufficient for EU intervention to focus on risk and to control quality, safety and efficacy in the product market, and that the thereby regulated market will operate in a manner that the public health benefits offered to individual patients and to the general public will outweigh their potential risks.[55] The market paradigm held the attractive promise that development and production can be incentivised through regulation and that scientific and technological change can be harnessed in a sufficiently flexible regulatory framework to the benefit of stakeholders. It also supported some of the more technical choices in regulatory design. Market creation in this particular domain justified the choice of a centralised instead of a decentralised framework for marketing authorisations and controls, and supported—as assessed by the Commission—the introduction of uniform European product standards replacing the fragmented and diverse national standards.[56] These all followed from that desired future state of the ATMP sector as imagined by the EU legislator in which ATMPs are prepared industrially or "manufactured by a method involving an industrial process".[57] The Regulation, however, did not address this matter directly. Beyond the presumption that the commercialisation opportunities offered by the new marketing authorisation pathway may lead to expansion in ATMP development and production, there was not much detail on how the translation of products into publicly available therapies and the resultant scaling up of the sector were going to be achieved.

Experiences and problem areas

The earlier overview of the Regulation already contained a number of indications as to where the weak spots of EU regulatory intervention in the ATMP market might lie. The competition, possibly contradiction, between the twin public health objectives of the Regulation, the insistence on regulating the ATMP sector as a market characterised by large-scale industrial production, and the cursory treatment of the potential

[53] Regulation 1394/2007 art.3.

[54] E.g. innovation, capital for investment, reward for investors and developers, availability of therapies to patients, and the treatment of illnesses through advanced therapies.

[55] Regulation 1394/2007, Recitals 6 and 13 of the Preamble state that the European ATMP market can be regulated satisfactorily focusing on their protection, distribution and use, as in case of other medicinal products for human use.

[56] A decentralised framework would mean that under the mutual recognition principle the Member States would have to trust the quality, safety and efficacy assessments of cell therapies and tissue engineered products made by other Member State authorities, which may rely on inadequate standards or which may lack sufficient scientific expertise. The Commission's 2014 Report already raised considerable suspicion towards the overuse of the "hospital exemption" allowing national authorisation under national standards. For developers, the high burdens of a centralised framework which offers access to the whole EU market need to be measured against the problems of enforcing mutual recognition in case the product is authorised on the basis of laxer national standards.

[57] Regulation 1394/2007, Recital 6 of the Preamble, contrasting it with a non-routine preparation of ATMPs to produce a custom-made product for an individual patient under the "hospital exemption".

ethical complications of ATMPs, in the case that they are erroneously managed in its application, place the Regulation under considerable strain capable of jeopardising its market creation and market integration objectives. Similar concerns may be raised with the Regulation's undertaking that it will provide a stable and predictable framework for the ATMP market and be able to move together with the rapid changes in science and technology in the domain. In general, it is questionable whether the regulatory burden was set for stakeholders, especially for SMEs, at an appropriate level. Ultimately, there is no guarantee that the ATMP market as imagined by the EU legislator will materialise, and it is also uncertain whether EU regulatory intervention, in its current form, has eradicated uncertainty and fragmentation in the nascent ATMP market.

The Commission's review

The 2014 review of the Regulation, which strived to produce an overall positive assessment of the new market,[58] to some extent confirmed these suspicions. The majority of the positive developments noted by the Commission related to the usage of the different incentivising instruments by stakeholders, and its overview of actual developments in the market was not particularly promising. The review could not provide reassurance that stakeholders—in light of the regulatory and administrative burdens imposed on them and considering the related development and maintenance costs—were wholly persuaded by the development and authorisation pathway offered.[59] The Commission was only able to conclude that the situation (i.e. the presence of ATMPs in the market) compared with the pre-Regulation period had not worsened.[60] Its main positive conclusion that the low number of marketing authorisations issued does not automatically mean that the new regulatory framework has stifled innovation in the sector[61] is a spin on the twin objectives of the Regulation. The parallel regulation of the innovation and the safety objectives enables assessing the success of the Regulation not simply as a matter of the number of ATMPs available in the market, but success may also follow from restricting their availability as a result of enforcing adequate quality, safety and efficacy controls. While the Commission is right that the lack of new products in the market does not in itself correlate with insufficient innovation and development, it is also true that the low number of marketing authorisations is alone not indicative of the Regulation ensuring that only the suitable products enter the market, especially when applications for marketing authorisation are scarce.

The review quite openly admitted that the boost to the market expected from EU intervention had so far failed to materialise. It indicated that while there is a promising amount of research in the field, product development processes remain long and there is a considerable translational gap between research and therapy, with significant drops in the number of products in the subsequent phases of the process.[62] It also identified major difficulties for developers, such as the lack of available funding, the lack of regulatory expertise, the low level of investment in the market, and the significant scientific and technological problems faced by researchers which could affect the success of product development.[63] Although the

[58] The Commission rejected a knee-jerk regulatory reaction to the slow emergence of the market by lowering regulatory standards, and it made further commitments to strengthening the Regulation and the balance created among its parallel objectives: see *Commission Report* COM(2014) 188 final, para.5.

[59] The Commission accepted that the marketing authorisation procedure had proven complex to manage and it had been challenging for applicants, especially, from the not-for-profit or the SME sector, and it conceded that "there is room for streamlining" and simplifying the procedure not only for the benefit of applicants, but also in order to ensure the robust assessment of ATMPs: see *Commission Report* COM(2014) 188 final, para.4.5.

[60] *Commission Report* COM(2014) 188 final, para.4.1.

[61] *Commission Report* COM(2014) 188 final, para.4.1.

[62] *Commission Report* COM(2014) 188 final, para.3.

[63] *Commission Report* COM(2014) 188 final, para.3; these are the variability of the source material (e.g. human cells), which make it difficult to demonstrate the homogeneity of the product, small batch sizes and the short shelf-life of the substances make extensive testing impossible, and clinical trials can be impossible under the normal regulatory

incentivising instruments of the Regulation were popular with developers, the Commission had to admit that the new regulatory framework, on the one hand, had not led to an increase in the number of marketing authorisations issued,[64] and on the other, had resulted in significant costs and burdens of regulatory compliance for developers, especially for SMEs.[65] It was recognised, in particular, that the reassessment of pre-Regulation products and development processes had been particularly burdensome for developers,[66] and that compliance in the post-marketing phase may damage the commercial prospects of developers as post-authorisation controls are enforced in the financially delicate period between gaining a marketing authorisation and carving out a market for the new product.[67]

Perhaps the most important threat to the success of the Regulation was identified from within the measure. The alternative decentralised authorisation pathway through the "hospital exemption" received heavy criticism. This was not unexpected, as academic analyses of the Regulation had indicated that despite its necessity so as to ensure the viability of a particular segment of the European ATMP market, the overly generous application of the "hospital exemption" could undermine the Regulation's central objectives,[68] and that the involvement of different national authorities could lead to the fragmentation of standards and cause regulatory uncertainty.[69] The Commission's review expressed clear worries over the Member States potentially abusing the "hospital exemption" and claimed that its widespread use—practically in place of the centralised marketing authorisation route—based on local product standards could be detrimental to public health.[70] The Commission also listed nearly every imaginable threat capable of undermining the ATMP framework: a competitive advantage enjoyed over those using the centralised marketing authorisation route, depriving patients and the market of an important instrument for obtaining and assessing information about the "efficacy and safety profile" of ATMPs, defeating the public health objective of the Regulation through the systematic administration of ATMPs without clinical trials, the

requirements. Further problematic points include: the amount and complexity of data required to support applications (para.4.1.1); the lack of a streamlined authorisation route in case of clear unmet medical needs (para.4.1.1); the lack of a distinction between autologous and allogeneic ATMPs as a matter of the applicable regulatory burden (para.4.4.2); and the separate assessment of the different components of "combined ATMPs" under the Regulation and under the medical devices framework (para.4.4.3).

[64] *Commission Report* COM(2014) 188 final, paras 4–5 and pp.46–47. The marketing authorisation applications submitted so far concerned in part ATMPs that had been available in the market, and in part ATMPs made available after the adoption of the Regulation.

[65] That this is not as simple as on paper is reflected in the considerable transitional period allowed from the 30 December 2008 entry into force of the Regulation for gene and somatic cell therapy products (three years), and for tissue engineered products (four years).

[66] Brévignon-Dodin and Singh, "ATMP in Practice" (2009) 15 *Journal of Commercial Biotechnology* 59, 62, also suggesting that the expected benefits of an integrated market in terms of size and competitive pressure may counterbalance cost implications of compliance.

[67] *Commission Report* COM(2014) 188 final, para.4.8.

[68] It was criticised on grounds of giving unfair competitive advantage to hospitals over SMEs, leading to different standards and a fragmented market on account of different national conceptions of what institutions and in what circumstances should rely on the exemption, enabling deviation from European standards based on an intention of avoiding the costs of compliance with those standards, and of placing much trust in national authorities of effectively enforcing adequately formulated national standards: see Brévignon-Dodin and Singh, "ATMP in Practice" (2009) 15 *Journal of Commercial Biotechnology* 59, 63.

[69] Faulkner, "Regulatory Policy as Innovation" (2009) 38 *Research Policy* 637, 646.

[70] *Commission Report* COM(2014) 188 final, para.4.2. This (i.e. that hospitals produce ATMPs on an industrial scale) had been highlighted before the adoption of the Regulation: see Faulkner, "Regulatory Policy as Innovation" (2009) 38 *Research Policy* 637, 643; and Hughes-Wilson and Mackay, "European Approval System for Advanced Therapies: Good News for Patients and Innovators alike" (2007) 2 *Regenerative Medicine* 5, 6.

fragmentation of the European ATMP market, difficulties in the cross-border administration of nationally authorised ATMPs, and the emergence of divergent national standards and divergent national practices.[71]

Market realities

While opinions may differ regarding whether the current state of the European ATMP sector is an indication of regulatory success or failure, the expectation that regulating the conditions of entry to the market will ensure that a new market and a new industry come to existence was certainly overly optimistic. It had been known to the EU legislator that innovative and development activity was sporadic in this sector and that the translation of research into products and therapies was burdened by severe difficulties of its own.[72] It must also have been clear that the market paradigm favouring the large-scale, industrial production of ATMPs was at odds with the current organisation of the sector populated predominantly by SMEs and public sector developers, and that gaining marketing authorisation for a product is unlikely to secure on its own the desired scaling up of development and production activities.[73] It seems, therefore, legitimate to question whether the selected regulatory paradigm was appropriate considering that it applies a broad-brush, all-purpose approach regulating the ATMP sector and has a limited ability to appreciate the realities of the domain. There remain serious doubts as to whether the Regulation's focus on establishing a risk-benefit balance as a prerequisite for creating a new industry and a new market, which approach dominates the EU's regulatory intervention with new biomedical technologies,[74] and its cursory treatment of non-risk and non-market issues, will not undermine its integrity and effectiveness in the course of its application. The choice of proportionality and subsidiarity as the principles of regulating the non-risk and the non-market issues of the ATMP sector[75] only seems to delay addressing the problems which may arise from the Regulation's somewhat distant treatment of the sector.

The fundamental issue with the Regulation is whether its public health objectives as conjoined by the EU legislator can indeed be successfully realised and reconciled in the application of the Regulation. This depends ultimately on the ability of developers to master the detailed rules governing the development, the authorisation and the marketing of ATMPs, and to produce ATMPs according to those rules which can enter and stay in the European market. While the incentives to use the new regime were reported by the Commission to be popular with developers, this alone does not indicate that the regulatory burden imposed on them was determined at an optimal level.[76] The regulatory hurdles may only be regarded as

[71] *Commission Report* COM(2014) 188 final, para.4.2. Interestingly, the Commission was interested only in the fine-tuning of the hospital exemption by clarifying its scope, ensuring the better notification of results to patients across borders, channelling data to the EMA, and clarifying the availability of further relevant derogations.

[72] Commission, *Human Tissue-engineered Products* (2003) and *Human Tissue-engineered Products* (2005). On the difficulties of translation, see D.M. Smith et al,, "Practicalities to Translation from the Clinic to the Market" in Charles C. Hong et al. (eds), *Chemical Biology in Regenerative Medicine* (Chichester: Wiley, 2014), pp.203–215.

[73] Commission, *Human Tissue-engineered Products* (2003) and *Human Tissue-engineered Products* (2005). On the potential hurdles of scaling up, see C. Wei Teng et al., "An Analysis of Supply-chain Strategies in the Regenerative Medicine Industry—Implications for Future Development" (2014) 149 *Economics of Industrial Production* 211.

[74] Bache et al., "The Defining Features of the European Union's Approach to Regulating New Health Technologies" in *European Law and New Health Technologies* (2013), pp.23 and 29, also holding that the relationship between risk and the creation of new markets must be "constructed as mutually supportive, not oppositional".

[75] Faulkner, "Regulatory Policy as Innovation" (2009) 38 *Research Policy* 637, 643.

[76] For example, Regulation 1394/2007's cross-reference in art.15(3) to the traceability requirements laid down in arts 8 and 14 of the Tissues and Cells Directive (Directive 2004/23) and arts 14 and 24 of the Blood Directive (Directive 2002/98 setting the standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components [2003] OJ L33/30) imposes obligations on developers as severe as establishing and maintaining systems for "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

appropriate for the ATMP sector if the developers which actually populate the market—having regard to their size, expertise or market power—are able to meet their legal obligations. There is something paradoxical in the Regulation's intentions to develop rules for a future ATMP sector in which market-savvy economic operators are responsible for the large-scale industrial production of ATMPs, when this desired transformation requires operators of a completely different economic pedigree to satisfy those rules and scale up their activities accordingly. The Regulation did not really address the fact that extraneous factors may also have an impact on the ability of developers to meet its regulatory burdens. Their failure to secure investment to finance products in the pipeline could threaten their survival in the potentially very long process of achieving the successful commercialisation of a new product. The characteristics of the potential end-markets, for example that these are essentially public markets, may also have an impact on how developers assess their prospects.[77] These circumstances also place considerable pressure on the centralised European marketing authorisation framework in the application of the Regulation. It has to spend effort and resources supporting and enhancing developer compliance, for instance by guiding resource-poor applicants hand-in-hand through the pre- and post-marketing authorisation process.

Certainty and flexibility in regulation

For the Regulation as a legal instrument, the most significant challenge was to satisfy stakeholder expectations for a clear and predictable, yet flexible and adaptable, regulatory framework. It was suggested around the time of the entry into force of the Regulation that the "prescriptive regulatory approach" which needs to be followed in order to create a certain and predictable regulatory environment may undermine the Regulation's ability to react flexibly to scientific and technological change and to promote the development of "innovative and complex" products.[78] There is nothing new in this dilemma for technology regulation.[79] The Regulation—declaredly—was not afraid of bringing the expectations of stability and reliability and the need to address risks in a manner that its application still manages to keep up with scientific and technological change under the same roof.[80] As indicated earlier, the solution was to place at the centre of the marketing authorisation process the assessment of ATMPs by the CAT which is expected ensure that cutting-edge scientific and technological knowledge are integrated into pre- and post-marketing assessment and controls under the Regulation.[81] The CAT was designated a number of

product is used" (art.15(1) (emphasis added)). An obligation of product and patient traceability applies also to the hospital, institution or private practice where the ATMP is used (art.15(2)). See further the obligations laid down in art.15(4)–(6). Their position is not helped by delay in the Commission adopting the guidelines foreseen in art.15(7) on the application of the traceability requirements.

[77] See A. Plagnol et al., "Industry Perceptions to Barriers to Commercialization of Regenerative Medicine Products in the UK" (2009) 4 *Regenerative Medicine* 549; and J. Rose and D. Williams, "The UK relative to other Single Payer-dominated Healthcare Markets for Regenerative Medicine" (2012) 7 *Regenerative Medicine* 429. See, in contrast, the raw data on therapies administered in C. Mason and E. Manzotti, "Regenerative Medicine Cell Therapies: Numbers of Units Manufactured and Patients Treated between 1988 and 2010" (2010) 5 *Regenerative Medicine* 307.

[78] P. Singh et al., "Exploratory Assessment of the Current EU Regulatory Framework for Development of Advanced Therapies" (2010) 16 *Journal of Commercial Biotechnology* 331, 335–336.

[79] See Vergès, "Scientific and Technological Evolution through the Legal Prism" (2014) 6 *Law, Innovation and Technology* 77, and the double expectations from technology regulation (the need for open-endedness ("flexibility") and the need to establish rules of engagement ("consistency")) in R. Brownsword, "So What does the World need Now? Reflections on Regulating Technologies" in R. Brownsword and K. Yeung (eds), *Regulating Technologies: Legal Futures, Regulatory Frames, and Technological Fixes* (Oxford: Hart Publishing, 2008), pp. 23–48 at pp.26–27.

[80] Regulation 1394/2007, Recital 13 of the Preamble refers to a regulatory procedure for ATMPs which "provides for sufficient flexibility, so as to easily accommodate the rapid evolution of science and technology".

[81] In relation to the CAT, see the general discussion on the reduced role of direct legal regulation in new technologies and on the emergence of self-regulation by actors responsible for developing and adopting new technologies in G.

tasks in order to fulfil this role. First, it is available for consultations on "any scientific assessment" of ATMPs regarding their quality, safety and efficacy.[82] It may also give advice to developers to determine whether their product qualifies as an ATMP. The CAT may be required to assist in the production of any further policy documents necessary for the effective application of the Regulation. Finally, it may be requested to provide general advice to the EMA or to the Commission on ATMPs.[83]

This choice of ensuring regulatory adaptability through the involvement of an expert committee is far from being uncontroversial. The CAT is endowed with considerable discretion in matters requiring scientific and technological assessment the boundaries of which are blurred by the uncertainties of the applicable science and also by inevitable progress in science and technology. Arbitrariness in CAT assessments—both in a substantive and in a procedural sense—is, therefore, very difficult to control in law, and there are not many guarantees available—apart from the rules on the terms of office of the members of the CAT[84]—which ensure in law that marketing authorisations are issued without undue delay following an adequate assessment of the product concerned. From the perspective of the CAT as an institutional actor, the risk of failing to meet unmet medical needs could be smaller than that of allowing an unsafe, ineffective or low quality ATMP to enter the market. Thus, the CAT may have a vested interest in slowing down the commercialisation of scientific advances and in erecting scientific entry barriers to the market. Furthermore, its different tasks may put the CAT in the uncomfortable position of representing and pursuing potentially conflicting interests at the same time. On the one hand, the CAT is required to incentivise and support developers so as to ensure their effective compliance with the Regulation, for instance by giving them guidance before they apply for a marketing authorisation. On the other, when examining applications for a marketing authorisation it proceeds in an essentially administrative process as the assessor of the safety, quality and efficacy of the products of the same developers. The dilemma here is that while the effective operation of the Regulation may demand a co-operative relationship between the EMA and developers, the significant legal and financial consequences for developers of the CAT's intervention in its different roles requires regulating a more formal and legally more accurately defined relationship between them. In the current framework, it falls ultimately on the legal remedies against decisions taken under the ATMP framework[85] to ensure that the participation of the CAT and the balance established thereby between regulatory flexibility and predictability are appropriate.

A hollowed-out instrument?

In order to steer away from the potential political and practical pitfalls of regulating the ATMP market, the Regulation opted to rely on the techniques of legislative delegation, legislative cross-references and legislative deference. As mentioned earlier, enacting the substantive rules of ATMP research and development was delegated to the Commission, the integration of ATMPs into existing frameworks of EU medicinal products regulation was ensured by cross-references to the relevant pieces of EU legislation, and the ethical issues of ATMPs were addressed by means of legislative deference to the applicable national rules. These ensured that a legislative text for the Regulation could in fact be prepared and the Regulation could be adopted in the EU decision-making process without undue political and legal delays.[86] The framework nature of the Regulation established in this way suggests that the EU legislator was not

Laurie et al., "Foresighting Futures: Law, New Technologies and the Challenges of Regulating for Uncertainty" (2012) 4 *Law, Innovation and Technology* 1, 9–10.

[82] Especially, on the quality, safety and efficacy of ATMPs, and to pass advice on any data generated in the development of ATMPs.

[83] The full list of tasks is regulated in Regulation 1394/2007 art.23.

[84] Regulation 1394/2007 arts 21 and 23.

[85] Regulated in Directive 726/2004 arts 9 and 10.

[86] Brévignon-Dodin and Singh, "ATMP in practice" (2009) 15 *Journal of Commercial Biotechnology* 59, 60–61.

particularly willing to engage in the comprehensive regulation of some of the most important substantive issues of the ATMP market.[87]

The inability of the Commission to deliver the delegated technological rules in time[88] gives a clear indication that these regulatory techniques are not entirely reliable. The cross-references to other sources of European medicinal products law combined centralised and decentralised structures of market regulation, which brought with it uncertainty and complications for the application of the Regulation.[89] The cross-references themselves are unable to ensure that in the application of the Regulation by a European agency the decentralised regulatory frameworks for medical devices, clinical trials and tissue and cell procurement[90] operating at the national level will be successfully integrated into the centralised framework of the Regulation. These linkages with decentralised regulatory frameworks could jeopardise the very objectives which originally supported the setting up of a centralised marketing authorisation framework for ATMPs. Their unsuccessful combination threatens the integration of the new market and reinforces or reintroduces diversity and fragmentation.[91]

The treatment of the ethics of the ATMP market by means of a legislative deference to the relevant national legal instruments is the most problematic choice of the Regulation.[92] While the regulatory technique itself in its functionality and simplicity is admirable, it practically draws a veil over the conflicts which may arise in the application of the Regulation and which can destabilise the ATMP market.[93] Ethical controversies are most likely to emerge because the Regulation promotes the development and the commercialisation of products the biological source materials of which are predominantly of human origin. The thereby applicable standards of bioethics prohibit the objectification, instrumentalisation and

[87] This largely corresponds with what Bache suggested as being a defining pressure in EU (bio)technology regulation which is to try to "square" the ethical implications of the market and national ethical differences "with the imperative of creating and optimizing the internal market": see Bache et al., "The Defining Features of the European Union's Approach to Regulating New Health Technologies" in *European Law and New Health Technologies* (2013), p.39.

[88] Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (proposed), ENTR/F/2/SF/dn D(2009) 35810. Only the GMP guidelines were adopted, Detailed guidelines on good manufacturing practice specific to advanced therapy medicinal products, ENTR/F/2/SF/dn D(2009) 35810. The adoption of the traceability guidelines is still pending "as additional experience was deemed necessary to better understand the type of adaptations required": see *Commission Report* COM(2014) 188 final, para.3.1. Regulation 1394/2007, Recital 20 of the Preamble saw the early adoption of the guidelines working together with stakeholders as crucial for the operation of the Regulation, mainly because the overall limited expertise on ATMPs available in Europe may not be at the disposal of the EU institutions and agencies, and there is a possibility of EU rules conflicting with the requirement of proportionality.

[89] Questioning whether the compound EU regulatory framework for the marketing authorisation of medical products provides the desired clarity and certainty—considering the potential overlaps between the parallel regulatory frameworks and the participation of different authorities placed at different geographical levels in the interpretation and application of the relevant rules—see Chowdhury, "Common Market but Divergent Regulatory Practices" (2013) 35 *Journal of European Integration* 635.

[90] Decentralisation could be supported by reasons of access, the availability of expertise, or by lacking support for European centralisation. It is a particularly risky scenario under the ATMP framework when the decentralised arrangements offered by the "hospital exemption" are used to avoid the burdens of the decentralised framework for clinical trials in Europe.

[91] Singh, et al., "Exploratory Assessment of the Current EU Regulatory Framework for Development of Advanced Therapies" (2010) 16 *Journal of Commercial Biotechnology* 331, 333.

[92] See Faulkner, "Regulatory Policy as Innovation" (2009) 38 *Research Policy* 637, 644. On the discretion available to Member States in this area, see A. Mahalatchimy, "Access to Advanced Therapy Medicinal Products in the EU: Where do We Stand?" (2001) 18 *European Journal of Health Law* 305.

[93] Human rights and ethics, in the context of EU new healthcare technologies regulation, offer a weak frame for regulation, and operate instead "as a link, inflection and support, or even as a 'false front', for the other frames", such as market-building and risk: see Bache et al., "The Defining Features of the European Union's Approach to Regulating New Health Technologies" in *European Law and New Health Technologies* (2013), p.30.

commodification of human biological material,[94] which stands in sharp contrast with the market paradigm followed by the Regulation and with its intention to reward developers by allowing the commercialisation of their products.[95] This is further exacerbated by the fact that despite the availability of overarching legal instruments, such as the Oviedo Convention on Human Rights and Biomedicine,[96] the ethical standards of human medical biotechnology and its commercialisation are regulated in the different European countries in a different manner and also in a rather diverse cohort of national regulatory instruments governing the different aspects of human biomedical technology.[97] This is particularly valid for an ethically highly controversial source material of ATMPs, human stem cells, including human embryonic stem cells, in the case of which the standards waiting to be applied under the Regulation by the different national regimes vary from permissive to prohibitive.[98] The legal deadlocks which may follow from ethical and legal diversity at the national level concerning the use and the commercialisation of (products containing) human biological material can entail that the same product in the different phases of its development and of its translation into therapies receives contradictory assessments at the European level and in the different Member States. This in turn erodes the central promise of the Regulation of regulatory predictability and consistency and undermines the core objective of integrating national markets and establishing, thereby, a level playing-field for stakeholders.[99]

Value diversity—and diversity in general—can undermine the operation of integrated markets even in more fully harmonised areas of the EU medicinal products market. Here, diversity may be the consequence of national legislation pursuing different bioethical agendas when implementing EU obligations and integrating them into existing ethics-influenced or ethics-based national regulatory constructions. For instance, there is evidence that while some national measures implementing the Tissues and Cells Directive followed a human rights, in particular a human dignity, oriented approach, focusing—for example, through the related non-commodification principle—on the protection of the autonomy and the integrity of the human body and its parts, others were dominated by the principle of informed consent and regulated the related procedures following the aim of asserting the rights of citizens and, in particular the rights of patients over the use of their body.[100] Since as a provider of source materials the tissue and cell "economy"[101] regulated at the national level is a crucial segment of the integrated ATMP market administered, as a rule, at the European level, ethics-induced fragmentation in this domain, for example, by limiting the availability and the use of tissues and cells for ATMP development, and by providing a potential ground for different

[94] See, inter alia, S. Wilkinson, *Bodies for Sale* (London: Routledge, 2003), pp.27–54.

[95] See, inter alia, C. Lenk and K. Beier, "Is the Commercialisation of Human Tissue and Body Material Forbidden in the Countries of the European Union?" (2012) 38 *Journal of Medical Ethics* 342.

[96] Oviedo Convention on Human Rights and Biomedicine, C.E.T.S. 164 (Oviedo Convention).

[97] See M. Favale and A. Plomer, "Fundamental Disjunctions in the EU Legal Order on Human Tissue, Cells and Advanced Regenerative Therapies" (2009) 16 *Maastricht Journal of European and Comparative Law* 89, 95–97.

[98] See, for instance, R. Isasi and B.-M. Knoppers, "Beyond the Permissibility of Embryonic and Stem Cell Research: Substantive Requirements and Procedural Safeguards" (2006) 21 *Human Reproduction* 2474; and R. Isasi and B.-M. Knoppers, "Mind the Gap: Policy Approaches to Embryonic Stem Cell and Cloning Research in 50 Countries" (2006) 13 *European Journal of Health Law* 9.

[99] Brévignon-Dodin and Singh, "ATMP in Practice" (2009) 15 *Journal of Commercial Biotechnology* 59, 64. See also the broader criticism that the regulatory initiatives in the EU in relation to some aspects of working with human tissues and cells "have not led to the desired level of regulatory harmony and the categorization of such products in individual MSs may well represent an obstacle for market entry in the case of particularly innovative products": N. Hoppe, "Innovative Tissue Engineering and its Regulation—the Search for Flexible Rules for Emerging Health Technologies" in *European Law and New Health Technologies* (2013), pp.109–124 at p.109.

[100] Mahalatchimy et al., "The Legal Landscape for Advanced Therapies" (2012) 39 *Journal of Law and Society* 131, 136–137, also mentioning that the institutional set-up could have an effect on the domestic regulatory emphasis, for instance combining procurement issues with marketing authorisation, and potentially with ethical oversight, or keeping these issues separate ensuring that no conflict of interests arise when competing concerns are assessed.

[101] Term borrowed from R. Mitchell and C. Waldby, *Tissue Economies* (Durham, NC: Duke University Press, 2006).

Member States to object to the domestic marketing of ATMPs, can lead to fragmentation in the ATMP market itself.

It seems, therefore, that the choice of legislative deference in the Regulation, which requires a decentralised treatment of the relevant ethical issues, is in conflict with its centralising intentions followed in order to establish an integrated ATMP market. Expecting developers to comply with both sets of rules and making them deal with the diversity of ethics-based regulation at the national level seems to contradict the message of the Regulation that market participants should look at Europe and the EMA when aiming to enter the European ATMP market. Developers are disfavoured in a number of ways. For them, ethics-based rules are part of their overall regulatory burden, and separating these rules as a matter of compliance and its locations from technological rules can be a source of confusion and irritation. Linking regulatory intervention to different geographical locations presents a risk for the integrity of the development process as it may require developers to diversify product development processes irrespective of whether that is scientifically, technologically or financially feasible. Developers involved in cross-border activities because of the resource and infrastructure needs of ATMP research and development are confronted with the task of simultaneous compliance with multiple ethics-based regulatory regimes located at the national level.[102] In the absence of EU harmonisation, the principle of mutual recognition[103] is available to manage regulatory diversity in the ATMP market. However, its ability to resolve conflicts arising from the application of different national rules may be undermined by the incommensurability of national ethical standards, and there is a real risk of the Member States denying horizontal co-operation and maintaining the non-equivalence of the applicable national measures.[104]

The alternative solution of regulating common European ethical standards for the ATMP market was not, however, available to the EU legislator. First, the EU competences system[105] and the subsidiarity principle under art.5 TEU—especially, when interpreted together with the EU's commitment to sustain Member State diversity—prevent the introduction of harmonised rules in these domains. The EU's regulatory intervention in the ATMP market, therefore, had little choice but to accept the competences of the Member States in regulating the ethics of ATMPs even if that meant a departure from its centralised regulatory paradigm. Secondly, the Regulation could not fall back on an unequivocal European moral common ground. Not even the perceivably common European language of human dignity and human rights—as expressed, in particular in the Oviedo Convention—could offer a solution.[106] Human dignity is not available as an ethics-based common *Grundnorm* for European biomedical regulation mainly because it is interpreted and used differently by the different ideologically influenced participants of the bioethical discourse.[107] Although EU legal instruments—either through detailed regulation or by means of morality clauses—have been projecting certain common ethical standards in biomedicine,[108] setting genuine uniform standards following the moral imperatives of human dignity is impeded by the incommensurability of

[102] For example, the importation of human embryonic stem cell lines from one Member State to another.

[103] See *Rewe-Zentral AG v Bundesmonopolverwaltung fur Branntwein (Cassis de Dijon)* (120/78) [1979] E.C.R. 649; [1979] 3 C.M.L.R. 494.

[104] See *Omega Spielhallen - und Automatenaufstellungs GmbH v Bundesstadt Bonn* (C-36/02) [2004] E.C.R. I-9609; [2005] 1 C.M.L.R. 5; and *Dynamic Medien Vertriebs GmbH v Avides Media AG* (C-244/06) [2008] E.C.R. I-505; [2008] 2 C.M.L.R. 23.

[105] See T. Hervey and H. Black, "The European Union and the Governance of Stem Cell Research" (2005) 18 *Maastricht Journal of European and Comparative Law* 11, 18–22.

[106] The pitfalls of choosing human rights as holding the potential for expressing common European ethical standards are discussed in A. Plomer, *The Law and Ethics of Medical Research* (Abingdon: Routledge-Cavendish, 2005).

[107] See R. Brownsword, "Bioethics Today, Bioethics Tomorrow: Stem Cell Research and the 'Dignitarian' Alliance" (2003) 17 *Notre Dame Journal of Law, Ethics and Public Policy* 15.

[108] See Directive 2001/20, Directive 2004/23 and Directive 98/44 on the legal protection of biotechnological inventions [1998] OJ L213/13 arts 5–7.

local ethical standards.[109] EU intervention was, thus, limited to questions of addressing risk and marketability, and it had to swallow the bitter pill that the market created is likely to be threatened by the Member States obstructing its operation on ethical grounds.[110] The Regulation's commitment that national ethical standards will be observed might have been introduced to reassure the Member States, but it may also provide an explicit ground for national opposition to market integration.

The deference to national ethical standards produced that hollowed-out regulatory instrument Brownsword warned against. As a trend in technology regulation, he identified conscious choices by regulators to legitimate their intervention in the service of human biotechnology with reference—based on good reason—to its public benefits, and to ignore the "legitimation crisis" which may follow from the unaddressed ethical issues and ethical diversity.[111] This behaviour follows from the dilemma that, on the one hand, if regulatory instruments are adopted on the basis of a strong, substantive ethical legitimacy, they can be challenged by legitimate claims of ethical diversity at the national level, and, on the other, if measures are based on weak ethical legitimacy—as they address the ethical issues, for instance by means of legislative deference to ethical standards regulated elsewhere—their legitimacy gained through emphasising the public benefits of biotechnology is likely to be eroded when substantive ethics-based opposition to the technology regulated is raised.[112] Such hollowed-out measures keep ethics only as an external benchmark and avoid its internalisation for practical—political or legal—reasons.[113] Pressed for time and pressured to conjure up a new EU biomedical technology market, the EU legislator might have seen this as an appropriate compromise.

Conclusion

The Regulation set out to create an integrated European market for ATMPs by establishing for developers a distinct centralised development and marketing authorisation pathway within the EMA framework. Its efforts to satisfy stakeholder expectation and to vitalise the ATMP sector have, however, been hindered by the challenges of regulating a market characterised by stakeholder vulnerability, uncertainty, rapid evolution and ethical diversity. While its main paradigms correspond with those of EU technology regulation and its regulatory techniques seem appropriate at a technical level, there remain considerable doubts concerning whether the Regulation has managed to address the problems and the needs of the ATMP sector appropriately. Despite the interest of stakeholders in some elements of the new regulatory framework, it seems that for market creation and market integration to happen the EU must first understand the impediments to the successful commercialisation and translation of ATMPs, and it must address the numerous issues left to the application of the Regulation to resolve. Fragmentation and uncertainty in the ATMP market, it seems, remain to haunt stakeholders and call into question the viability of the EU's plans for a large-scale ATMP industry.

[109] See, in the discourse on stem cell patenting, A. Plomer, "Constitutional Limits on Moral Exemptions in European Patent Law" in A. Bakardijeva et al. (eds), *Festskift till Marianne Levin* (Stockholm: Nordsedts Juridik, 2008), pp.487–502.

[110] See Hughes-Wilson and Mackay, "European Approval System for Advanced Therapies" (2007) 2 *Regenerative Medicine* 5, 6.

[111] R. Brownsword, "Human Dignity, Ethical Pluralism, and the Regulation of Modern Biotechnologies" in T. Murphy (ed.), *New Technologies and Human Rights* (Oxford: Oxford University Press, 2009), pp.19–84 at p.40.

[112] Brownsword, "Human Dignity, Ethical Pluralism, and the Regulation of Modern Biotechnologies" in *New Technologies and Human Rights* (2009), pp.19–84 at p.40.

[113] Morality clauses in EU legislation do not necessarily mean the internalisation of ethics in technology regulation as they may be introduced with allowing a margin of appreciation in their application at the national level, as in the case of arts 5–7 of Directive 98/44.