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# *BIOETHICS AND EUROPEAN UNION: THE ADVANCED THERAPY MEDICINAL PRODUCTS' CASE*

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# *BIOETHICS AND EUROPEAN UNION: THE ADVANCED THERAPY MEDICINAL PRODUCTS' CASE*

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**Abstract:**

Advanced Therapy Medicinal Products (ATMP) are medicinal products which are based on human genes, cells and tissues. They are completely framed by European Union Law. They are covered by the European pharmaceutical general legislation and by a *lex specialis*: the regulation (EC) N°1394/2007 on ATMP. This legal framework has been accompanied with the adoption of many guidelines related to ATMP. Furthermore, ATMP raised important ethical questions which can not be ignored: human cloning, research on embryonic stem cells, chimeras … They principally come from the legal difference between the human body and its elements and the products derived from them or containing them.

However, EU law does not provide any treaty provisions conferring powers to the EU institutions to regulate ethical standards as such. EU principally has an economic purpose and ethics would be a Member States' prerogative. Hence, if the EU regulates ATMP and if ATMP and bioethics are undeniably linked, what about bioethics as regards the EU governance of ATMP?

This paper aims to demonstrate that even though the EU does not have a treaty conferred power to regulate ethics; it is active in this field through the regulation of ATMP. On the one hand, the most controversial ethical issues are excluded from the two main binding texts applying to ATMP (i.e. the directive on tissues and cells and the regulation on ATMP). On the other hand, and going beyond these two texts, many particular ethical considerations have been infiltrated within norms directly or indirectly related to ATMP.

*Key words:* Advanced Therapy Medicinal Products, European Union, Bioethics

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Advanced Therapy Medicinal Products (ATMP) are medicinal products which are based on human genes, cells and tissues. They raised important ethical questions which can not be ignored. The main reason for ethical concerns regarding ATMP comes from the legal difference between the human body and its elements and the products derived from them or containing them. The human body elements such as genes, cells and tissues are legally submitted to the regime of persons. As such, they are commonly protected by several human rights principles such as the respect of the human dignity, the respect of the integrity of the human body, the inalienable and inviolable characters, the non-commercialisation principle… However, when they are "transformed" into medicinal products, they are submitted to the market rules as goods or products, which are, by nature, subject to property rights. The distinction between persons and things, as an ancillary well known law rule, has been applied to the human body elements not without some difficulties. The latter are linked to the moral values attached to the human beings and their body. The use of human genes, cells and tissues raised mainly the problematic of human cloning, the level of respect to be given to the embryo and consequently the possible use of human embryonic stem cells. Nevertheless, ATMP lead to the development of new treatments either more efficient or nonexistent hitherto. As such, they would enhance the level of protection of human health. Thus, ATMP are closely linked to bioethics which could be defined as *"the determination, so far as that is possible, of what is right and wrong, good and bad, about the scientific developments and technological developments of biomedicine"*[1].

The European Union (EU) provides a legal framework for ATMP notably to guarantee a high level of health protection for European patients and to foster the competitiveness of European undertakings. Being medicinal products, they are covered by the general European pharmaceutical legislation which is principally constituted of directive 2001/83/EC on the Community code relating to medicinal products for human use[2]. Tissue-engineered products (TEP) lied outside any EU legislation although gene therapy and cell therapy have been regulated as medicinal products under the Community general legal framework. In order to bridge this regulatory gap, the EU institutions agreed on a new regulation addressing all advanced therapies, including TEP within a coherent and single framework.

On 13 November 2007, the European Parliament and the Council adopted the regulation (EC) N°1394/2007 on advanced therapy medicinal products and amending directive 2001/83/EC and regulation (EC) N°726/2004 ( Here after "regulation on ATMP")[3]. It applied from 30 December

[1] D. Callahan, The social sciences and the task of bioethics, Daedalus, 1999, N° 128, p. 275-294

[2] Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, OJ L311, 28.11.2001, p. 67. Directive as amended by Commission Directive 2003/63/EC, OJ L159, 27.06.2003, p 46, and Directive 2004/27/EC, OJ L136, 30/04/2004, p.34

[3] Regulation (EC) N°1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) N°726/2004 OJ L324, 10/12/2007, p.121

2008[4]. The regulation on ATMP is a *lex specialis* setting up a legal system stricter than the one enforceable to other medicinal products.

Human cells and tissues contained in ATMP are covered by directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells[5] (here after "directive on tissues and cells") for donation, procurement and testing while further aspects are covered by the regulation on ATMP[6]. The regulation on ATMP also referred to directive 2001/20/EC[7] on clinical trials[8] and to several guidelines for which the adoption is done or ongoing related to the specificities of ATMP regarding good clinical practices, good manufacturing practices, risk management…

Hence, if the EU regulates ATMP and if ATMP and bioethics are undeniably linked, what about bioethics as regards the EU governance of ATMP?

The adoption of the directive on tissues and cells and of the regulation on ATMP reflects the political conflict between the European Commission and the Council as well as the European Parliament regarding the EU competence to legislate on ethical matters. Although ATMP are completely framed at EU level, ethics is considered to be a prerogative of Member States. According to the principle of the conferred competences, "*the Union shall pursue its objective by appropriate means commensurate with the competences which are conferred upon it in the Treaties*"[9]. But there are no treaty provisions conferring powers to the EU institutions to regulate ethical standards as such. EU principally has an economic purpose (its vocation was originally purely economical) whereas ethical choices representing the fundamental values of the society come under national authorities and the direct expression of their political views[10]. Indeed, the European Commission supported by the Council considers that "*regulating on ethical matters is the competence of Member States*"[11]. In the same way *"the Commission also asserted that the principle of subsidiarity*

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[4] However, article 29 of the regulation on ATMP provides a transitional period. Advanced therapy medicinal products "which were legally on the Community market in accordance with national or Community legislation on 30 December 2008", shall comply with this regulation no later than 30 December 2012 for tissue engineered products and no later than 30 December 2011 for the others. This period is important because it implies no treatment interruption. However, the expression "legally on the market" is raising problems. Indeed, there are differences of what is "legally on the market" or not according to the Member States.

[5] Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L102, 07/04/2004, p. 48

[6] Article 3 and Recital (14) of the regulation on ATMP, cf. note 3

[7] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 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, OJ L121, 01/05/2001, p. 34

[8] Article 4 and Recital (16) of the regulation on ATMP, cf. note 3

[9] Article 3§6 of the consolidated version of the Treaty on European Union, OJ C83, 30/03/2010, p. 13 (ex-article 5§1 of the European Community Treaty). However, the doctrine of implied powers and ex-article 308 of the EC Treaty (new article 352 of the Treaty on the functioning of the European Union, OJ C83, 30/03/2010, p. 47-199) undermine this principle. See notably, S. Douglas-Scott, Constitutional Law on the European Union, 21 June 2002, Longman, p. 160; J.H. Weiler, The transformation of Europe, Yale Law Journal, 1991, V. 100, p. 2403.

[10] M. Tallacchini, Governing by values. EU Ethics: Soft Tool, Hard Effects, Minerva, 2009, N° 47, p. 281-306

[11] Commission report on embryonic stem cell research provides basis for discussion on ethics, Brussels, 7 April 2003, IP/03/506.

*demands that the Commission leave the "prerogatives to legislate on matters of ethics to the Member States themselves"* and consequently the Commission is unable to *"impose any constraints on the freedom of states to lay down the conditions under which they wish to regulate research"*[12].

Nevertheless, the adoption of texts (binding or not) applying to ATMP is part of the EU initiative to enlarge its intervention on economics to include health and to become a wider political Union. The legal basis of the Treaties at issue are article 168§4a [ex-article 152§4 of the European Community Treaty (Here after "EC Treaty")] on the protection of human health and article 114 (ex-article 95 of the EC Treaty) on the approximation of laws regarding the establishment and the functioning of the internal market. The directive on tissues and cells is based on ex-article 152§4 of the EC Treaty whereas the regulation on ATMP is based on ex-article 95 of the EC Treaty. It is notably through the adoption's processes of these two binding texts that the European Parliament hardly defended the integration of ethical aspects within the EU legislation. But the European Parliament also sustains ethical positions through non binding law such as its numerous resolutions against human cloning[13]. The European Commission also got interested in ethics – historically, she was the first one with the Biotechnology Initiative in 1980's[14]- and emphasized the need for ethical discussions on the development of biotechnology[15]. In 1991, the establishment of the Group of Advisers on the Ethical Implications of Biotechnology (which became the European Group on Ethics in Science and New Technologies (EGE) when its areas of applications were extended[16]) implied that ethics will always be, at least, "considered" within the EU in these areas. Its opinions even non binding have a strong weight and have been very often mentioned during the adoption of binding texts related to biotechnology, such as those related to ATMP. Even if the EU does not have a conferred competence in ethics, it is however active in this field through questions of ATMP which are closely linked.

Focusing on the principal texts related to ATMP, i.e. the directive on tissues and cells and the regulation on ATMP, it appears that the most ethical controversies related to human cloning, chimera and hybrid and embryonic cells were widely discussed at the European Parliament. Even though the latter pressed on the Council and the Commission, most of its amendments were defeated. This paper will highlight the way of exclusion of the most sensitive ethical controversies during the adoption of the

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[12] In response to European Parliament Question P-2852/00, cited in T. K. Hervey and H. Black, The European Union and the Governance of stem cell research, Maastricht Journal of European and Comparative Law, 2005, 12 (3), p. 11- 48

[13] Resolutions of the European Parliament on the ethical and legal problems of genetic engineering and "in vivo" and "in vitro" artificial insemination of 16 March 1989; on the cloning of human embryos of 28 October 1993; on cloning of 20 September 1996 and 12 March 1997; on human cloning of 15 January 1998, 30 March 2000 and 7 September 2000.

[14] COM (1983) 672; see S. Hennette-Vauchez, L'émergence d'un droit communautaire de la biomédecine, RTD eur. 45 (1), Janv.-mars 2009

[15] Commission's Communication to the European Parliament and Council 'Promoting the competitive environment for industrial activities based on biotechnology within the Community', 1991, (SEC (91) 629 final). According to M. Tallacchini, "after the first European ethics body was created, the language of the Commission suddenly changed radically, shifting from the need for market normalization and legitimation to an ad hoc narrative about ethics as a way to "represent" citizens' values, to bring society closer to European institutions and to establish the European identity", cf. note 10

[16] Commission Decision on the renewal of the mandate of the European Group on Ethics in Science and New Technologies, 11 May 2005, 2005/383/EC

directive on tissues and cells and of the regulation on ATMP (I). Then, through a wider approach going beyond the two texts studied in the first part, it will be shown that some specific ethical aspects are nevertheless part of the EU governance of ATMP. Even if the EU uses a flexible approach, several ethical principles or considerations within texts related to ATMP can be identified (II).

## I. The exclusion of the most controversial ethical issues

Focusing on the directive on tissues and cells and on the regulation on ATMP, it will be shown up what are the main so-called "ethical amendments" of the European Parliament regarding particular "ethically sensitive" tissues and cells and products derived from them which were not retained in the final text of regulation on ATMP and/or of directive on tissues and cells. However, this part is not exhaustive regarding all of the controversies raised by ATMP.

### A. European Parliament's arguments regarding ethical controversies raised by ATMP

The European Parliament which represents the European citizens became the most protective EU institution regarding ethical values. An analysis of its proposed amendments during the adoption of the directive on tissues and cells and the regulation on ATMP confirms this reality. The main so called 'ethical amendments' of the European Parliament are related to human cloning, human-animal hybrids or chimeras and to the modification of the germ line (1) as well as particular tissues and cells, especially human embryonic cells and products derived from them (2).

#### 1. Human cloning, hybrids or chimeras and modification of the germ line

Regarding the directive on tissues and cells, the main "ethical amendments" of the European Parliament aims principally to prohibit human cloning.

Firstly, the European Parliament provided that Member States must explicitly ban the use of tissues and cells from cloned human embryos and of hybrids derived from germ cells or totipotent cells of human origin[17]. This mandatory ban was based on ethical reasons, on reasons connected with "*the*

[17] Amendment 8, Recital (7) of the European Parliament in 1st reading, Report on the proposal for a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells (COM(2002) 319 – C5-0302/2002 – 2002/0128(COD)), 25 March 2003, A5-0103/2003

*extremely high medical risk involved*" and on the repeatedly oppositions of the European Parliament[18] and the Council of Europe[19] on any form of human cloning.

Secondly, Member States shall at least prohibit research on human cloning for reproductive purposes and research designed to create human embryos solely for research purposes or to supply stem cells, including by means of the somatic cell nuclear transfer. Inversely to the associated justification, these activities undermine respect for life and human dignity and involve the use of human beings including the embryo as a material[20]. As a consequence, the European Parliament tried to make binding the prohibition of any form of human cloning which it repeatedly claimed.

Regarding the regulation on ATMP, three Committees of the European Parliament were in charge of the European Commission proposal on ATMP: the Committee on the Environment, Public Health and Food Safety (ENVI), the Committee on Industry, Research and Energy (ITRE) and the Committee on Legal Affairs (JURI). Their amendments notably aim to prohibit products which modify the human germ line and/or which are derived from human-animal hybrids or chimeras.

On the one hand, these three Committees uphold the integration of a ban on products modifying the human germ line: *"No authorisation shall be granted to products modifying the germ line genetic identity of human beings"*[21]. It was justified by reference to the Oviedo Convention which makes clear that human dignity is compromised when the inheritance of genetic identity is altered. Moreover, products which modify the human germ line are excluded from clinical trials by directive 2001/20/EC[22] and they are not legally patentable under directive 98/44/EC[23]. Thus, to be harmonised with the existing EU legislation, they should not be eligible for authorisation under the regulation on ATMP.

On the other hand, ENVI, JURI and ITRE also wished to integrate a ban on products derived from human-animal hybrids or chimeras or containing tissues or cells originating or derived from human animal hybrids or chimeras. However, the transplantation of somatic animal cells or tissues to

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[18] Reference is made to several resolutions of the European Parliament (cf. note 13) and to the European Parliament and Council Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions, OJ L 213, 30.7.1998, p. 13–21.

[19] Reference is made to the Convention for the protection of human rights and the dignity of the human person with regard to the application of biology and medicine (4 April 1997) and the annexed protocol prohibiting the cloning of human beings (12 January 1998); and Recommendation 1046 of the Council of Europe Parliamentary Assembly on the use of human embryos and foetuses in scientific research (24 September 1986).

[20] "The European Union like the Member States should regulate and focus research efforts on techniques that do not undermine respect for life and human dignity and should prohibit any technique involving the use of human beings as a material, even at the embryo stage", Justification Amendment 30, article 4§2b (new) of the European Parliament in 1st reading, cf. note 17

[21] Amendment 14 of ITRE, Opinion, 20/06/2006, Amendment 19 of JURI, Opinion, 17/07/2006, and Amendment 21 of ENVI, Draft Report on the proposal for a regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (COM(2005)0567 – C6-0401/2005 – 2005/0227(COD)), 30/05/2006, provisional 2005/0227 (COD).

[22] "No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity", Article 9§6 of Directive 2001/20/EC

[23] Article 6§2 (b) of Directive 98/44/EC, cf. note 18

the human body for therapeutics purposes or xenotransplantation would be allowed *"as far as it does not interfere with the germ line*"[24]. These Committees justified this ban recalling that the physical and mental integrity of the person and human dignity must be respected as it is underlined in articles 1 and 3 of the Charter of Fundamental Rights of the EU (here after "the EU Charter")[25]. They consider that *"the creation of human-animal hybrids or chimeras is a threat to the right to integrity of a person and a violation of human dignity*"[26]. ENVI and JURI also provided definitions[27] for "chimera"[28] and "hybrid"[29]. ENVI's Committee also added that *"the Directive 98/44/EC on the legal protection of biotechnological inventions stresses that the production of chimeras from germ cells is excluded from patentability. Therefore, no authorisation under this regulation should be granted to products containing or derived from such tissues and cells"*[30].

2. Embryonic stem cells and products derived from them

The adoption of a directive on tissues and cells gave rise to numerous tensions around the regulation of specific cells and tissues especially embryonic stem cells. Once again, the European Parliament introduced several "ethical amendments". The main ones will be considered.

Firstly, it tried to introduce a right of Member States to prohibit the use of particular cells, which should be especially germ cells, foetal and embryonic cells: Member States have a **right** to ban donation, experimentation, processing, storage, distribution and use of any other kind of particular cells or human tissues or of cells of a particular origin and of products originating from particular tissues or cells, or particular tissues or cells having a particular origin.[31]

Secondly, the European Parliament encouraged the use of "insensitive" or at least the less sensitive cells and tissues by specific positive **actions**: the promotion at EU and Member States levels

[24] See notably: Amendments 22 of the Draft Report on the proposal for a regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (COM(2005)0567 – C6-0401/2005 – 2005/0227(COD)), 30/05/2006, provisional 2005/0227 (COD); Amendments 20 of the JURI's Opinion

[25] OJ C 364, 18/12/2000, p. 1-22

[26] See notably: Amendments 6and 22 of the Draft Report on the proposal for a regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (COM(2005)0567 – C6-0401/2005 – 2005/0227(COD)), 30/05/2006, provisional 2005/0227 (COD); Amendments 3 of the ITRE's Opinion; Amendments 5 and 20 of the JURI's Opinion

[27] These definitions are based on the Canadian assisted human reproduction Act of 2004.

[28] "Chimera means: an embryo into which a cell of any non-human life form has been introduced; or an embryo of any non-human life form into which a human cell has been introduced; or an embryo that consists of cells of more than one embryo, foetus or human being", Amendment 15 of JURI's Opinion and Amendment 18 of ENVI, Draft Report. The second possibility of meaning for "chimera" comes from the JURI'S Opinion.

[29] "Hybrid means: a human ovum that has been fertilised by a sperm of a non-human life form; an ovum of a non-human life form that has been fertilised by a human sperm; a human ovum into which the nucleus of a cell of a non-human life form has been introduced; an ovum of a non-human life form into which the nucleus of a human cell has been introduced; or a human ovum or an ovum of a nonhuman life form that otherwise contains haploid sets of chromosomes from both a human being and a non-human life form", Amendment 16 of JURI's Opinion and Amendment 19 of ENVI, Draft Report.

[30] Amendment 20 of the JURI's Opinion

[31] The ban may also be extended to the importation of such tissues or cells or products. Amendment 8 of the European Parliament in 1st reading, recital (7), cf. note 17

and obstacles'removal. It underlines *"there is no consensus within the European Union as to whether, and in what circumstances, embryonic stem cells may be processed. The processing of stem cells, and in particular the creation of stem cells in cases in which the embryos from which they originate has to be destroyed, is scientifically and ethically controversial and illegal in many Member States"*[32]. On the contrary, the processing of adult stem cells and of stem cells from the umbilical cord seems to be not (or rather less) scientifically and ethically controversial within EU Member States. That is why, such non controversial alternative solutions should be specifically promoted by the EU and the Member States and obstacles must be removed.

Thirdly, the European Parliament considered that if Member States authorise the use of particular tissues and cells, they should respect the minimum quality and safety standards laid down by the directive as every tissues and cells shall be covered. Hence, it proposed a new paragraph 1a for article 2 providing that *"this Directive shall also apply to: a) haematopoietic peripheral blood, placenta and bone marrow stem cells; b) reproductive cells (eggs, sperm); c) feotal tissues and cells, adult and embryonic stem cells"*[33]. The logic of the European Parliament could be the following: If it is legally unfeasible and/or politically unacceptable to make compulsory for Member States to ban the use of ethically sensitive tissues and cells, at least their uses should be controlled by the respects of minimum standards. But minimum standards should be extended to specific standards for sensitive tissues and cells: Additional tests should also be required for embryonic stem cells, and cells and tissues derived from them given rise to their *"well-established inherent ability to form tumours […] and their potential to form cancer through many different routes"*[34].

In the same way, the European Parliament considered that if Member States do not prohibit the use of germ cells and embryonic and foetal stem cells (which shall respect the directive's standards), they shall specifically regulate the use of cells of an ethically 'sensitive' origin *"by means of appropriate legislation"*[35].

Therefore, the European Parliament did not try to integrate direct mandatory ban on the use of particular tissues and cells such as germ cells and foetal and embryonic stem cells. However, it used strong disincentives: a right to ban for Member States, the promotion of non controversial alternative solutions, and control by the insertion within the scope of the directive and by specific appropriate national legislation.

Regarding the regulation on ATMP, the European Commission tried to avoid the sensitive debate on the use of human embryonic stem cells (hESC), which already took place during the

[32] Amendment 9, recital 7a (new) of the European Parliament in 1st reading, cf. note 17
[33] Amendment 20, article 2§1a (new) of the European Parliament in 1st reading, cf. note 17
[34] Amendment 73, annex V section 2a (new) of the European Parliament in 1st reading, cf. note 17
[35] Amendment 31, article 4§4a (new) of the European Parliament in 1st reading, cf. note 17

adoption of the directive on tissues and cells[36]: *"The issue of embryonic stem cells was extensively debated during the adoption of the Directive on the quality and safety of human tissues and cells (Directive 2004/23/EC). In this context, the legislators have recognised that there is, to date, no consensus among Member States upon which harmonised decisions at EU level could be taken on the use or prohibition of embryonic stem cells"*. Therefore, the European Commission suggested to follow the same logic than the one followed for the directive on tissues and cells: a Member State can authorise or forbid the use of a specific kind of human cells, such as hESC, as *"the regulation of advanced therapy medicinal products at Community level should not interfere with such decisions"*[37]. Consequently, article 28 of the proposal modifies the directive 2001/83/EC as following: "*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. The Member States shall communicate the national legislation concerned to the Commission"*[38].

However, the JURI's Committee tried to exclude explicitly ethical controversies related to hESC from the proposal. It principally proposed to exclude ATMP that *"contain or are derived from human embryonic and foetal cells, primordial germ cells and cells derived from those cells*"[39]. The justification of such amendment has to be found under recital (6): this regulation is based on ex-article 95 of the EC Treaty which is a single market harmonisation measure: *"It is not designed to cover situations in which significant national legislative differences are intended to remain (c.f. ECJ Case C-376/98[40]). It is therefore necessary to exclude from the scope of this regulation products using materials which are controversial and for which differing Member States legislative provisions are intended to remain. In any case, products using these materials are unlikely to be ready to be placed on the market in the foreseeable future*"[41].

Thus, according to the JURI's Committee, as products based on embryonic and foetal cells are sensitive from an ethical point of view, they could not be covered by a harmonisation measure (a regulation based on ex-article 95 of the EC Treaty), otherwise Member States would enforce different legal rules. Moreover, the JURI's Committee provides that Member states have the right to refer to article 30 of

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[36] See M. Blanquet et N. De Grove-Valdeyron, « Les enjeux et les apports du règlement communautaire concernant les médicaments de thérapie innovante », RAE 2006/4, p. 687 and M. Favale and A. Plomer, « Fundamental disjunctions in the EU legal order on human tissue, cells & adavanced regenerative therapies », Maastricht Journal of European and Comparative Law, 2009, 16 (1), p. 89-111.

[37] "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", recital (6) of the European Commission proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 {SEC(2005) 1444}, COM/2005/0567 final - COD 2005/0227

[38] New article 4§5 of directive 2001/83/EC created by article 28 of the European Commission proposal, cf. note 37.

[39] Amendment 12 of the JURI's Opinion

[40] According to this case-law : regarding public health, "the Treaty excludes any harmonisation of laws and regulations of the Member States designed to protect and improve human health […] Other articles of the Treaty may not, however, be used as a legal basis in order to circumvent the express exclusion of harmonisation".

[41] Amendment 2 of the JURI's Opinion

the EC Treaty when they want to prohibit or restrict the access of certain medicinal products (such as those based on hESC) to their market as this regulation is a partial harmonisation measure[42].

Most of the above-mentioned ethical amendments of the European Parliament were rejected. They were related to the most controversial aspects related to ATMP on which Member States' approaches are very diverse. Far away to do a choice at the European level even through a flexible manner on the most sensitive questions, they are relied on Member States which benefit from a wide action margin within the final version of the directive on tissues and cells and the regulation on ATMP

B. The final versions of the directive on tissues and cells and the regulation on ATMP

Concerning the directive on tissues and cells, most of the so-called "ethical" amendments of the European Parliament have been defeated and especially those related to the prohibition of research on human cloning, the use of tissues and cells from cloned human embryos and of hybrids derived from germ cells or totipotent cells of human origin. The legal basis for the directive on tissues and cells was ex-article 152§4 of the EC Treaty (new article 168§4a) on the protection of human health. According to the European Commission and the Council[43], ethical provisions proposed by the European Parliament cannot be accepted as *"they fall outside the scope of Article 152 that provides for public health protection and not the implementation of ethical objectives as such"*[44]. The European Parliament had argued that this justification given by the Commission and the Council was *"formal"* and *"by no means valid"* as "*all the 'ethical issues' addressed are also linked to protecting the health of donors and recipients"*[45]. This argument has been taken into account regarding the ethical principles of donation[46] but not regarding the use of particular cells and tissues.

However, the European Parliament obtained the extension of the scope of directive on tissues and cells even though it is a recital which is not legally binding contrary to the articles of the directive. It provides: *"This Directive should apply to tissues and cells including haematopoietic peripheral blood, umbilical-cord*

[42] Amendment 43 of the JURI's Opinion

[43] "In particular, the Council shares the Commission's argument that amendments of an ethical nature are not acceptable, since they fall outside the scope of Article 152 of the Treaty", Common Position adopted by the Council Council with a view to the adoption of a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells, 9 July 2003, 10133/03

[44] See Amended Proposal for a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells (presented by the Commission pursuant to Article 250 (2) of the EC Treaty), COM/2003/0340 final - COD 2002/0128

[45] Explanatory Statement, European Parliament, Recommendation for second reading on the Council common position adopting a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (10133/3/2003 – C5-0416/2003 – 2002/0128(COD)), 12 November 2003, A5-0387/2003

[46] See part II. Of this article

*(blood) and bone-marrow stem cells, reproductive cells (eggs, sperm), foetal tissues and cells and adult and embryonic stem cells"*[47].

Furthermore, the final text of the directive does not provide a right for Member States to ban the use of particular tissues and cells it only provides the directive *"**should not interfere with**"*[48] and *"**does not affect**"*[49] the decisions of the Member States prohibiting the donation, procurement, testing, processing, preservation, storage, distribution or use of any specific type of human tissues or cells or cells from any specified source, including germ cells and embryonic stem cells.

Even though most of the amendments were not retained regarding the most sensitive issues on particular cells and tissues, the European Parliament obtained to protect them by their insertion within the scope of the directive. Consequently, the minimum quality and safety standards are the same in all of the EU member States even regarding specific type of human tissues or cells or cells from any specified source, including germ cells and embryonic stem cells. Member States are free to authorise or prohibit their uses but if they are authorised, they should respect the provisions of the directive on tissues and cells.

Concerning the regulation on ATMP, the amendments of the European Parliament which provided a ban for products which modify the human germ line and/or which are derived from human-animal hybrids or chimeras were defeated. The Council also rejected the exclusion of ATMP that contain or are derived from human embryonic and foetal cells, primordial germ cells and cells derived from those cells. It is interesting to notice that the exclusion of such products from the scope of the regulation on ATMP would have deprived them of the benefit of the numerous incentives and notably the economical ones provided by this regulation. It would thus have been more economically interesting to develop "insensitive" or "more ethical" ATMP[50]. Paradoxically, it would also have impeded any control on them whereas the requirements of the regulation on ATMP are quite "heavy" notably regarding traceability and stricter than those provided for "classical" medicinal products. The approach of the European Parliament which wished to exclude sensitive ATMP from the scope of the regulation on ATMP is contrary to the one it had regarding the integration of sensitive tissues and cells within the scope of the directive on tissues and cells.

Furthermore, similarly to the directive on tissues and cells, the regulation on ATMP *"**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"*[51]. And according to article 28§3 which amends directive

[47] Recital (7) of Directive 2004/23/EC, cf. note 5
[48] Recital (12) of Directive 2004/23/EC, cf. note 5
[49] Article 4§3 of Directive 2004/23/EC, cf. note 5
[50] Cf. note 36
[51] Recital (7) of Regulation (EC) N°1394/2007, cf. note 3

2001/83/EC by adding the following article 4§5: "*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. The Member States shall communicate the national legislation concerned to the Commission. The Commission shall make this information publicly available in a register"*. It could be noticed that the text of article 28 of the regulation on ATMP is more cautious than article 4§3 of the directive on tissues and cells as the terms *"**shall not affect**"* are used instead of *"**does not affect**"*.

Finally, the regulation on ATMP avoids any position regarding the controversies on which Member States are divided such as the use of human embryonic cells. It just follows the approach of the directive on tissues and cells.

It is therefore interesting to highlight that the uses of the most "ethically sensitive" tissues and cells- such as human embryonic stem cells- and products which are derived from them, are respectively covered by the directive on tissues and cells and by regulation on ATMP if they are authorised according to the concerned national legislation. Member States are left free to prohibit the donation, procurement, testing, processing, preservation, storage, distribution or use of any specific type of human tissues or cells. They are also free to adopt restrictive rules reflecting national cultures on 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. In both texts, the action margin of Member States is very wide. It relies on the subsidiarity principle and on the partial harmonisation. On the one hand, the subsidiarity principle requires, in areas which do not fall under the exclusive competence of the Community, that the Union should only act when the proposed objectives cannot be sufficiently achieved by the Member States and can be better achieved by the Community[52]. On the other hand, Article 28 of the regulation on ATMP permits Member States to apply national legislations prohibiting or restricting the use of any specific type of human or animal cells, *"on grounds not dealt with the aforementioned Community legislation"*. Even though the explicit reference to ex-article 30 of the EC Treaty[53] was defeated, ATMP could benefit from its limitations given rise to the partial harmonisation of the regulation on ATMP and to the principle of free movement of goods enforceable to ATMP. The public morality would probably be the most relevant limitations which could be invoked by Member States to restrict or prohibit the use of "specific type" of medicinal products. However, they have to

[52] Article 5 of the EC Treaty
[53] Article 36 of the Treaty on the functioning of the European Union, OJ C83, 30/03/2010, p. 47-199

respect the proportionality principle[54]. Also, Member States measures shall not constitute *"a means of arbitrary discrimination or a disguised restriction on trade between Member States"*[55].

Even if the EU considers that regulating ethics is a Member States' prerogative, ethical aspects can be found within the EU legislation and within non binding law. In spite of the defeat of the most controversial amendments, especially regarding human embryonic cells, several ethical aspects have been infiltrated within the EU texts applying to ATMP. Beyond the directive on tissues and cells and the regulation on ATMP, ethical considerations are present at almost all stages of ATMP development.

## II. The infiltration of particular ethical considerations

Ethics and ethical principles have been taken into account and recognised during all stages of development of ATMP from research until commercialisation going beyond the directive on tissues and cells and the regulation on ATMP. Considering binding norms as well as non binding norms, the manner to integrate ethics always reflects flexibility. This part aims to identify the ethical principles and considerations within the norms related to ATMP and demonstrate the EU flexibility approach in this context. The studied norms are either directly (1) or indirectly (2) related to ATMP.

### A. Norms directly related to ATMP

The norms which are directly related to ATMP and which include ethical principles are the directive on tissues and cells, the directive on clinical trials and the regulation on ATMP. These norms as EU secondary law are binding. Moreover, there are also many guidelines (non binding) which are related to ATMP. They have been adopted by the European Medicines Agency with the involvement of the Committee for Advanced Therapy (CAT) and/or the Committee for Medicinal Product for Human Use (CHMP)[56], and/or by the European Commission. Most of the time, these guidelines do not contain ethical aspects as they are very technical, but they always refer to above-mentioned relevant secondary law. However, we will pay attention to one guideline adopted by the European Commission and related to clinical trials which contains ethical considerations.

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[54] "restrictions may be justified only if they are suitable for securing the attainment of the objective pursued and do not go beyond what is necessary in order to attain it": see Case C-36/02 *Omega* [2004] ECR I-9609, paragraph 36, and Case C-438/05 *International Transport Workers' Federation and Finnish Seamen's Union* [2007] ECR I-0000, paragraph 75

[55] See note 53

[56] Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products, 20 November 2008, EMEA/149995/2005; Procedural Advice on the certification of quality and non-clinical data for small and medium-sized enterprises developing Advanced Therapy Medicinal Products, 17 April 2009, EMEA/CAT/418458/2008 (corr. 1 (23/09/09),…

It should preliminary be noticed that a kind of sliding occurred as ethical aspects are sometimes considered either on the ground of fundamental rights or on the ground of safety and public health objectives[57].

On the one hand, regarding fundamental rights, the directive on clinical trials provides that *"the accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration"*[58]. Moreover, both the directive on tissues and cells and the regulation on ATMP respect the fundamental rights and observe the principles reflected in the EU Charter and take into account as appropriate the Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine[59]. The EU Charter recognizes the human dignity and accordingly the right to the integrity of the person especially in the fields of biology and medicine with the free and informed consent, the prohibition of eugenic practices, the prohibition on making the human body and its parts as such a source of financial gain, the prohibition of the reproductive cloning of human beings[60]. Although, the European Parliament tried to encompass the respect of the fundamental rights, the EU Charter and the Oviedo Convention within the directive's body, these amendments were never retained. With the Lisbon Treaty[61], which entered into force on 1st December 2009, the EU Charter obtained the same legal value as the Treaties[62] and the European Union *"shall accede to the European Convention for the Protection of Human Rights and Fundamental Freedoms"*[63]. But the formulation used regarding these principles within the EU Charter and the Oviedo Convention let a wide margin of discretion to Member States. It permits to maintain an acceptable co-existence of the Member States specific rules which express their moral and legal national political choices.

On the other hand, regarding safety and public health objectives, both the directive on tissues and cells and the regulation on ATMP notably provides that *"Voluntary and unpaid tissue and cell donations are a factor which may contribute to high safety standards for tissues and cells and therefore to the protection of human health"*[64]. Recital (2) of the regulation on ATMP also provides that *"the essential aim of any rules governing their [ATMP] production, distribution and use must be to safeguard public health"*. Similarly, Recital (2) of the directive on tissues and cells provides *" […]In order to safeguard public health and to prevent the transmission of*

[57] See M. Blanquet et N. De Grove-Valdeyron, « Les enjeux et les apports du règlement communautaire concernant les médicaments de thérapie innovante », RAE 2006/4, p. 687.
[58] Recital (2) of the directive 2001/20/EC, cf. note 7
[59] Recital (22) of Directive 2004/23/EC, cf. note 5 and recital (8) of Regulation (EC) N° 1394/2007, cf. note 3
[60] Article 3§2 of the EU Charter, cf. note 25
[61] Treaty of Lisbon amending the Treaty on the European Union and the Treaty establishing the European Community, signed at Lisbon, 13 December 2007, OJ C 306, 17/12/2007, p. 1.
[62] Article 6§1 of the consolidated version of the Treaty on European Union, OJ C 83 of 30/03/2010, p. 13
[63] Article 6§2 of the consolidated version of the Treaty on European Union, OJ C 83 of 30/03/2010, p. 13
[64] Recital (19) of directive 2004/23/EC, cf. note 5 and Recital (15) of Regulation (EC) N° 1394/2007, cf. note 3

*infectious diseases by these tissues and cells, all safety measures need to be taken during their donation, procurement, testing, processing, preservation, storage, distribution and use".*

In this presented context of respect of human rights and protection of safety and public health, more specific ethical issues are taken into account.

Firstly, the directive on tissues and cells applies to ATMP which contains human tissues and cells for the donation, procurement and testing of those cells or tissues[65]. This directive on tissues and cells includes ethical principles which obtained a legal value given rise to their integration within the directive. Indeed, these principles are provided by the "recitals" but also by the article of the directive. However, according to S. Hennette-Vauchez, ethical principles originally only appeared within the recitals of the directives[66]. In 1993, the EGE provided: *"Yet, it is wondering whether the amendments [regarding ethical considerations] are to be considered as part of the directive's body. The appropriate place to address and resolve some of those considerations seems to be the recitals of the directive"*[67]. But, in the most recent texts, such as the directive on tissues and cells and regulation on ATMP, ethical considerations are placed in the recitals as well as in the directive's or regulation's body within the articles.

The main ethical and legal principles which can be identified within the directive on tissues and cells are: voluntary and unpaid donations, consent, non profit basis of procurement of tissues and cells, data protection and confidentiality.

Regarding the principle of voluntary and unpaid donations, article 12§1 of directive on tissues and cells provides *"Member States shall endeavour to ensure voluntary and unpaid donations"*. However, a limitation to this principle has been adopted as *"donor may receive a compensation, which is strictly limited to making good the expenses and inconveniences related to the donation"* following the amendments of the European Parliament. Recital (15) of regulation on ATMP also provides *"as a matter of principle, human cells or tissues contained in advanced therapy medicinal products should be procured from voluntary and unpaid donation"*. In that case, Member States define the conditions under which compensation may be granted.

Regarding the principle of procurement on non profit basis, *"Member States shall endeavour to ensure that the procurement of tissues and cells as such is carried out on a non profit basis"*[68]. This is also recalled within the regulation on ATMP: *"Member States should be urged to take all necessary steps to encourage a strong public and non-profit sector involvement in the procurement of human cells and tissues"*[69].

Regarding the principle of consent, according to article 13§1 of the directive on tissues and cells, *"The procurement of human tissues or cells shall be authorised only after all mandatory consent or authorisation*

[65] Article 3 of the regulation (EC) N° 1394/2007, cf. note 3
[66] Cf. note 14
[67] EGE, Opinion N°3 on ethical questions arising from the Commission proposal for a Council directive on legal protection for biotechnological inventions, 30/09/1993
[68] Article 12§2 alinea 2 of Directive 2004/23/EC, cf. note 5
[69] Recital (15) of Regulation (EC) n° 1394/2007, cf. note 3

*requirements in force in the Member State concerned have been met"*. The Commission directive 2006/17/EC[70], which supplements the directive on tissues and cells, sets out technical requirements for the donation, procurement and testing of human tissues and cells[71]. It provides that the consent has to be obtained in accordance with article 13 of the directive on tissues and cells before the procurement of tissues and cells as well as several requirements regarding living and deceased donors.

Finally, according to 14§3 of the directive on tissues and cells: *"Member States shall take all necessary measures to ensure that the identity of the recipient(s) is not disclosed to the donor or his family and vice versa, without prejudice to legislation in force in Member States on the conditions for disclosure, notably in the case of gametes donation"*.

It should be noticed that the vocabulary used for ethical aspects seems quite weak as it only implies recommendations although it is binding when it is integrated in the directive's body. The expression used are: "*Member States shall endeavour*", *"Member States shall, in keeping with their national legislation, take all necessary measures"*, *"shall be made"*,… However, according to S. Hennette-Vauchez, recommendations can be transformed into imperative specific criteria. She qualifies this process as a "solidification process"[72].

Secondly regarding clinical trials, recital (16) of the regulation on ATMP appears quite wide as it provides: *"Clinical trials on advanced therapy medicinal products should be conducted in accordance with the overarching principles and the ethical requirements laid down in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulation and administrative provisions of the Member State relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use"*. More specifically, article 4 of regulation on ATMP only referred to articles 6 (7) and article 9 (4) and (6) of the directive 2001/20/EC on clinical trials which set up specific conditions for national ethics committees to act with gene and somatic cell therapy medicinal products. As a consequence, these conditions also apply to tissue engineered products as well as to combined ATMP. Furthermore, the European Commission adopted guidelines in accordance with the regulation on ATMP. The "detailed guidelines on good clinical practice specific to advanced therapy medicinal products"[73] contains some ethical considerations regarding the role of the Ethics Committee for clinical trials

[70] Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, OJ L 38, 09/02/2006, p. 40

[71] Annex IV 1. 1. 1. a of the Commission directive 2006/17/EC, cf. note 70

[72] She gives the following example: For instance, the directive on tissues and cells provides: *"Member States shall endeavour to ensure voluntary and unpaid donations of tissues and cells"*. From this recommendation, the EGE deduced that *"no financial incentives have been offered to donate embryos for research at any stage, in line with Art. 12 of Directive 2004/23"* (Opinion N° 22 « Recommendations on the ethical review of hESC FP7 research projects"), Cf. note 14

[73] 3 December 2009, ENTR/F/2/SF/dn D(2009) 35810 : "The final adoption of this guideline by the College of Commissioners is foreseen once more practical experiences have been gained with the specificities of clinical trials involving advanced therapy medicinal products. Pending the final adoption of this guideline, it is recommended to apply the rules and principles set out in this text".

involving an advanced therapy investigational medicinal product (ATIMP). It should in particular check the arrangements *"for traceability as regards provisions for subject data protection and confidentiality*[74]*, for follow up before and after the end of the trial […]*[75]*, when follow up needs to include close contact and offspring of the recipients*[76]*, the written informed consent as regards ethical concerns of particular relevance for ATIMPs*[77]*, the circumstances where a representative of the sponsor experienced in the administration of the ATIMP needs to be present during the application of the ATIMP to the subject"*[78]. This guideline also provides what should be taken into account by the Ethics Committees when assessing the ethics of a clinical trial involving an ATIMP: *"the irreversible nature of certain ATIMP applications, and the information provided to subjects in that context; the peculiarities of situations where the donor is a relative of the subject to be included in the trial, in particular the protection from "sibling/parent" pressure"*[79]. It is already unexpected to observe that the European Commission gives recommendations to the Ethics Committees for the ethical assessment of a clinical trial involving an ATIMP. But it is even more surprising that recommendations of the European Commission given to the Ethics Committees are more verbose than those given to the national competent authorities.

Thirdly, regarding the ethical aspects of the regulation on ATMP, it does not only refer to the directive on tissues and cells, to the directive on clinical trials and to further guidelines. It also sets up a centralised and unique marketing authorisation at the EU level. A sixth Committee is created within the European Medicine Agency, the Committee for Advanced Therapy (CAT) which plays a major role for the assessment of ATMP. It is interesting to notice its members shall be chosen for their scientific qualification or experience in scientific areas relevant to ATMP, including notably ethics[80]. Thus, it could be expected that the assessment of ATMP by the CAT will also be made from an ethical's point of view.

As it has been shown several ethical issues have been taken into account within norms directly related ATMP through a flexible approach coming from the wording used and/or from the character non binding of the ethical provisions. However, the complete EU framework regarding ATMP being recent, it is interesting to observe that ethical issues are also present within norms either less specific

74 Point 47(a) of the guideline, cf. note 73
75 « including after subjects withdrawn from the study and including the information (alert card) to be provided to each subject for use in the event of problems arising after the end of the trial », Point 47 (b) of the guideline, cf. note 73
76 Point 4 (c) of the guideline, cf. note 73
77 Point 47(d) of the guideline, cf. note 73
78 Point 47(e) of the guideline, cf. note 73
79 Point 48 of the guideline, cf. note 73
80 "…the final composition of the Committee for Advanced Therapy provides appropriate and balanced coverage of the scientific areas relevant to advanced therapies, including medical devices, tissue engineering, gene therapy, cell therapy, biotechnology, surgery, pharmacovigilance, risk management and ethics", Article 21§2 of Regulation (EC) N°1394/2007, cf. note 3

regarding biotechnology in general and/or human rights or pointed out specific ethical issues which indirectly apply to ATMP.

B. Norms indirectly related to ATMP

The main norms which are indirectly related to ATMP and which contains ethical considerations are the decisions for the adoption of framework programmes for scientific and technological objectives, the directive on the legal protection of biotechnological inventions[81], and soft law such as the resolutions of the European Parliament and the Opinions of the EGE.

At the research stage, the EU provides an ethical assessment of the research projects it funds. Indeed, the EU financing of research projects is notably conditioned by the respect of fundamental ethical principles recognised in Member States' national laws, EU law and international law. This is assessed by an experts' panel. The manner to take into account ethics at the research stage within the EU has evolved through the adoption of successive Framework Programs for research and technological development (FP). Although several references to ethics have occurred though the first three FP, it is the 4th FP (1994-1998) which stated for the first time the existence of binding ethical rules. From the 4th FP, questions regarding biomedical research and notably embryonic stem cells research became very important. The 4th FP explicitly forbade the modification of the genetic constitution of human beings and cloning[82]. This interdiction has also been integrated within the 5th FP (1998-2002)[83] after the opinion of the European Group on Ethics[84] required by the European Commission. It became more problematic for the 6th FP (2002-2006)[85] as two kinds of cloning were distinguished (the so called "reproductive" and "therapeutic cloning"). The general ban was not considered appropriated and tensions occurred around this 6th FP. Finally, it was adopted without any dispositions regarding the former interdiction. A moratorium on the financing of such research was adopted and applicable until 31 December 2003 but the problem of its lack of legal value was raised.

[81] Directive 98/44/EC, cf. note 18

[82] "No research modifying, or seeking to modify, the genetic constitution of human beings by alteration of germ cells or of any stage of embryo development which may make these alterations hereditary, nor research seeking to replace a nucleus of a cell of an embryo with a nucleus taken from a cell of any person, embryo or subsequent development of an embryo, known as cloning, will be carried out under this framework programme", Decision N°1110/94/EC of the European Parliament and of the Council of 26 April 1994 concerning the fourth framework programme of the European Community activities in the field of research and technological development and demonstration, OJ L 126, 18/05/1994, pp. 1-33.

[83] Decision N°182/1999/EC of the European Parliament and of the Council of 22 December 1998 concerning the fifth framework programme of the European Community for research, technological development and demonstration activities (1998 to 2002), OJ L 26, 1.2.1999, p. 1–33

[84] European Group on Ethics, Opinion n°10, Ethical aspects of the 5th Research Framework Programme, 11/12/1997

[85] Decision N°1513/2002/EC of the European Parliament and of the Council of 27 June 2002 concerning the sixth framework programme of the European Community for research, technological development and demonstration activities, contributing to the creation of the European Research Area and to innovation (2002 to 2006), OJ L 232, 29.8.2002, p. 1–33.

Consequently, the Council adopted a decision[86] which authorised research on embryonic stem cells under conditions such as systematic ethical review and submission of the research project to a regulatory Committee. However, research activities aiming at human cloning for reproductive purposes, intended to modify the genetic heritage of human beings which could make such changes heritable, or intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer, shall not be financed under the 6th FP. At the end of 2004, several calls for research projects regarding stem cells were published within the 6th FP. The same problems were raised for the adoption of the 7th FP (2007-2012)[87] as the European Parliament wished and obtained to introduce again a general ban concerning reproductive cloning as well as therapeutic cloning. However, *"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 State(s) involved"* in accordance with the "subsidiarity" principle. Moreover, the EU does not finance research activities which destroy human embryos, including for the procurement of stem cells. However, this does not prevent the EU to fund subsequent steps involving human embryonic stem cells (hESC): only research activities involving hESC in culture can receive European funds[88]. The EU financed neither the creation of embryos for research purposes- however; it financed researches using supernumerary embryos - nor the research on embryos and embryonic cells in a State which forbids it.

Thus, an ethical assessment is provided for all research projects concerning ATMP to be funded by the EU with a specific and limitative frame regarding ATMP based on embryonic cells. This way of governance has been called 'governance by dominium' as it would avoid the problems of legislative process by using financial incentives to attain public policy objectives[89].

Moreover, regarding the directive on the legal protection of biotechnological inventions, ATMP should be patentable if the three characters of the patentability are fulfilled: they must be new, they must involve an inventive step and they must be susceptible of industrial application[90]. However, they shall be considered as non patentable where their commercial exploitation would be contrary to 'public

[86]Council Decision N°2002/834/EC of 30 September 2002 adopting a specific programme for research, technological development and demonstration: "Integrating and strengthening the European Research Area" (2002-2006), OJ L 294, 29.10.2002, p. 1-43.

[87] Decision N°1982/2006/EC of the European Parliament and of the Council of 18 December 2006 concerning the Seventh Framework Programme of the European Community for research, technological development and demonstration activities (2007-2013), OJ L 412, 30.12.2006, p. 1–43

[88] Declarations of the Commission of 24 July 2006, OJ L 412, 30. 12. 2006, p. 42, and Rules for submission of proposals, and the related evaluation, selection and award procedures, version 3, 21 August 2008, COM (2008) 4617.

[89] See T. Daintith, "The techniques of Governement" in J. Jowell and D. Oliver (eds.), The changing Constitution, OUP, 1994, p. 209-236 and T. K. Hervey and H. Black, The European Union and the Governance of stem cell research, Maastricht Journal of European and Comparative Law, 2005 12 (3), p. 11- 48

[90] Article 3 of Directive 98/44/EC, cf. note 18

order' or "morality"[91]. A non exhaustive list of non patentable inventions is provided: *"(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"*[92]. Given rise to these limitations it seems that ATMP can be covered by products patents. However, the patentability of processes appeared more controversial and the coverage could be discussed[93]. The patentability of ATMP which involves elements of the human body is controversial as other biotechnological inventions because it is principally in conflict with the principle of the non-commercialisation of the human body. However, according to this directive, ATMP could be patentable if the above-mentioned conditions are respected. Here again, the patentability of ATMP is conditioned by ethical principles which became legal principles by their insertion within this directive[94].

Finally, ethical aspects related to ATMP appeared in many 'soft law" rules. The aim is not to provide an exhaustive list of all these 'soft law' measures, but to understand the role they can play to integrate ethics within the EU governance of ATMP. According to T. K. Hervey and J.V. McHale, measures of 'soft law' may be significant forces in the EU integration process. First, *"they may provide an interpretative reference point for measures of 'hard law"*[95]. For instance, the EU Charter, as a soft law measure before obtaining the value of primary law with the Lisbon Treaty, was often used to interpret hard law provisions[96]. Moreover, disincentives might come from soft law measures which indicate that a specific activity is considered illegal and/or non patentable as contrary to ethics such as the repeated opposition to human cloning provided by the EGE opinions[97] and the resolutions of the European Parliament[98]. Second, *"They may promote convergence through articulation of agreed statements of good practice and recommendations, against which national policies are measured, eventually prompting voluntary changes to bring national systems in line with an agreed 'European norm' "*. In this context, the opinions of the EGE are very important. They are taken into account within minimum harmonisation measures such as the directive on tissues and cells at EU level. They could also operate at national level as a reference for the national legislators and for national ethics committees. Third, *"they may carve out areas of 'Community concern', where formal legal competence is lacking, thus paving the way for future developments in action taken by EU institutions, sometimes ultimately leading to the enactment of binding and directly effective EU-level legal provisions"*. Here again, the EU Charter can be cited,

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[91] "However, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation", Article 6§1 of Directive 98/44/EC, cf. note 18

[92] Article 6 §2 of Directive 98/44/EC, cf. note 18

[93] Regarding the patentability of stem cells, see T. K. Hervey and H. Black, The European Union and the Governance of stem cell research, Maastricht Journal of European and Comparative Law, 2005 12 (3), p. 11- 48

[94] Cf. note 93

[95] T. K. Hervey and J.V. McHale , Health Law and the European Union (2004), Cambridge University Press

[96] See for instance C-377/98, Pays-Bas v Parliament and Council, 09/10/2001

[97] See for instance EGE Opinions N°9 of 28 May 1997on "Ethical aspects of cloning techniques" and N°15 of 14 November 2000 on "Ethical aspects of human stem cell research and use"

[98] Cf. note 13

as the vocation of the EU was originally economical. With the development of a more political Union, the EU Charter, initially non binding, became binding.

**Conclusion**

Even though the EU regularly recalled that regulating ethics is a Member States' prerogative, several ethical issues are integrated within the EU norms related to ATMP due to the inseparable link between the governance of ATMP and the ethical questions it raised. The European Parliament has been playing a major role for the protection of bioethics values notably through its numerous amendments. The analysis of bioethics through the ATMP governance shows up the limits of the EU categorisation regarding the sharing of competences between the EU and its Member States and the market, public health and fundamental rights grounds.

The most controversial issues regarding human cloning, uses of embryonic and germ cells, creation of hybrids and chimeras have been excluded from the EU binding secondary law as it has been shown through the study of the EU directive on tissues and cells and the regulation on ATMP. These questions are dealt with at the national level as the margin of discretion of Member States is very wide given rise to the principle of subsidiarity, and the minimum and partial harmonisation.

However, several ethical aspects have infiltrated the EU governance of ATMP with the strong influences of the European Parliament and the EGE. But it seems that the EU tried to present ethical principles either as fundamental rights or as objectives of safety and public health. It also always uses a flexible approach. Regarding the general principles of bioethics such as the respect of the human dignity and the reference to the fundamental rights, when they are considered, it is either within the recital of binding secondary law or within soft law. Therefore, it constitutes only a recommendation although this would probably change with the new primary law value of the EU Charter through the adoption of the Lisbon Treaty. It could be envisaged that the EU Court of Justice would strengthen the competencies of the EU, principally on the basis of the EU Charter and of public health. However, by all appearances, the EU Court of Justice will not do it for Poland and for the United Kingdom on the basis of the EU Charter. Indeed, article 1 of Protocol N°30 on the application of the Charter of fundamental rights of the European Union to Poland and to the United Kingdom provides: *"The Charter does not extend the ability of the Court of Justice of the European Union, or any court or tribunal of Poland or of the United Kingdom, to find that the laws, regulations or administrative provisions, practices or action of Poland or of the United Kingdom are inconsistent with the fundamental rights, freedoms and principles that it reaffirms"*[99]. Furthermore, *"To the extent that a provision of the Charter refers to national laws and practices, it shall only apply to Poland or the United Kingdom to the extent that the rights or principles that it contains are recognised in the law or*

[99] Article 1 of Protocol N°30 on the application of the Charter of fundamental rights of the European Union to Poland and to the United Kingdom, OJ C83 of 30/03/2010, pp. 313-314

*practices of Poland or of the United Kingdom"*[100]. Thus, this protocol can have two consequences. On the one hand, the protocol directly impedes the EU Court of Justice to extend the EU competencies on the basis of the EU Charter where it is in contradiction with Polish and English laws. But as it has already been done, the EU Court of Justice could subtly use other legal basis such as EU secondary law at the risk of political incident. On the other hand, as this protocol refers only to Poland and to the United Kingdom and does not concern any other member State, would it indirectly mean that the EU Court of Justice could extend the EU competencies on the basis of the Charter for other EU member States?

Furthermore, more specific ethical principles such as "voluntary and unpaid donation" and "consent" are integrated within the binding part of secondary law but in flexible formulation referring to the national legislation. They can be more detailed within soft law such as guidelines. Here again, Member States are quite free. Nevertheless, the effect of the infiltration of such ethical principles even through a very flexible manner should not be underestimated[101]. Indeed it could have a strong impact on Member States and for instance on entities which want to be funded by the EU for their researches.

But if bioethics within EU law could be considered as an unacceptable secrete objective to completely and relevantly frame ATMP in the context of the European integration[102], it should also be considered as a tool, notably because as 'subsidiarised' it strengthens national sovereignties legitimizing State-based ethics[103].

[100] Article 2 of Protocol N°30 on the application of the Charter of fundamental rights of the European Union to Poland and to the United Kingdom, cf. note 99

[101] V. Tournay, De la bioéthique à l'action publique en matière de biotechnologies : la production des thérapies cellulaires, cahiers internationaux de sociologie, N°53, Vol. CXXI (Juillet-Décembre 2006)

[102] From a general point of view, see: S. Saurugger, Théories et concepts de l'intégration européenne, Presses de Science-Po, 2010.

[103] For the all of characteristics of EU ethics as a tool, see M. Tallacchini, Governing by values. EU Ethics: Soft Tool, Hard Effects, cf. note 10