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Cells' Safety in Europe towards an *Ethical Safety*

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Abstract

To encourage and maximise the use of human biological material in Europe, the European Commission instigated a main Directive in 2004 (Directive 2004/23/EC), four technical ones in 2006 (Commission Directives 2006/17/EC and 2006/86/EC) and in 2015 (Commission Directives (EU) 2015/565 and (EU) 2015/566). They encourage the donation of tissues and cells for transplant purposes in the safeguard of public health. Another major aim of Directive 2004/23/EC is to guarantee recipients' safety in transplantation. Hence, measures for accreditation of establishments storing, preparing and distributing tissues and cells are required to be implemented in Members States' jurisdictions. In addition, adequate training is required for the personnel directly involved in such activities. Despite the adoption of a "full legislation," the EU legal framework for cells cannot be seen as totally harmonized. In this article we first address the issues posed at the European level by the uses of human cells as therapeutic agent with regards to their qualification: body elements? Medicinal product? We study the ways to address these bioethical dilemmas at an EU level. Then we discuss the impact of this qualification in terms of safety through the definition of safety's measures and their limits regarding the directive's scope. We conclude with the emergence of an "ethical safety".

Keywords

human cells, safety, EU law, ethics

1 Introduction

The European Union, in its effort to understand the quality of human cells, has had to consider two preliminary questions: what are the aspects of cells which need to be regulated on a European level? To what extent is the European Union competent in the matter and what underlying principles should govern its actions? Health safety has emerged as the core concern of a European action meant to provide quality and safety rules applicable to the therapeutic uses of human cells, in order to achieve a high level of health protection.

1.1 *The Medical Uses of Human Cells*

It is useful to recall that human cells can be used as therapy agents. This is a time-tried method since blood transfusions have been applied as therapy since WWII, becoming widespread in the course of the 1960s.¹ Biotechnology gave rise to a multitude of processes which have made it possible to isolate, transform and control blood components (platelets, serum, cells, stem cells etc...), marking the birth of modern stem-cell therapy.² Today's stem-cell therapy, far from being restricted to blood diseases, now targets many complex diseases (neurodegenerative, muscular or cardiovascular). Its object is to treat, prevent or diagnose these diseases, putting particular emphasis on regeneration (regeneration of deficient cells, tissue or even organ regeneration) – the stated ambition of advanced therapy medicinal product³ manufacturers. The pace of science in cell use and regenerative medicine has quickened over the past few decades, thanks to the discovery of stem cells⁴ and induced pluripotent stem cells (IPS).⁵ The biological fragmentation that was observed has partially translated into the fragmentation of legal instruments, since the use of blood⁶ and the use of cells fall under separate regulations. Once isolated and “treated”, cells may thus be used for therapeutic purposes, as “drugs” intended to cure the very person they were collected from – a process known as autologous transplantation- or to cure a third person – a process known as allogenic transplantation. Making the distinction is of paramount importance when considering donations of elements of the human body. According to the rules of bioethics, the concept of donation implies the coexistence of two wills: that of the donor and that of the recipient. But this notion is obviously inoperative concerning autologous transplantations where donor and recipient are one and the same person. Such distinction also has an impact on safety procedures, since allogenic transplantations require dual risk assessment (donor and recipient), while in the case of autologous transplantations the risk assessment concerns a single person. This provided a framework for developing European regulations in the field of cell safety under the prism of risk assessment, identification and management.

1.2 *The Safe Cells*

Cell safety relies on the postulate that EU citizens are entitled to receive quality health care at minimal or no risk to their lives. The European Charter of Patients' Rights⁷ and the Directive

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¹ P. Hervé, J.-Y. Muller and P. Tiberguien, *La transfusion sanguine demain*, Ed John Libbey Eurotext, 2005, p.3; C. Waldby And R. Mitchell, *Tissue Economies- Blood, Organs, and Cell Lines in Late Capitalism*, (Duke University Press, Durham, 2006), pp. 2-3, 10.

² *Ibid.*

³ For a scientific presentation of cell therapy visit: <http://www.inserm.fr/dossiers-d-information/therapie-cellulaire> (an INSERM initiative).

⁴ The first skin transplants from stem cells took place in the course of the 1970s.

⁵ Prof. Shinya Yamanaka and Prof. John Gurdon received the Nobel Prize of Medicine in 2012 for this discovery.

⁶ The sources we have chosen to indicate refer to European legislation which has been transposed into internal State domestic law. State domestic law shall only be mentioned when specific provisions from EU law exist. For cell safety please visit Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 33, 08/02/2003, p. 30–40.

⁷ European Charter of patients' rights, Active Citizenship Network, 2002, http://www.activecitizenship.net/images/patientsrights/poster_england.pdf. Article 8 Right to the observance of

on the Application of Patients' Rights relative to cross-border health care⁸ affirm the validity of such demands. Beyond the obligation to deliver safe health care, the safety demands encompass the transplant procedure itself, as described in a package of directives⁹ applicable to cells (hereinafter Tissues and Cells Directives). The main objective of this package is to minimize the risks inherent in transplantations involving third-party donors (risk minimization being applicable to both the donor and the recipient) when human cells are used, and particularly when they are stored in biobanks. The field of application of the directives was intended to be vast enough to ensure comprehensive legal protection across the whole transplant chain, from the donor to the recipient. For this reason, two complementary Directives added technical requirements to the main Directive setting quality and safety standards for the therapeutic uses of human cells in Europe.¹⁰ The first one¹¹ covers the donation chain and the control of tissues and cells, the second one¹² deals with storage operations and any associated practices (such as the distribution of serious undesirable events and their reporting procedures). Consequently the objectives of developing a consistent risk-management and public-health approach for this activity on a European scale seem to have been achieved. These rules have been transposed by Member States, thus ensuring the harmonization of the framework,¹³ however several gaps in the legislation remain,¹⁴ particularly in regard to ethical constraints concerning the use of elements of the human body. There is lingering unease about the way European institutions address bioethical issues, even though the quality and safety of cells have been harmonized.

quality standards. Each individual has the right of access to high quality health services on the basis of the specification and observance of precise standards.

Article 9 Right to safety.

Each individual has the right to be free from harm caused by the poor functioning of health services, medical malpractice and errors, and the right of access to health services and treatments that meet high safety standards.

⁸ Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare, OJ L 88, 04/04/2011, pp. 45–65, recital 10.

⁹ Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 07/04/2004, pp. 48–58. Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, OJ L 38, 09/02/2006, pp. 40–52. Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells, OJ L 294, 25/10/2006, pp. 32–50. Commission Directive 2015/565/EC of 8 April 2015 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells, OJ L 93, 09/04/2015, pp. 43–55. Commission Directive 2015/566/EC of 8 April 2015 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells, OJ L 93, pp. 56–68.

¹⁰ Directive 2004/23/EC; *ibid.*

¹¹ Directive 2006/17/EC; *ibid.*

¹² Directive 2006/86/EC; *ibid.*

¹³ Member States submit a progress report on the transposition of these legal tools on a yearly basis, but it is a fact that harmonisation cannot be deemed as perfect as Member States have resorted to very different means to transpose these tools into national legislation. European institutions have acknowledged the resulting heterogeneity. See the European Parliament Resolution of 11 September 2012 on Voluntary Unpaid Tissue and Cell Donations (2011/2193(INI)), OJ C353, 31/12/2013, pp. 31–38.

¹⁴ Report from the Commission to the European Parliament, the Council, the European Economic And Social Committee And The Committee Of The Regions on the implementation of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC setting standards of quality and safety for human tissues and cells, 21 April 2016, COM(2016) 223 final.

2 The 'Human' Characteristic of Cells : An Ethical Issue for the European Regulation

According to the EU Tissues and Cells Directive, human cells are understood to be "Individual human cells or a collection of human cells when not bound by any form of connective tissue".¹⁵ This purely scientific definition needs to be complemented *rationae personae* and *rationae materiae*. Firstly, considering the persons that cells are collected from, it is necessary to distinguish between cells taken from living persons and cells taken from deceased persons.¹⁶ Making this distinction has consequences for information and consent,¹⁷ as well as on future uses of the cells. The Directive 2004/23/EC covers both forms of donations and stipulates in Recital 16 that:

Tissues and cells used for allogeneic therapeutic purposes can be procured from both living and deceased donors. In order to ensure that the health status of a living donor is not affected by the donation, a prior medical examination should be required. The dignity of the deceased donor should be respected, notably through the reconstruction of the donor's body, so that it is as similar as possible to its original anatomical shape.

As to its field of application, the Directive lists in the main body of text the biological sources to which it is not applicable and the biological sources to which it may be applicable under certain conditions. The object of these lists is to overcome the difficulties that may arise in case of dual characterization (should a source fall within the scope of two legal instruments for instance) or in case of shared competence (with the internal legislations of member States). Concerning tissue sources, the Directive excludes blood cells and blood components, the latter being covered by the Directive 2002/98/EC.¹⁸ Other exclusions were justified insofar as their objects fell under different regulatory approaches. On the one hand, the organs or elements of organs whose function is to be used for the same purpose as the entire organ in the human body¹⁹ required "a different policy approach due to their specific nature and the severe shortages that result in many patients going untreated".²⁰ On the other hand, the "tissues and cells used as autologous transplantation within the same surgical procedure",²¹ call for quality and safety considerations of an "entirely different"²² nature as they are not "at any time, stored in a bank." "Conditional sources" are made up of hematopoietic stem cells, the cord blood cells and embryonic stem cells to which the Directive 2004/23/EC claims that it "should" apply.²³ The field of application is also restricted as the Directive expressly states that it does not apply to fundamental research activities insofar as it only covers cells used for "human applications".²⁴

¹⁵ Directive 2004/23/EC Art. 3.

¹⁶ Minors do not seem to be excluded from this distinction.

¹⁷ Consent must be enlightened and must have been given having full knowledge of the facts by the living person even when the organs are collected from a deceased person. Recommendations on points requiring information to be delivered prior to collecting the consent are set out in the afore-mentioned Annex to Directive 2004/23/EC.

¹⁸ Directive 2004/23/EC Art. 2 b).

¹⁹ Directive 2004/23/EC Art. 2 c).

²⁰ 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 COM (2002) 319, OJ EC C227 E, 24.09.2002, pp. 505-521.

²¹ Directive 2004/23/EC Art. 2a).

²² Directive 2004/23/EC, recital (8).

²³ Directive 2004/23/EC recital 7, The commonly admitted interpretation is that if the use of these cells is legal in one Member State then the Directive shall apply. *A contrario*, a ban on the use of these cells by national legislation shall result in the non-application of the Directive.

²⁴ Directive 2004/23/EC Art. 1.

Having established a framework to determine the field of application of the Directive 2004/23/EC, the Commission has limited itself to defining the quality and safety standards that all Member States must adopt, and has left out the bioethical questions underlying the use of elements of the human body for therapeutic purposes. Yet some of those taking part in the institutional debate in Europe have taken a clear stance, since the European Group on Ethics and the judge himself have been compelled to consider this matter.

2.1 *Bioethics Dilemmas in Regulating the Use of Cells*

Cell therapy usually requires manipulating the cells after collecting them, using in vitro amplification, purification and sometimes modification procedures.²⁵ These transformations alter the legal characterization of cells as part of the human body. Using humans to cure humans raises a number of issues associated with turning elements of the human body into commodities as health products,²⁶ the safety and efficiency of which are required to be assessed prior to their commercialisation²⁷ (marketing authorization, authorization to commercialise, etc.). The most widely known of these products – medicinal products - are very precisely defined in EU law.²⁸ It follows that cells, after being transformed and transplanted, and according to the extent to which they were manipulated, may well become characterized as either health commodities or medicinal products, thus losing their initial nature – i.e. elements of the human body. It is easy to grasp that all this results from the affirmation of bioethical principles related to the protection of the human body and its elements. EU law²⁹ affirms a series of principles which have been enshrined by its Member States. Banning the use of the human body as a commodity³⁰ and its commercialisation,³¹ unpaid donations, confidentiality protection and voluntary donations are clearly affirmed as cardinal principles. Still the Union has made but a tepid commitment, remaining entrenched behind the notion of national competence, as it has every time it has had to decide on ethical matters. This has translated into the affirmation of the said principles by means of declaratory statements³² or, by lodging them into the recitals of statutory instruments,³³ and more recently into the EU Charter of Fundamental Rights,³⁴ which lends them a broad scope.

This contrasts with organ donations as these principles have historically been applied to organ transplantations raising different controversies. What makes us ponder the possibility

²⁵ See <http://www.institut-biotherapies.fr/biotherapies/la-therapie-cellulaire/>.

²⁶ A. Mahalatchimy and E. Rial-Sebbag (coords.), *L'humain médicament*, (Quaderni, Editions de la Maison des Sciences et de l'Homme 2013), p. 6 and following.

²⁷ In France the *Agence Nationale de Sécurité du Médicament et des Produits de Santé* (ANSM: National Agency for the safety of medicinal products and health products) carries out the assessment, in Europe the European Agency for Medicinal Products (EMA) is competent.

²⁸ Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products, OJ 022 , 09/02/1965, pp. 369 – 373, modified.

²⁹ European Parliament resolution of 11 September 2012 on voluntary and unpaid donation of tissues and cells (2011/2193(INI)), OJ C353, 31/12/2013, pp. 31-38.

³⁰ Affirmed by the European Chart of Fundamental Rights, article 1 relative to the Dignity of the human person and article 3 on the Right to Integrity, which refer to “The prohibition on making the human body and its parts as such a source of financial gain”.

³¹ While the non-merchandisation of the human body can be understood as a general bioethical principle prohibiting any form of remuneration for the use of the body, the non-commercialisation can be understood in a more restrictive manner as the prohibition of market distribution for profit.

³² See recommendation quoted above.

³³ Concerning Directive 2004/23/EC see notably recitals 18 and 19 employing a « soft » terminology for the recognition of these principles, “As a matter of principle, tissue and cell application programmes should be founded on the philosophy of voluntary and unpaid donation...3, or “Voluntary and unpaid tissue and cell donations are a factor which may contribute to high safety standards for tissues and cells...”.

³⁴ Adopted in 2000.

of cells acquiring a different nature and becoming “medicinal products” - products that may be commercialized on the market – is the extent of the biological manipulations they are subjected to and their potential “industrialization”. The principle of free movement of Goods applies to health products which can be the object of financial transactions. The three required criteria of transformation, industrialization and commercialization being met, should it be inferred that the legal characterization of cells has *de facto* been modified? Still it should be pointed out that, *in fine*, these principles are always upheld between the donor and the recipient since no donor may be remunerated for a donation, all donors must be correctly informed of the use that is to be made of their cells, and donors must also express freely and clearly their consent. However these principles may well not be upheld should cell therapy processes be put on the market as this would entail the immediate commercialization of “product-cells”. Similar questions arise concerning the principles governing the use of cells for therapeutic purposes, which have recently been categorized as advanced therapy medicinal products (ATMP), exempted advanced therapy medicinal products³⁵ and, under French law, cell therapy medicinal preparations (PTC),³⁶ the latter not being subjected to an industrial process and therefore not being categorized as a medicinal product given the limited extent of the manipulations involved. The latter category – preparations- was created in France even before the regulation on advanced therapy medicinal products was adopted in order to address the ethical dilemma posed by the notion of non-commercialisation.³⁷ This category has greatly evolved since, its technical requirements now proving to be more relevant than its ethical requirements.³⁸

These *bioethics dilemmas* also arise when it comes to the nature of the cells likely to be used for therapeutic purposes, particularly human embryonic stem cells. These cells were discovered in the late 1990s and were found to have extremely interesting properties concerning organ and tissue regeneration, which makes them highly covetable. Their lack of maturity implies a high potential for self-renewal and differentiation, and the application of biotechnology processes might eventually make it possible to repair any damaged tissue or organs in the body. Obviously the main issue raised by the use of such cells lies in their embryonic nature. Their availability implies the use of an embryo which will *de facto* never have the possibility of becoming a foetus. What some might term instrumentalization and commodification of an embryo, others regard as a major scientific advance. Debate is rife in many European countries such as France, where for many years defenders and opponents of embryonic research have engaged in heated discussions, despite the adoption of the latest law on embryonic research in 2013.³⁹ In this context the EU has always declined to take a stance one way or the other, leaving each state to assume responsibility for any bioethical choices to

³⁵ Categories adopted in the Regulation (EC) N° 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) N°726/2004, OJ L324, 10/12/2007, pp.121-137.

³⁶ A. Mahalatchimy, E. Rial-Sebbag, V. Tournay and A. Faulkner, “The legal landscape for Advanced Therapy Medicinal Products: material and institutional implementation of European Union rules”, *Journal of Law and Society* 39(1) (2012) 131-149.

³⁷ E. Rial-Sebbag and F. Taboulet, “Encadrement juridique des essais cliniques de thérapies innovantes : état de la question en droit français” in: F. Dufort and A.L. Saives (Eds.), *Le Médicament : Conception, Production et Consommation : Perspectives Interdisciplinaires pour un Avenir Commun*, (digital edition available on <http://www.geirsomedicaments.uqam.ca/congres2005/ActesCongres2005.pdf> 2006), 309-318.

³⁸ See a description of the different categories on the ANSM website, <http://ansm.sante.fr/L-ANSM2/Medicaments-de-therapie-innovante-et-preparations-cellulaires-a-finalite-therapeutique/Les-preparations-cellulaires-ou-tissulaires/%28offset%29/6>.

³⁹ X. Bioy and E. Rial-Sebbag, “L'évolution de la recherche sur l'embryon, une question de principes”, *Les Petites affiches, La loi* (251) (2013) 4-12.

be made.⁴⁰ Yet Europe has not withdrawn from the ongoing debates, be they specifically targeted on embryonic research or of a more general nature – such as the emergence of human cells for therapeutic purposes.

2.2 The European Integration of Some Bioethical Considerations

Despite the unresponsiveness of some European institutions, bioethical considerations regarding the use of cells for therapeutic purposes appear to be a major issue in many European countries. Although the issue of bioethics is and should be addressed at the state level, if only to allow each culture and legal policy to express their singularity, the Union could not disregard the concerns it raises.⁴¹ Regarding the principle of free movement, it has to be reminded that patients are entitled to receive care in various countries of the Union⁴² - a freedom also granted to health products. It follows that, for the sake of remaining consistent, the safety of people and products must be effective and harmonized. The products and elements of the human body are indeed covered by directives. But as previously stated the rules apply only partially as States were given considerable leeway in defining which cells are to be covered. This is counterproductive in terms of safety as it gives a limited impact to these rules designed to achieve a high degree of health protection. Inversely, the European Group on Ethics (EGE) and the Court of Justice of the European Union (CJEU) have recently been working towards a more effective integration of bioethical principles by the whole of the EU member States.

2.2.1 The Influence of the European Group on Ethics for the Regulation of Human Cells Uses

The European Group on Ethics (EGE) was created in 1991,⁴³ delivering many opinions on cells use. However few of them tackle the question of safety. It is the opinion on the *Ethical Aspects of Human Tissue Banks*⁴⁴ published in 1998 that needs to be referred to. Although relatively old, this opinion remains of legal interest as it was produced at the time the governing principles of biobanks were in the process of being thought up, and health security matters were brought into the limelight.⁴⁵ In this context the EGE, who in the introductory statements of Opinion n°11 extended its proposals to cells, assimilating them to tissues, built its reasoning around two main axes: the respect of ethical principles and of health safety rules. As to ethical principles, the EGE pointed out that any actions involving tissue/cell transplantations must be guided by “respect for the dignity and freedom of the human person,

⁴⁰ See notably Directive 2004/23/EU recital 12 “This Directive should not interfere with decisions made by Member States concerning the use or non-use of any specific type of human cells, including germ cells and embryonic stem cells. If, however, any particular use of such cells is authorised in a Member State, this Directive will require the application of all provisions necessary to protect public health, given the specific risks of these cells based on the scientific knowledge and their particular nature, and guarantee respect for fundamental rights. Moreover, this Directive should not interfere with provisions of Member States defining the legal term "person" or "individual".”

⁴¹ A. Mahalatchimy, “Bioethics and European Union: the Advanced Therapy Medicinal Products’ case”, *Opinio Juris in Comparatione* 2(3) (2010), www.lider-lab.sssup.it/.../367-opinio-juris-in-comparatione-vol-22010.html

⁴² Directive 2011/24/EU, *Ibid.*

⁴³ Created initially as the “Group of advisers to the European Commission on the ethical implications of biotechnology”, it became the “European group on ethics in science and new technologies” on December 1997.

⁴⁴ EGE Opinion n° 11, *Ethical Aspects of Human Tissue Banking*, (1998), http://ec.europa.eu/bepa/european-group-ethics/docs/avis11_en.pdf.

⁴⁵ It should be reminded that in France particularly the mad-cow crisis or the contaminated blood crisis took place when the first great French law on health safety was in the making, Act no 98-535 of 1st July 1998 relative to the Reinforcement of the Health-Monitoring System and the Health-Safety Control Procedures for Products for Human Use, JORF n°151 of 02/07/1998, p. 10056.

as well as by the common good”.⁴⁶ The next major issue that came into consideration was commercialization and a distinction was made – as we also did – between the financial relations that may exist when the donor and the recipient enter a contract, and those occurring when transformed elements of the body are commercialized. The conclusions reached by the EGE pointed to a lack of harmonization between Member States, each developing legal policies based either on fair compensation for the donor considering the constraints imposed, or on voluntary altruistic donations. The latter arguments seem to have prevailed on the grounds that they are “based on solidarity”.⁴⁷ Equally inspiring was the desire to prevent Man from being seen as an object (i.e., a reservoir for tissue and organs). The objective of unpaid donations is also “to avoid all risk of exploitation of the most underprivileged who might be led, in doubtful conditions of health, to donate tissue exclusively or primarily for financial reasons”.⁴⁸ Consequently several principles needed to be enshrined when it came to donations: respect for the body of the donor (be it a living or a deceased donor), and for the notions of providing information and collecting consent;⁴⁹ as for the recipient, of paramount importance are the right to a safe transplantation,⁵⁰ and also the protection of their medical data and history. The operational dimensions of safety are considered as “vital, as the European Union has set itself the objective of guaranteeing each citizen a “high level of human health protection”. This protection must extend to tissue donors and recipients, and to all health care professionals - whose work involves collecting, manipulating and using human tissues.”⁵¹ As a consequence various safety issues emerged concerning “research on the personal, medical and family history of the donor in order to detect all possible transmissible diseases”⁵² and also the supervision of the procedure under the responsibility of a medical doctor, in a suitable place and with the assistance of trained personnel. Let us recall that several years later, in 2004, these very sanitary arguments underpinned the adoption of the first Tissues/cells Directive. Additionally, according to the EGE, the patentability of stem cells calls into question the fundamental principle of banning the use of the human body and its elements for profit, a ban based on the principle of non-commercialisation of the human body.⁵³ Whereas stem cells lines which have been “modified by in vitro treatments or genetically modified so that they have acquired characteristics for specific industrial applications”⁵⁴ are patentable, isolated stem cells and non-modified stem cell lines are not.

This is because non-modified, isolated stem cells do not meet the industrial applicability criteria as they are “so close to the human body, the foetus or to the embryo they have been isolated from, that their patenting may be considered as a form of commercialisation of the human body”.⁵⁵ On the other hand isolated stem cell lines have a large range of potential industrial applications – too numerous to describe. Their range of application would be too extensive to be the object of a patent. So, using as a criterion the modification of stem cells and stem cell lines, the EGE considered that “as to the patentability of processes involving human stem cells, whatever their source, there is no

⁴⁶ EGE opinion n°11, *ibid.*

⁴⁷ *Ibid.*

⁴⁸ *Ibid.*

⁴⁹ The necessity to provide accurate information to donors and collect their consent is clearly affirmed in Directive 2004/23/EC, Art. 13.

⁵⁰ It is important to note that the principle of safety is not limited to its operational role but is closer to a fundamental right.

⁵¹ EGE opinion n°11.

⁵² *Ibid.*

⁵³ EGE Opinion n°16, *Ethical aspects of patenting inventions involving human stem cells* (2002), http://ec.europa.eu/bepa/european-group-ethics/docs/avis15_en.pdf

⁵⁴ *Ibid.*

⁵⁵ *Ibid.*

specific ethical obstacle, in so far as they fulfil the requirements of patentability”.⁵⁶ But on this point, one of the EGE members, Professor Günter Virt, expressed a dissenting opinion, claiming human Embryonic Stem Cells (hESC) and hESC lines must not be made patentable “because we cannot get embryonic stem cell lines without destroying an embryo and that means without use of embryos. This use as material contradicts the dignity of an embryo as a human being with the derived right to life”. The Court upheld this argument – using a *ratio decidendi* of a more ethical than legal nature -⁵⁷, to rule on the non-patentability of human embryonic stem cells, and gave legal clout to part of the principles established by the EGE.

2.2.2 The–Olivier Brüstle / Greenpeace EV Case: Consequences of Recent Development Regarding Patentability of Human Cells

In the case of *Dr Brüstle v. Greenpeace*, a German Federal court referred to the CJEU, asking that it interprets a provision of the Directive on the legal protection of biotechnological inventions.⁵⁸ The court questioned the application of article 5, paragraph 1 of the Directive, which prohibits that “The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene”, can constitute patentable inventions, and article 6(2)c) which excludes any use of human embryos for industrial or commercial purposes. The issue at stake was the patentability of an invention aimed at producing neural precursor cells, which involves the use of stem cells obtained from a human embryo at the blastocyst stage. The “referring court asks the Court, in essence, whether an invention is unpatentable even though its purpose is not the use of human embryos, where it concerns a product whose production necessitates the prior destruction of human embryos or a process for which requires a base material obtained by destruction of human embryos” (§47). This case gave the Court the opportunity to pronounce a ruling on two fundamental aspects of the use of embryonic stem cells in matters of patentability. Firstly, the Court took the initiative to define the human embryo in the sense of the Directive, in very broad terms, as “any human ovum after fertilisation, any non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted and any non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis” (§38), refuting the distinction between human pre-embryo and human embryo⁵⁹ and bringing very different realities together under the same category.⁶⁰ Secondly, the Court excluded the possibility of obtaining a patent where the invention results from the destruction of an embryo, even in the context of research and as part of the commercial and industrial activities falling under the scope of the Directive. It followed that neither the Court nor M. Yves Bot, the Advocate General, in his opinion,⁶¹ concurred with or referred to opinion n°15 of the EGE, which stated that patent prohibition must rely on patentability criteria. On the contrary, in diverging from that opinion and in adopting a dissenting position with respect to opinion n°16 of the EGE, the Court

⁵⁶ *Ibid.*

⁵⁷ Academics are in agreement on this point. See particularly: S. H. E. Harmon, G. Laurie and A. Courtney, “Dignity, plurality and patentability : The Unfinished Story of Brüstle v. Greenpeace”, *European Law Review* 38(1) (2013) 92-106; C. Noiville and L. Brunet, “Brevetabilité des cellules souches embryonnaires humaines : quand la réalité technico-économique est rattrapée (non sans ambiguïtés) par l'éthique”, *Revue des contrats* (2) (2012) 593-605

⁵⁸ Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, OJ L 213 , 30/07/1998, pp.0013 – 0021. This decision was not based on the Tissue and cell Directive.

⁵⁹ A. Mirkovic, “La recherche sur l'embryon stoppée à Luxembourg ?”, *AJ Famille* (2011), 518-518.

⁶⁰ K. Triller Vrtovec and C. Thomas Scott, “The European Court of Justice ruling in Brüstle v Greenpeace: the impacts on patenting of human induced pluripotent stem cells in Europe”, *Cell Stem Cell* (2011), pp. 502-503.

⁶¹ Opinion of Prosecutor, Yves Bot, 10 March 2011, C-34/10, Oliver Brüstle v Greenpeace Ev.

seemed to base its decision more specifically on the very nature of the embryo, applying to it the principle of respect for human dignity. Although this decision does not strictly speaking concern the topic of cell safety, still it is useful in outlining the field of application of the provisions on cells in the European Union from a bioethical point of view. But the Court's ruling should be considered to be binding only to a certain extent, for two reasons. In the first place, the ban on patents does not imply a ban on research. It is solely the legal protection granted by patents which cannot be obtained, research activities on embryonic cells remaining covered by national laws, so the impact of this decision on research must not be exaggerated.⁶² Secondly, although in this particular case it is not very clear whether the patent ban is based on the very nature of the embryo or on the principles governing patent grant,⁶³ the Court specifies that *a contrario* and in compliance with recital 42) of the Directive, the use for the purpose of therapy or diagnosis applicable and useful to the human embryo may justify the grant of a patent.

In this context it is plain that EU institutions are ill at ease when required to rule on bioethical questions and to arbitrate between the market and the ethical values⁶⁴ inherent in the field of detached elements of the human body.⁶⁵ On the contrary, safety requirements are largely harmonized and standardized on a European scale.

3 The Quality and Safety of Human Cells : A Major Field of Action for the European Union

Safety requirements for biological elements are not a priority for the European Union exclusively. They are also a core concern for both the World Health Organization (WHO) and the Council of Europe. In 2010 the WHO adopted several guiding principles on human cell, tissue and organ transplantations.⁶⁶ Highlighting not only the therapeutic potential that human organ and cell transplantations have acquired over the past few years, but also the corruption and traffic that may arise when developing a market centered on the elements of the human body, "The following Guiding Principles are intended to provide an orderly, ethical and acceptable framework for the acquisition and transplantation of human cells, tissues and organs for therapeutic purposes". 11 principles are listed to define this framework and emphasize the moral values that should underpin donations (altruism, non commercialization) and the respect for persons (anonymity, respect of privacy). This legal framework does not ignore safety as its n° 10 guiding principle states that "High-quality, safe and efficacious procedures are essential for donors and recipients alike. The long-term outcomes of cell, tissue and organ donation and transplantation should be assessed for the living donor as well as the recipient in order to document benefit and harm. The level of safety, efficacy and quality of human cells, tissues and organs for transplantation, as health products of an exceptional nature, must be maintained and optimized on an ongoing basis. This requires implementation of quality systems including traceability and vigilance, with adverse events and reactions reported, both nationally and for exported human products". In 2013 the

⁶² J. L. Davies and A. Denoon, "Brüstle decision is unhelpful, but not catastrophic", *Cell Stem Cell* (9) (2011), 500-501.

⁶³ J. Hauser, "Brevetabilité des inventions sur l'embryon (suite et fin)", *RTD civ.* (2012), pp. 85-87.

⁶⁴ S. Henneville-Vauchez, "Biomedicine and EU law : unlikely encounters ?", *Legal Issues of Economic Integration* 38 (1) (2011) 5-31.

⁶⁵ M. Favale and A. Plomer, "Fundamental disjunctions in the EU legal order on human tissue, cells & advanced regenerative therapies", *Maastricht Journal of European and Comparative Law* 16 (1) (2009) 89-111.

⁶⁶ WHO guiding principles on human cell, tissue and organ transplantation, Geneva 2010, http://www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf

Council of Europe published the first guide on the quality and safety of tissues and cells,⁶⁷ after dealing with organ safety⁶⁸ in a separate book. The guide collects updated information in order to give transplant specialists a useful overview of the most recent advances in the field. It provides valuable advice and information to professionals dealing with donations, banks, transplantations and any other clinical applications of cells and tissues, with the objective to enhance the quality of such complex procedures and reduce their risks.

The Union is not lagging behind, although its competence in matters of health protection appears to be a recent acquisition. That competence was acknowledged in 1992 by the Maastricht Treaty,⁶⁹ and was reinforced by the Treaty of Lisbon which reaffirmed that the Union has the obligation to ensure a high degree of human health protection, an objective which, according to the terms of the treaty, must be clearly stated in the definition and implementation of all the policies and actions of the Union.⁷⁰ Whether viewed as a “threat to health”⁷¹ or as a “health safety” requirement,⁷² cell safety is clearly stated to be a public health priority by the Union. Tissue and cell transplant activities have greatly increased in the Union, notably thanks to improved collection, storage and transplantation methods. The elements of the human body appear to be acquiring more and more “mobility”. The fact that they can be preserved and exchanged across the European territory causes these elements to be constantly moving, which implies that all member States should grant an even degree of safety concerning their use. This is the reason why safety has been regulated at EU level and now covers the whole transplant chain. However, new methods of cell storage in banks question the relevance of this framework.

3.1 European Safety Standards for the Use of Human Cells

In the context of multiple health crises which have prevailed since the 1990s, the stated intent to minimize the risks of transmission of infectious diseases through the adoption of concrete measures largely led to the adoption of the Directive 2004/23/EC.⁷³ Furthermore the structuring of storage activities and activities related to the delivery of cells for transplantation purposes resulted in the emergence of structured and organized cell banks and of new professions requiring specific qualifications.

3.1.1 The Internal Safety of Human Cells⁷⁴

The concept known as biological safety spells the conditions for achieving what may be termed as material safety for the elements of the human body. The situation is slightly different concerning the safety of people themselves, since the clinical selection of donors and their information and consent (understood as one of the components of cell traceability and quality) are essential. There are two key parameters in the cell transplant chain that must imperatively be taken into account in order to minimize risks.⁷⁵ Firstly, cells must be “healthy”, meaning that it must be ascertained that they will not contaminate the donor.

⁶⁷ European Council, *Guide to the Quality and Safety of Tissues and Cells for Human Application*, (1st Edition, 2013), available on <http://www.edqm.eu/fr/Guides-transfusion-graft-DEQM-1607.html>.

⁶⁸ *Guide to the Quality and Safety of Organs for Graft*, 5th Edition (2013), available on <http://www.edqm.eu/fr/Guides-transfusion-graft-DEQM-1607.html>.

⁶⁹ Maastricht Treaty, 1992, Article 129, modified Amsterdam Treaty.

⁷⁰ For a comprehensive history of EU competence in matters of health see N. De Grove-Valdeyron, *Droit européen de la santé*, (Paris LGDJ, 2013), particularly p. 19 and following pages.

⁷¹ See Europa website, synthesis on European legislation, Public Health, http://europa.eu/legislation_summaries/public_health/threats_to_health/index_en.htm.

⁷² European Commission, DG SANCO, Commission européenne, http://ec.europa.eu/health/index_en.htm.

⁷³ *Ibid.*

⁷⁴ Directive 2006/17/EC of the EU Commission mainly dealt with the matter.

⁷⁵ The risks involved are of two kinds: on the one hand the risk of a disease being transmitted, on the other the risk of rejection in case of immunological incompatibility.

Secondly, the donor and the recipient must be biologically compatible. These elements do not suffice to ensure the quality and security of transplantation, and it is also necessary to inform the donor and the recipient of the risks incurred.

There is a vigilance procedure designed to detect infections and make sure that the medical histories of donors are known - hence the standardized questionnaires and protocols used when carrying out the required tests, set out in Directive 2006/17/CE and its appendices. These “standard operating procedures” (SOPs)⁷⁶ must make it possible to gather the information necessary to ensure the quality and safety of collection procedures, and to establish the motivation and will of the donor.⁷⁷ The data provided concern the identity of the donor, the information relative to the consent or the authorization obtained from the donor or their family, the assessment of the donor selection criteria and the assessment of the laboratory tests required for donors.⁷⁸ These SOPs also apply to the procurement, conditioning, labeling and transport procedures applicable to cells and tissues until they reach their point of destination – the tissue bank or, where the tissues and cells are to be delivered directly, the medical team in charge of using them, or also, in the case of tissue/cell samples, the laboratory in charge of carrying out the tests.⁷⁹ Appendix I of the Directive complements this instrument insofar as it standardizes the collection procedure for the information required for the clinical selection of donors, be they living or deceased donors. The object of the previously mentioned selection is to establish the medical and surgical histories of donors and enquire about their clinical situation. It relies on criteria based on the analysis of risks related to the use of specific cells/tissues. Among such criteria are a physical examination, a study of the medical and behavioural history, biological tests, post-mortem examination (for deceased donors). As to biological safety, the details of the tests – particularly those aimed at detecting infections diseases (various forms of hepatitis, HIV etc.), are recorded in appendices III and IV. The list of required tests was complemented in 2012 and appendices I and III⁸⁰ were modified. Finally the same level of requirements to ensure cells ‘safety has been implemented for imported cells with the adoption of the Commission Directive (EU) 2015/566 of 8 April 2015⁸¹.

3.1.2 The External Safety of the Uses of Human Cells

Directive 2006/86/EC⁸² was designed to optimize the use of human cells in a secured environment. It complements the frame with elements concerning the establishments storing and delivering cells and their staff. The goal of the requirements set out in the Directive is to minimize risks associated with donations and to allow only establishments subjected to regular controls and abiding by high quality standards uniformly accepted in the European territory to exercise their activity as cell banks. The objective is to ensure that actors comply with the technical requirements set out in the Directive, and that they act in conformity with scientific practice.

Establishments handling human cells and tissues have the obligation to comply with current safety standards on the one hand, and to take appropriate steps to ensure traceability and notify competent authorities of any serious undesirable event on the other hand. The establishments covered by the Directive are considered to be either *procurement*

⁷⁶ Directives 2006/17/EC and 2006/86/EC define them as “written instructions describing the steps in a specific process, including the materials and methods to be used and the expected end product”.

⁷⁷ Directive 2006/17/EC, Art. 3.5.

⁷⁸ *Ibid.*

⁷⁹ The stages of this procedure are laid out chronologically in Annex IV of the 2006/17/EC Directive.

⁸⁰ Commission Directive 2012/39/EU of 26 November 2012 amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cell, OJ L 327, 27/11/2012 pp. 24 – 25.

⁸¹ See note 9.

⁸² *Ibid.*

organizations (a health care establishment, a hospital department or any other organization that may engage in activities related to procuring human tissues and cells and may or may not be approved, appointed, authorized or licensed as a tissue establishment), or as *establishments responsible for human applications* (a health care establishment, a hospital department or any other organization which carries out clinical applications involving human tissues and cells). These establishments must have obtained approval, an appointment, an authorization or a license prior to exercising their activities.⁸³ They are subjected to standardized forms of internal control with a detailed mode of operation ensuring the implementation of the authorization requirements applicable to establishments⁸⁴ and to the traceability of cells.⁸⁵

Member states must also design and set up external control mechanisms based on inspections.⁸⁶ The notification system for serious undesirable reactions has been codified, making it the responsibility of the competent authorities of each country to collect information and produce a yearly report⁸⁷ to be communicated to the Commission⁸⁸ in the manner they judge suitable. In 2009 the Commission initiated a quick-alert system for tissues and cells on a European scale that has been upgraded as a web platform for use by competent national authorities in 2013. Four types of alert were defined, concerning respectively safety and quality defects, information notifications, illegal or fraudulent activities, and epidemiological notifications.⁸⁹ Between 2013 and 2015, 102 alerts have been encoded.⁹⁰

The Directive also stated that staff working in the said establishments must undergo specific training in order to operate with complete safety. It is therefore strongly advisable for the staff to be qualified and receive on-site training so as to maintain their level of knowledge and stay abreast of advances in their field.⁹¹ Although this frame is quite comprehensive, its relevance has been called into question due to the emergence of new practices, notably in the field of cell banks.

This legal regime has been complemented by the adoption of a set of technical requirements to reinforce the traceability of the cells from the donor to the recipient and vice versa. Hence, the Commission Directive (EU) 2015/565 of 8 April 2015⁹² has created an IT system for the attribution of a uniform labelling of cells in Europe (Single European Code).⁹³

3.2 The Emergence of an Ethical Safety in the Face of Cell Offers from Private Banks

Even though when the EGE delivered its opinion on tissue banks⁹⁴ it already viewed cell banks as one of the pillars of the activities involving cells, these establishments have

⁸³ Directive 2006/86/EC, Art. 3.

⁸⁴ Directive 2006/86/EC, annex I.

⁸⁵ Directive 2006/86/EC, annex II.

⁸⁶ Commission Decision of 3 August 2010 establishing guidelines concerning the conditions of inspections and control measures, and on the training and qualification of officials, in the field of human tissues and cells provided for in Directive 2004/23/EC of the European Parliament and of the Council, OJ L 213, 13.8.2010, p. 48–50.

⁸⁷ Directive 2006/86/EC Art. 7.

⁸⁸ Directive 2006/86/EC art.8.

⁸⁹ European Commission, Report on the rapid alert system for human tissues and cells (RATC) (2010- 2012), SANCO D4/IS/ac ARES (2013).

⁹⁰ European Commission, Rapid Alert system for human Tissues and Cells (RATC) Summary of 2015 activities, 20 May 2016, SANTE B4/PC/ ARES(2016).

⁹¹ Directive 2006/86/EC, annex I B.

⁹² See note 9.

⁹³ Commission Decision of 3 July 2015 establishing a model for agreements between the Commission and relevant organisations on the provision of product codes for use in the Single European Code, C(2015) 4460 final.

⁹⁴ EGE, Opinion n°11, *op. cit.* Although this opinion applies to cells insofar as they are assimilated to tissues, only the usefulness of hematopoietic stem cells in umbilical cord blood is explicitly mentioned.

developed considerably over the past few years. This is essentially due to the enhancement of the conditions of preservation but also to the use of cells being prescribed for other better known, better understood and better mastered applications. The discovery of new types of cells (stem cells or IPS) has sparked the growing interest of researchers for samples, insofar as they opened new therapeutic perspectives – no longer only curative but now also regenerative. Needless to say, the curiosity aroused in the scholarly world soon spilled into the industrial world, given the potentially significant added value of the discovery. A number of public-private partnerships emerged, a development which the EU strongly encouraged and to which it lent its backing in a research framework.⁹⁵ A different activity consisting purely and simply of “cell services” provided via private cell banks emerged concomitantly. The development of private cord blood banks only magnified the trend. These banks offer autologous use and conservation services of cord-blood cells (for the persons concerned or their families) directly to private individuals, for a –generally- annual fee. In the particular field of cord blood, resources are scarce as the volume of cells collected is small, and reserving that element for private use makes it unavailable for allogenic use. Obviously this operation, whose scientific feasibility remains to be demonstrated, results in flouting the notion of unpaid altruistic donations made for the common good. Today the scientific community agrees that autologous use of cord blood cells is justified in very rare cases, showing the enticement to take out a “biological insurance” for any type of regeneration that may be needed in the future through the storage of cord blood cells in private banks to be deceitful at best.

The phenomenon had been analyzed by the EGE in Opinion n°19⁹⁶ (2004), issuing cautious conclusions about the necessity to preserve free enterprise (which could be regulated in this particular case) as well as the ethical requirements governing the sharing of resources and the way those resources can be made available to those who might need them most for therapeutic purposes. Strictly concerning safety, the EGE did not fail to remind that no discrimination should take place between public and private organizations, reiterating its statement that “Commercial cord blood banks have to observe the same quality standards as any other tissue bank”. Consequently the EGE praises the European Parliament and European Council Directive adopted on March 2nd, 2004 on “setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, which provides for a legal European framework, namely in terms of authorization, licensing,, accreditations, inspections, controls, promotions and publicity and staff experience”.⁹⁷ On ethics, the EGE expresses its support for nonprofit public banks and its reluctance towards commercial, profit-making banks which challenge the principle of non-commercialisation of the human body : “ While some members of the Group consider that this [commercial] activity should be banned, the majority of the Group considers that the activities of these banks should be discouraged but that a strict ban would represent an undue restriction on the freedom of enterprise and the freedom of choice of individuals/couples”.⁹⁸ So it seems clear that concerning the safety of citizens, the aspect that should prevail is *ethical safety*. The offer as it was in 2004 and as it developed in the following years, has exposed the regulatory disparities among EU Members States. Certain States as France⁹⁹ have banned private banks

⁹⁵ See the latest instrument adopted in the matter, Regulation (EU) No 1291/2013 of the European Parliament and of the Council of 11 December 2013 establishing Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020) and repealing Decision No 1982/2006/EC, JO L 20/12/2013, pp.104-173.

⁹⁶ EGE, Opinion n°19 *Ethical aspects of umbilical cord blood banking* (2004).

⁹⁷ *Ibid*, p.24

⁹⁸ *Ibid*.

⁹⁹ This prohibition was enacted after overcoming many unexpected judicial hurdles and is now enshrined in the law on bioethics revised in 2011 (Interpretation of art. 1241-1 of the Code of Public Health which states that cord blood cells and placenta blood donations may only be anonymous, unpaid and altruistic). On this subject see, X. Bioy and E. Rial-Sebbag, “Les ressources biologiques devant le Conseil constitutionnel. Note sous

from coming into existence, others have authorized it (the United Kingdom), and others yet have worked out private-public regimes (Spain). Thus ethical safety is not ensured, when it should address the globalized demand for therapeutic cells with a globalized offer providing access to those cells. The private capture of resources entails a form of discrimination detrimental to sick individuals for whom resources are no longer available, allowing what could be termed as individualistic use to spread.

European institutions took a stance in 2012, when the European Parliament adopted a resolution on voluntary tissue and cell donations.¹⁰⁰ As the private offer developed (and with it a series of therapies lacking prior trials in certain Member States) a form of cellular tourism seemed to extend, making it necessary to reaffirm the cardinal ethical principles governing the use of human body elements. The resolution acknowledges the changes taking place in the field and reminds that the principles of consent, information, unpaid donations and of course the whole of the measures guaranteeing safety (traceability, cooperation among states etc.) must be made to apply in the new cases. One section of the resolution deals exclusively with cord blood banks, the Parliament calling for Opinion 19 of the EGE to be revised in order to acknowledge the developments, and highlighting the governing options that may be implemented in the future. Starting from the postulate that private and public establishments alike work for the common good according to the principle of non-commercialisation which is applicable across the spectrum, the Parliament encouraged public and private partners to set up new modes of collaboration. We support the idea that, as ensuring the financial soundness of blood cord public bank networks has proved to be an arduous task for the public sector, the private sector could bring valuable relief if partnerships were reinforced, so long as they met similar ethical and safety requirements. *De facto* the threat of discrimination would decrease significantly and effective equal access to health care could be achieved. Operational safety and ethical safety would thus be reinforced. Although the EU Parliament is calling for Directive 2004/23/EC to be modified in order to include the new practices, it will undoubtedly be necessary to take into account the new storage offers made available by private banks, notably for IPS.¹⁰¹ Those who promote such offers have so far been well inspired to only make them available to European citizens, the bank being established in a third country. But it is highly likely that the European Union will be one of the next lands to conquer, calling into question our concept of ethical safety¹⁰² where patient safety is concerned.¹⁰³

This issue will probably include more questions in the future¹⁰⁴ notably in the scope of the realization of clinical trials which are emerging for cell therapy as long as research ethics structures used for clinical trials across Member States could be seen as a possible future direction for EU regulation of human materials.¹⁰⁵ Ethical controversies on safeguards to be respected in clinical trials are currently discussed in some Members States¹⁰⁶, fostering European institutions awareness and, we hope, a common European reaction.

Société Cryo-Save France [Prélèvement de cellules du sang de cordon ou placentaire ou de cellules du cordon ou du placenta]”, *Constitutions* (3) (2012) 474-478.

¹⁰⁰ *Ibid.*

¹⁰¹ CELLECTIS, a French biotechnology company, announced in July 2013 the launch of a private IPS cell bank in Singapore, an operation which cost the applicant the sum of 47000 euros. See <http://tempsreel.nouvelobs.com/economie/20130708.OBS8542/exclusif-un-nouveau-pas-vers-l-immortalite.html>.

¹⁰² A large number of these new issues is to be studied within the framework of the project EUcelLEX, FP7 - Gr n° 601806 (Coord. Emmanuelle Rial-Sebbag).

¹⁰³ The link between cell safety and patient safety is still tenuous and we can but recommend that in the future these provisions be brought closer together.

¹⁰⁴ A. Blasimme and E. Rial-Sebbag, “Regulation of Cell-Based Therapies in Europe: Current Challenges and Emerging Issues”, *Stem Cells and Development* 22(S1) (2013), 14-19.

¹⁰⁵ J. V. McHALE and A. MAHALATCHIMY, “EU law and policy on human materials” in T. K. HERVEY and C. A. YOUNG, “Research Handbook in EU Health Law and Policy”, Edward Elgar, 2016/2017, *In press*,

¹⁰⁶ A. Abbott, “Stem-cell ruling riles researchers”, *Nature* (495) (2013) 418-419.