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European Commission
DG Health and Consumers
Health and Consumers Directorate-General
Unit D5 'Medicinal products – authorisations, EMA'

Via e-mail:
SANCO-ADVANCEDTHERAPY-REPORT@ec.europa.eu

Public Consultation on the Regulation on Advanced Therapy Medicinal Products
Cytori is pleased to have the opportunity to respond to the Public Consultation on the Regulation of Advanced Therapy Medicinal Products (**ATMPs**). Cytori is one of the world's leading regenerative medicine companies, manufacturing medical devices for the extraction, concentration and storage of adult stem cells derived from adipose tissue.

Cytori and the Celution Device
Cytori Therapeutics Inc. is a publicly listed company with its headquarters in San Diego, USA.

Cytori manufactures Celution®, a medical device which enables stem cells to be derived from a patient's own adipose tissue for therapeutic use. Celution is a closed, automated system which can be used to prepare a regenerative medicine product based on the patient's own cells at the point of care (in theatre, at the bed side, or within a hospital). As the cells are generally extracted and processed within one hour, the Celution device enables clinicians to extract and use adipose-derived stem cells within the same surgical procedure.

Stem cells derived from a patient's own adipose tissue are recognised as one of the best sources of therapeutically relevant stem cells. The Celution device has been available for use in Europe since 2006, during which time more than 5,000 patients have been treated using adipose-derived stem cells obtained using the Celution device without any serious safety concerns or adverse incidents.

Numerous clinical trials are underway globally to investigate various therapeutic applications of these cells, and Cytori is actively pursuing a number of these therapeutic applications with clinical partners around the world, including:

- The treatment of cardiovascular disease for patients who have undergone myocardial infarction or suffer from chronic myocardial ischaemia; and
- Post-mastectomy breast reconstruction.

Beyond these trials, we are aware that a number of clinicians are independently using the Celution device to investigate the use of adipose-derived stem cells to assist the treatment of (for example) wound healing, renal failure and peripheral artery disease. More details about our on-going clinical trials are enclosed as Appendix 1.
Cytori has also developed a system (known as the StemSource Cell Bank) to allow patients to store their own cells for future use.

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General Comments regarding the European Regulatory Framework

Rather than addressing the individual topics raised in the Consultation document, we thought it would be useful to provide a brief overview of our experience and approach, which may help explain Cytori's perspective.

In our view, there is no need to change the current regulatory framework established by various EU Directives and Regulations as regards autologous stem cells used within the same surgical procedure. However, as explained below, there is an urgent need for a more coordinated and clear approach to the interpretation of those regulations.

1. **ATMP Regulation and EU Tissues and Cells Directive**

   It is important at the outset to emphasise that a number of clinical applications of cells are not regulated as ATMPs. The fact that some cell-based therapies should be outside the scope of the ATMP Regulation is recognised within the ATMP Regulation itself and associated legislation such as the Tissues and Cells Directive (the **EUTCD**)[1]. It is worth stressing that the ATMP Regulation places ATMPs within the existing regime for Medicinal Products as set out in the Medicinal Products Directive[2]. We attach (Annex 1) a short note explaining our understanding of the legal framework applicable to autologous grafts of cells within the same surgical procedure.

   The alternative approach could have the unintended effect of criminalising a large number of well-established surgical procedures using the patient's own tissues and cells (such as *Cardiac Artery Bypass Grafts* using saphenous veins or *Spinal Fusion* using bone grafts). The ATMP Regulation was not enacted in order to prohibit procedures such as these.[3]

   Rather, the regulatory requirements related to the Celution device and the use of that device in a clinical context are set out in the Medical Device Directive, the professional standards applicable to the clinicians using the device, the requirements applicable to the clinics in which the procedures are conducted and general law (such as consumer protection statutes).

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[1] 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.

[2] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[3] Recently, a prominent Italian surgeon Professor Mario Marazzi expressed frustration at the prospect of losing the ability to use an existing therapy ("autologous skin") to treat burn patients as a result of an expansive interpretation of the ATMP Regulation: http://www.medtecheurope.org/blogposts/145/40/blog/2013/02/25/Asking-a-butcher-to-bake-bread-makes-no-sense-so-why-ask-EMA-to-approve-medical-devices

2. **Medical Device Directive**
Medical device laws require Cytori to:

- ensure that the Celution device satisfies applicable *Essential Requirements*, as set out in the Medical Device Directive, addressing the quality and safety of the Celution device;
- obtain a certificate of conformity from a Notified Body (the organisation which has responsibility for confirming that a medical device conforms to the applicable standards) to confirm that the technical, scientific and clinical evidence supports the conclusion that the device satisfies the applicable Essential Requirements;
- propose specific clinical indications for the Celution device, which are also verified by the Notified Body;
- establish and pursue a post-marketing surveillance plan (which itself must be verified on an ongoing basis by the Notified Body) to assess the clinical use of the device in the real world. In the case of the Celution device, Cytori has committed to conducting a number of Post-Marketing Clinical Follow-Up studies; and
- report any serious adverse incidents[4] to regulatory authorities.

These are onerous and ongoing regulatory requirements and, as such, it should not be thought that the Celution device is used without regulatory scrutiny or vigilance.

3. **Professional Requirements**
Clinicians using the Celution device must do so in accordance with applicable clinical and professional standards. There is no reason to doubt that these standards will be applicable to the use of autologous cells. In fact, as mentioned in Annex 1, autologous grafts of cells within the same surgical procedure are exempted from the requirements of the EUTCD as patient safety is addressed by these other clinical and professional standards.

Inconsistent application of EU regulations and Directives

In our experience, the UK regulatory and commercial environment facilitates rather than obstructs the translation and commercialisation of regenerative medicine. As set out above, the framework is demanding, but clear and consistent. Earlier this month, we received formal written confirmation from another national Competent Authority that the cells generated using the Celution device and used within the same surgical procedure (a specific procedure) should not be regulated as a medicinal product.

Unfortunately, EU Regulations and Directives have not been implemented or applied harmoniously throughout all EU Member States, and we have found certain other national regulators to be inconsistent and unduly restrictive in their approach to the regulation of regenerative medicine. In this dynamic and fluid field, regulators can adopt an overly restrictive approach, and misapply rules intended for other scenarios or products. In some contexts and countries, this has led to regulatory inertia, with officials unwilling to issue clear and practical guidance, focusing instead on the arbitrary misapplication of rules. In contrast, the UK has published guidance on some key points of interest to Cytori, and this has greatly helped us shape our plans for the future.

[4] The obligations relating to serious adverse incidents are set out in the Medical Device Directive:

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While good and proportionate regulatory oversight is crucial, a clear route to market and clinical application is the main driver of technological progress and patient benefit.

CONSULTATION TOPICS

We will only comment on the regulation of autologous therapies delivered to patients within the same surgical procedure using a point of care medical device. We are satisfied that such therapies are not regulated as ATMPs. As a result, we will not be commenting on either:

- the requirements for a marketing authorisation of an ATMP (topic 2.1); or
- the competence of the EMA to review compliance with the Essential Requirements for any combined advanced therapy medicinal products (topic 2.2); or
- the incentives for the development of ATMPs (topic 2.4).

We would like to make some brief comments about the Hospital Use Exemption (topic 2.3) and the scope of the ATMP Regulation (topic 2.5) generally.

2.3. Hospital exemption.
The Advanced Therapy Regulation empowers Member States to authorise the use of advanced therapy medicinal products in hospitals for individual patients in the absence of a marketing authorisation. The so-called hospital exemption provides for flexibility to address the situation of medicinal products prepared on a non-routine basis and used in a hospital under the exclusive professional responsibility of a doctor for individual patients; however, a too large application of this exemption may discourage the application for marketing authorisations.
Please provide your views on the application of the hospital exemption.

We believe that the hospital use exemption[5] is a sensible and pragmatic recognition of the reality of clinical practice and particularly the clinical use of autologous cells. Clinical therapies using autologous cells were used for many years prior to the adoption of the ATMP Regulation.

We are aware of the criticism of the exemption and we accept that the exemption is

[5] Article 3(7) of the Medicinal Products Directive and Article 28(2) of the ATMP Regulation.

> Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.
>
> Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

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inconsistently applied across Europe. However, while this exemption does not have a direct application to Cytori, we would strongly defend the existence of the exemption and the recognition of the rights of doctors to practice medicine and the rights of patients to make informed decisions about treatment, particularly using the patient's own cells.

We strongly support greater clarity in the application of this exemption and more consistent enforcement. We would not support any effort to abolish the exemption on the basis that this will disproportionately inhibit the clinical development of cell-based therapies.

A product that would otherwise be considered an unauthorised ATMP is exempted from the full requirements obtain a marketing authorisation if it is prepared on a *non-routine* basis according to specific quality standards, and *used within the same Member State* in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an *individual medical prescription* for a *custom-made product for an individual patient.*

Member States shall:

- authorise "manufacturing of these products" and
- ensure that national traceability and pharmacovigilance requirements as well as specific quality requirements referred to in this paragraph shall be equivalent to those … in respect of ATMPs for which authorisation is required.

We are aware of a request for an amendment such that the exemption would cease to apply once an ATMP for that indication has been granted a marketing authorization. We believe that such an amendment may create additional uncertainty. In this regard, we note that the longstanding "specials" exemption in Article 5(1)[6] of the Medicinal Products Directive does not specify that the exemption ceases to apply once an authorised medicinal product is available for the patient: this is left to national competent authorities to determine.

We believe that any attempt to interfere with this provision in the context of cell-based therapies will be problematic at best. The clinical use of autologous cells has a number of unique features which mean that it is difficult to fit into conventional medicinal product frameworks. The therapies are often heterogeneous cell populations with heterogeneous modes of action and no clear active pharmaceutical ingredient. As a result it would be difficult to ascertain exactly what makes two "products" sufficiently "similar" to merit the abolition of the exemption.

> *By way of example, let us assume that a marketing authorization is issued for a particular tissue engineered product (being a homogeneous population of a particular type of mesenchymal stem cell) manufactured in a certain way for the treatment of a specific condition (say GVHD), would the exemption apply to:*

[6] A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

(a) the use of a heterogeneous mixture of cells that included that particular type of MSCs;
(b) the use of MSCs other than the authorised type of MSC;
(c) the use of MSCs manufactured in a different manner; and/or
(d) the use MSCs to treat other immune conditions (e.g. Crohn's Disease)?

This becomes even more complicated if the authorized medicinal product is a population of allogeneic cells and the proposed therapy will involve autologous cells.

We would rather recognize and defer to the medical practitioner's professionalism and allow the doctor and the patient to make informed decisions about the treatment of each patient on a case-by-case basis.

The better approach would be to encourage national competent authorities to adopt common quality requirements and restrict promotional conduct. This is the approach adopted in the UK in 2012. The UK law implementing the Hospital Use Exemption[7] essentially restates the basic requirements of the exemption and added two clarifying points. The first is a prohibition on the publication of any advertisement relating to the medicinal product. The second related requirement is that the sale or supply of the medicinal product must only be in response to an unsolicited order. These requirements are repeated in the UK law Specials Exemption and reflect the guidance as regards the promotion and sale of authorised medicinal products for off-label uses.

2.5. Scope and adaptation to technical progress.

The Advanced Therapy Regulation applies to gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products.
Please provide your views on the scope of the Regulation and in particular as to whether the scope should be modified to take account of technical progress.

Cytori believes that the existing scope of the regulatory framework in Europe is proportionate and strikes an appropriate balance in the interests of patients – namely facilitating the development of new therapies while protecting patients. As a result,

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[7] Reg 171 of the *Human Medicines Regulations 2012* regarding *Exempt advanced therapy medicinal products*:
(1) The prohibitions in regulation 46 (requirement for authorisation) do not apply in relation to an advanced therapy medicinal product (an "exempt advanced therapy medicinal product") if the following conditions are met.
(2) Condition A is that the product is prepared:
  (a) on a non-routine basis;
  (b) in the United Kingdom; and
  (c) according to specific quality standards equivalent to those provided for advanced therapy medicinal products authorised under Regulation (EC) No 726/2004.
(3) Condition B is that the product is used—
  (a) in a hospital in the United Kingdom;
  (b) under the exclusive professional responsibility of a doctor; and
  (c) in order to comply with an individual medical prescription for a product made to order for an individual patient.
(4) Condition C is that no advertisement relating to the medicinal product is published by any person.
(5) Condition D is that the sale or supply of the medicinal product is in response to an unsolicited order.
(6) In this regulation "publish" has the meaning given in regulation 277(1) (interpretation Part 14 advertising).

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Cytori does not see any need to expand the scope of the ATMP Regulation.

In fact, we see the opportunity to amend the ATMP Regulation to recognize the fact that ATMPs using autologous cells to be distinguished from ATMPs using allogeneic cells given that the risks associated with the use of autologous cells are dramatically lower than the risks associated with the use of allogeneic cells.
The over-regulation of regenerative medicine (or an inconsistent interpretation) will stifle innovation and force those developing the technology (and their jobs) to move to more constructive jurisdictions. This could also deprive patients in Europe of the opportunity to access the therapeutic potential of their own cells. We hope that the Commission will support the existing regulatory framework and encourage regulators to continue to adopt a proportionate and pragmatic approach to the regulation of stem cells.

We confirm that nothing in this submission is confidential.

Yours faithfully,

Christopher J. Calhoun
Chief Executive Officer

Kenneth K. Kleinhenz
Vice President,
Regulatory Affairs & Quality Assurance

Dr. Marc H. Hedrick, MD
President

Annex 1
Regulatory Framework regarding Cells used as an Autologous Graft within the Same Surgical Procedure

1. EU Tissues and Cells Directive ("EUTCD")

Cells used as an autologous graft within the same surgical procedure are explicitly exempted from the EU Tissues and Cells Directive under Article 2(a)[8]. The rationale for this is in Recital 8 to that Directive:

> *"Tissues and cells used as an autologous graft (tissues removed and transplanted back to the same individual), within the same surgical procedure and without being subjected to any banking process, are also excluded from this Directive. The quality and safety considerations associated with this process are completely different."*

This issue was explicitly considered at a meeting of the Competent Authorities for Tissues and Cells at a meeting on 23-24 June 2011,[9] which considered autologous grafts within the same surgical procedure. The meeting expressly considered the use of the Cytori Celution device in reconstructive surgery. The meeting conclusively confirmed that:

- the procurement of stem cells from adipose tissue using the procedure described in relation to the use of the Celution device;
- when used in relation to the same individual within the same surgery process;
- in the same operating room; and
- when cells used with the same essential function (e.g. adipose-derived regenerative cells restoring the adipose mass of the breast following mastectomy for breast cancer), should be exempt from the EUTCD based on Article 2(a).

The philosophy underpinning this decision should apply to the regulation of such therapies and the use of such cells. In short, the quality and safety considerations associated with autologously derived material extracted within the same surgical procedure are different to those which apply to other cells and tissues.
As a result, such cells would not bear any donation or product codes that apply to cells that fall within the remit of the EUTCD.

2. Interaction between the ATMP regulation and the EUTCD

The ATMP Regulation expressly relies on the EUTCD in a number of crucial respects. By way of example, Article 2(1) of the ATMP Regulation incorporates various definitions from the EUTCD (as well as the Medicinal Products Directive 2001/83). Clearly it was intended that the ATMP Regulation would be read in conjunction with the existing legislative framework.

Article 12(a) of the ATMP Regulation (regarding "Special immediate packaging") requires that the packaging of an ATMP must include: "the unique donation and product codes, as referred to in Article 8(2) of" the EUTCD. This requirement is replicated in

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[8] This Directive shall not apply to … tissues and cells used as an autologous graft within the same surgical procedure.
[9] http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_mi_20110623_en.pdf at para 3.3.

paragraph (m) of Annex III of the ATMP Regulation[10]. Given that cells used as an autologous graft within the same surgical procedure are exempted from the requirements of the EUTCD, there would not be any codes.

Similarly, Article 14(5) of the ATMP Regulation (regarding post-authorisation follow-up of efficacy and adverse reactions, and risk management) specifies that "If serious adverse events or reactions occur in relation to a combined advanced therapy medicinal product, the Agency shall inform the relevant national competent authorities responsible for implementing Directives 90/385/EEC, 93/42/EEC and 2004/23/EC." Again, given that cells forming an autologous graft within the same surgical procedure are exempted from the requirements of the EUTCD (2004/23/EC), a notification to the relevant competent authority would not be relevant as that competent authority would not have any jurisdiction.

Finally, Article 15(3) of the ATMP Regulation (regarding traceability) specifies that: "Where an advanced therapy medicinal product contains human cells or tissues, the marketing authorisation holder, as well as the hospital, institution or private practice where the product is used, shall ensure that the traceability systems established in accordance with paragraphs 1 and 2 of this Article are complementary to, and compatible with, the requirements laid down in Articles 8 and 14 of Directive 2004/23/EC ..." Again, given that cells forming an autologous graft within the same surgical procedure are exempted from the requirements of the EUTCD (2004/23/EC), there would not be any traceability systems.

In short, it is clear that the ATMP Regulation requires that the cells themselves are already regulated by the EUTCD. To rephrase, only cells that are regulated by the EUTCD could constitute ATMPs. As a result, if the cells are excluded from the EUTCD (by way of example by Article 2(a) of the EUTCD), then the ATMP Regulation cannot apply to the cells. Further, we submit that this is precisely why the Medicinal Products Directive has two threshold requirements: the product must be (i) placed on the market and (ii) produced industrially.

3. The ATMP Regulation

In addition to the points above about the EUTCD and the dependence of the ATMP Regulation on the EUTCD, cells used as an autologous graft within the same surgical procedure are not be regulated under the ATMP Regulation for the following reasons.
If (as would likely be the case for any cells obtained using the Celution device) such cells are viable and are administered with a view to regenerating, repairing or replacing human tissue, then they will only be regulated as ATMPs if the cells are:

- *placed on the market*[11];
- *produced industrially*[12]; and
- *substantially manipulated* or <u>not</u> intended for the *same essential function.*[13]

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[10] Paragraph (m) of Annex III of the ATMP Regulation requires: *The manufacturer's batch number and the unique donation and product codes referred to in Article 8(2) of Directive 2004/23/EC.*
[11] Article 2(1) of the Medicinal Products Directive 2001/83.
[12] Article 2(1) of the Medicinal Products Directive 2001/83.
[13] Article 2(1)(c) of the ATMP Regulation.

3.1 Placed on the market and produced industrially

To be clear, the ATMP Regulation amends the Medicinal Products Directive by adding a new category of medicinal products, namely ATMPs. Article 2(1) of the Medicinal Products Directive contains two fundamental threshold requirements before a medicinal product is regulated. First the product must be *placed on the market*. Second, it must be *produced industrially* (or produced by a method involving an industrial process). These two fundamental requirements were recognised by the Committee for Advanced Therapies in a classification decision that it issued on 17 August 2011[14].

We do not propose to comment on the meaning of these two requirements or their application to ATMPs in this note. If you would like additional commentary on these points, please do not hesitate to ask. However, we believe that cells obtained using the Celution device and used as an autologous graft within the same surgical produce are neither *produced industrially* nor are they *placed on the market*. In fact, in many regards, an autologous graft of cells within the same surgical procedure is more a service than a product.

The more common discussion in relation to ATMPs focuses on the two criteria added for tissue engineered products (the applicable subset of ATMPs). In order to be an ATMP, the cells would need to be either *substantially manipulated* or not intended to be used for the *same essential purpose* in the recipient as in the donor. As discussed below, we are confident that cells obtained using the Celution device which are used as an autologous graft within the same surgical produce would not be considered to be substantially manipulated or intended to be used for a purpose other than their original essential function.

3.2 Substantial Manipulation

Annex I[15] of the ATMP Regulation lists manipulations that are <u>not</u> considered "substantial". Cells that are manipulated in the ways listed in Annex I are not considered to have been "engineered".

Most of the actions listed in Annex I make it clear that an isolated or concentrated cell population would not constitute substantial manipulation. In a number of its classification decisions, the Committee for Advanced Therapies has not suggested that extraction of sub-populations of stem cells for autologous

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[14] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/08/WC500110644.pdf

[15] Manipulations referred to in the first indent of Article 2(1)(c) that will be considered "minimal" include (10.12.2007 EN Official Journal of the European Union L 324/137):

- cutting,
- grinding,
- shaping,
- centrifugation,
- soaking in antibiotic or antimicrobial solutions,
- sterilisation,
- irradiation,
- cell separation, concentration or purification,
- filtering,
- lyophilization,
- freezing,
- cryopreservation,

use (e.g. CD133+ bone marrow cells[16]) would constitute "substantial manipulation. Further, on 24 July 2012, the CAT also confirmed that *autologous, non-manipulated lipoaspirate containing adipocytes and stromal vascular fraction* intended to be used as *a natural, autologous lipofiller*" is not an ATMP.[17]
In light of the above, cell populations generated using the Celution device are not considered to have been substantially manipulated.

For completeness, we note that regardless of the actions listed in Annex I, the test as set out in the definition of an "engineered product" specifies that a cell will only have been *substantially manipulated* if the *relevant* biological characteristics, physiological functions, or structural properties have been changed. The *relevant* biological characteristics, physiological functions or structural properties are those that are relevant to the *intended* use of the cell. As a result, the focus should be on the intended use of the cells themselves. The applicable test is not a change in the primary or dominant characteristics, but rather the changes in the characteristics relevant to the intended use.

This point may be illustrated by considering the example of a cell population has two potential physiological functions: immunosuppression and the promotion of angiogenesis. In this example, the clinician intends to use the cells for the angiogenic function and has no interest in the immunosuppression function.
In this case, the question of whether the cells have been substantially manipulated should focus on the impact of the manipulation on the angiogenic function of the cells. The extent to which a cell's immunosuppression function has been altered (if at all) should be irrelevant. One could argue that so long as the angiogenic functions have not been substantially manipulated, then the cells should not be considered substantially manipulated even if the immunosuppression functions have been substantially altered. This influences the consideration of the second requirement of the test as to whether cells constitute tissue engineered products; namely the cells must be used for the same essential function in the recipient as in the donor.

3.3 Same Essential Function

Provided that the cell has not been substantially manipulated, it will not be considered an ATMP if *the cells are not intended to be used for the same essential function or functions in the recipient as in the donor.*[18]

As described above, the focus should be in the intended use of the cells rather than the source of the cells. Provided that the clinician intends to use the cells for a purpose that they can or do perform prior to explant, then it would appear as though they would be used for the same essential function for the purposes o the ATMP Regulation.

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16 http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500118207

17 http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/10/WC500134164.pdf

18 Article 2(1)(c) of the ATMP Regulation.

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By way of example, the essential function of a cell that promotes angiogenesis would appear to be angiogenic. Accordingly, these cells will continue to be angiogenic wherever they are placed in the body. Thus, irrespective of the source of a patient's own angiogenic cells, so long as these cells are transplanted with the intention that they perform an angiogenic role in the new location, then they are continuing to be used for the same essential function.

This is consistent with the statements in the *travaux preparatoires* that the ATMP Regulation does not apply to transplants. The *travaux preparatoires* states that "non-substantially manipulated cartilage cells used to replace cartilage, even elsewhere in the body" would not be regulated by the ATMP Regulation as this is a "transplant".[19]

Similarly, cells (such as mesenchymal cells) that modulate the immune reaction to an episode are being used for the same essential function when they continue to be used to modulate the immune reaction irrespective of the location. The fact that mesenchymal cells also perform a haematological restoration function is irrelevant to the intended clinical use.

The *travaux preparatoires* gives an example of the use of autologous cells to repair/regenerate cardiovascular tissue. This is given as an example of a product that would fall within the scope of the Hospital Use Exemption. However, the discussion states that the resulting product might otherwise be considered to be an ATMP if the cells were substantially manipulated. There is no suggestion that such use of these cells would constitute non-homologous use.[20]

The Celution device is currently approved for use in soft tissue reconstruction. Clinicians using the cells obtained from the Celution device in such surgery intend to take advantage of the innate essential function of the cells (promotion of angiogenesis and immune modulation) to facilitate engraftment of the newly transplanted adipose tissue.

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[19] Commission Staff Working Document Annex to the *Proposal for a Regulation on Advanced Therapy Medicinal Products, Impact Assessment,* Brussels 16 November 2005.

[20] The following example is taken from paragraph 8.2.3.2 (*Scope*) of the Commission Staff Working Document, Annex to the: *Proposal for a Regulation on Advanced Therapy Medicinal Products, Impact Assessment*, Brussels, 16 November 2005:

> A hospital developing an in-house, non-industrial technology based on autologous cells to repair/regenerate cardiovascular tissue for a given patient, treated in the same hospital. In this case:
>
> - the resulting product may be considered as an advanced therapy product, if the cells are substantially manipulated;
> - however, it is prepared in full and used in a hospital, in accordance with a medical prescription for an individual patient.
> - This case would therefore not be covered by the proposed Regulation, as it falls outside its scope.

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Summary

The Celution device has been used in more than 5,000 procedures in Europe since 2006 without any serious adverse incidents. The device is regulated as a medical device with specific approved indications. Local professional bodies regulate the clinicians using the device. Finally, the sites in which the procedures have been conducted must also satisfy local quality and safety standards.

The cells obtained and used in autologous grafts within the same surgical procedures using the Celution device in accordance with its approved indications are:

(1) never placed on the market;
(2) not produced industrially;
(3) not substantially manipulated;
(4) used for the same essential function in the donor as in the recipient.

As a result, such cells are not (and should not be) regulated as ATMPs.