Ethical Aspects related to Human Tissue engineered products: Some considerations for a Future European Regulatory Framework
STAKEHOLDERS CONFERENCE: "THE FUTURE EUROPEAN REGULATORY FRAMEWORK FOR HUMAN TISSUE ENGINEERED PRODUCTS" (BRUSSELS, 16 APRIL 2004)

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The creation of a future harmonised regulatory framework at the European level on Human Tissue Engineered Products, makes necessary to develop a specific approach, both from a legal and from an ethical point of view, to the aforementioned issue. To some extent, problems which will have to be analysed are common to the ones present at other Biomedical areas, but specificity of Human Tissue Engineered Products suggests the importance of a detailed and particular approach.

Basically, when considering the whole process leading to the production of Tissue Engineered Products, three main aspects arise, each of which deserves a careful consideration:

1. Obtention and collection of tissues
2. Product elaboration using genetic engineering
3. Clinical use of the product

In order to analyse the ethical and legal problems associated with each of these stages, we will proceed to a separate evaluation.

I. Obtention and collection of tissues

At this initial stage, different questions have to be considered.

A/ Donor's consent

Firstly, and related to the conditions of donation: free, informed and specific consent has to be required, what is clearly stated under the Directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and

distribution of human tissues and cells. The same criteria is established under the European Convention on Human Rights and Biomedicine (including protocol from 2002). At this point, problems could arise in relation with freedom to revoke consent. Even when freedom to revoke consent to the loss of physical integrity, especially in case of donation of a body part, is a long-established and undisputed legal principle (as an essential guarantee of the donor's free will and an expression of the sacred inviolability of the body) this does not mean, that even after donation the donor retains discretionary powers over the dissociated parts/substances of his body, meaning ultimately the power to withdraw his authorization and to reclaim sovereignty over them. On the contrary, the need to adapt traditional thinking on separated body parts to the new context created by recent achievements in biomedicine forces the point that, once donation has occurred on a basis of voluntary, conscious and informed consent, the donor renounces his ownership of, sovereignty over and all other rights regarding the ceded parts, substances or tissue, provided these are used for the purpose which legitimised the donation and in respect of which consent was given. Only where there is a discrepancy between the originally use of body parts and the actual use to which they are put –whether because relevant data were withheld from the donor which might have precluded or conditioned his consent or because such data unexpectedly come to light in the course of events– does the possibility arise of the donor revoking his original consent or claiming compensation for deception or resulting moral damage (without prejudice to administrative or penal measures to penalize dishonest or unlawful behaviour in this field).

On the other side, the eventual subjection of minors or legally incapacitated adults to procedures which compromise their physical integrity should be considered under a restrictive point of view. In principle, and following the general criteria established by European Convention on Human Rights and Biomedicine (1997) and by its additional protocol from 2002, it seems to be the better option not to authorized (to forbid) any extraction of substances, elements, products and tissue from the bodies of minors and incapacitated adults without any direct therapeutic or diagnostic benefit to the same.

B/ Traceability vs. confidentiality

The second aspect which has to be considered at this stage is the one related with traceability. The development of Human Tissue Engineered Products creates new needs of regulation in the field of anonymisation and pseudonimysation. On one side,

traceability of tissues and cells should be guaranteed, but on the other side it is absolutely necesary to ensure a certain level of confidentiality to the donor in order to avoid the abusive use of his/her personal data, affecting intimacy and the right to the private life. In other words, privacy and anonymity against the background of traceability of tissue donors and recipients for safety purposes is an issue in the field of Human Tissue engineered products.

In order to protect both interests it is absolutely necesary to develop diferent processes so as to ensure the purpose aforementioned. These processes could consist, among others, in the anonymisation of the data, which should have the effect of disabling the individual's identification or of avoiding the linking of such data with the person to which they belong. In occasions it has also appeared as an alternative process the pseudonymisation of the data, although it is certain that this last process offers a more limited protection of the data.

Anyway, in the field of Human Tissue Engineered Products we have to make an option between anonymisation and pseudonimysation, having to take into account that a double purpose is being searched: on one hand confidentiality related to the donor himself, and on the other to ensure traceability of the tissues and cells employed.

1. Anonymisation

The Directive 95/46/CE does not give a definition on what should be understand under anonymisation, but as it was indicated above we can establich the juridical effects regarding the personal data that have been subjected to such a process, i.e. that are anonymous.

Nevertheless, indirectly it can be deduced what the Directive understands when talking of anonymisation. In accordance with the aforementioned Directive, the anonymisation refers to any process which makes no longer possible the identification of the interested person (recital nº 26). This recital seems to entail an absolute impossibility of identification due to the anonymisation process. Art. 2, b seems to follow this same orientation. But, on the other hand, recital 26 also establishes that “to determine whether a person is identifiable, account should be taken of all the means *likely reasonably* to be used either by the controller or by any other person to identify the said person” (the underlined has been added). The word "reasonably" seems to be opposed to the

statement of the Directive previously mentioned: with "reasonably" the level of demand of identification impossibility is limited to a certain degree (the "reasonable").

2. Pseudonymisation

Pseudonymisation as such does not implies data to be anonymous or to be related to a non identifiable person. In order to know if the data are anonymous or pseudonymised, we have to consider if they require or not unreasonable procedures or disproportionate efforts to achieve the person's identification.

Keeping in mind pseudonymisation procedures that are used habitually, in most of the cases the data will be identifiable person's data and not anonymous data. Consequently, pseudonymised data will be subjected to the principles of protection of personal data. Pseudonymisation could be an adequate mean to be used when in a medical or genetic research it is necessary to maintain the identity of the subjects involved in that research and consequently the anonymisation of the data is not possible.

Data pseudonymised are usually subjected and they should continue being subjected to the regime of protection of personal data. Taking into account that the pseudonymisation is a temporary and reversible system of protection, the data submitted to pseudonymisation have to be considered data of identifiable persons and have to be protected that way, which does not differ from the system of protection established for identified persons.

On the basis of the aforementioned arguments, we can establich which is the technical procedure considered more adecuate in the case of donation of Human Tissues and Cells to undergo Human Tissue Engineered Products. On the one hand, the need to guarantee the interests of the patients (safety purposes) has to be balanced with the right to confidentiality and to private life corresponding to the donor of tissues.

In this case, and having to choose one of the technical procedures previously mentioned (anonimysation and pseudonimysation) it seems that the first one (anonimysation), especially when irreversible, makes impossible the necessary traceability of the tissue. Due to this fact, in our opinion it would be preferable to opt for a pseudonimysation in order to guarantee the privacy of the personal and sensitive data (which can be obtained

from the tissue and cells donated) of the donor, being possible, if necessary to determine who the donor is. On top of that, if the technique applied is the pseudonimysation, this personal and private data will benefit from the protection afforded by Directive 95/46/EC.

Related to this aspect the Directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells, considers essential to ensure the traceability of tissues and cells (art. 10), but on the other hand states "Members States shall take all necessary measures to ensure that all data, including genetic information, collated within the scope of this Directive and to which third parties have access have been rendered anonymous so that the donor and the recipient are no longer identifiable". It seems that the use of the concept of "anonymous" data, as used by the aforementioned Directive does not match with the one set by Directive 95/46/EC. In this case, the Directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells refers to a pseudonimysation process and not to an anonymisation one.

C/ Possible use of stem cells in order to obtain human tissue.

In case of use of such cells, well-known legal and ethical aspects have to be considered. At this stage, the national regulation in force differs greatly between the European countries, having these legal constrictions to be taken into account in order to undergo any process which implies the use of stem cells. In the Spanish case, a recent legal modification has come into force: considering the opinions in favour of research with embryo cells expressed by the scientific community, broad sectors of society who are potential beneficiaries of such research, and the government's advisory bodies –the National Commission on Assisted Human Reproduction and the Advisory Committee on Ethics in Scientific and Technical Research-, surplus embryos obtained previously to a fixed data should be made available for research on the condition that they cannot be used for the initial reproductive purpose. Only under this circumstance can a research interest be posited as an alternative to the destruction (or thawing) of the embryos, in all cases with the consent of the genetic parents where this wish can be made know. Finally, it has to be said that Spanish Law 45/2003, of 21th November creates in Spain the National Centre of Transplants and Regenerative Medicine, some of whose functions are to coordinate and to promote the transplantation of human organs, tissues

and cells in Spain, and to promote research with tissues and cells according to the legislation in force and to the international treaties signed by Spain.

II. Product (Human Tissue) elaboration using genetic engineering

At this stage it is essential to set the necessary safety measures (specific, and adapted to the level of risk corresponding to the application) in order to avoid the creation of further risks.

It is necessary, in the field of Human Tissue Engineered Products, to consider the need of clinical trials (regulated by the Directive 2001/20/EC) in order to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal products, and/or to identify any adverse reactions to one or more investigational medicinal products and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal products with the object of ascertaining its (their) safety and/or efficacy.

III. Clinical use of the product

Related with the second stage (product elaboration using genetic engineering) and with this third one (clinical use of the product), the main issue that has to be considered is the one associated with the need of a new specific regulation in this field, or on the contrary, the possible application of the legislation in force both at the European and at the national level, on medical devices or on pharmaceutical products.

In principle, neither the regulation on medical devices nor the one on pharmaceutical products are sufficiently specific to provide enough safety for the patient. The development of a new specific regulation seems necessary to guaranty the different interests affected by Tissue Engineered Products. These new regulation, should be developed taking basically into account the existing framework on tissues and cells (obtention, banking, etc.), in order to ensure an adequate coordination between the different stages of the process (1. obtention, 2. production, 3. clinical use).

General principle in this field is the prohibition of economic gain for the donor -even when private companies obtain a commercial benefit from the product- (art. 12 of the Directive on tissue banking states “Member states shall encourage voluntary and unpaid

donations of tissues and cells (….)". Following Bock/Ibarreta/Rodríguez-Cerezo (Human Tissue-engineered products. Today's market and future prospects, October 2003), we can state that even when ownership of donated tissue is not discussed (a court decision in the USA in 1990 denied ownership to patients of cells harvested during the course of medical treatment), the making of profits with donated tissues by companies without compensating the donor, is an issue. In this point, we substantially agree with the criteria established on the Directive on tissue banking, contrary to the obtention of a financial gain by the donor, but we consider that a system similar to the one set by the UNESCO International Declaration on Human Genetic Data (2003) should be put in place. In its art.19 the aforementioned declaration states:

Article 19 – Sharing of benefits
(a) In accordance with domestic law or policy and international agreements, benefits resulting from the use of human genetic data, human proteomic data or biological samples collected for medical and scientific research should be shared with the society as a whole and the international community. In giving effect to this principle, benefits may take any of the following forms:
(i) special assistance to the persons and groups that have taken part in the research;
(ii) access to medical care;
(iii) provision of new diagnostics, facilities for new treatments or drugs stemming from the research;
(iv) support for health services;
(v) capacity-building facilities for research purposes;
(vi) development and strengthening of the capacity of developing countries to collect and process human genetic data, taking into consideration their specific problems;
(vii) any other form consistent with the principles set out in this Declaration.
(b) Limitations in this respect could be provided by domestic law and international agreements.

By establishing one such system we will ensure that one part of the benefits obtained by companies will be devoted to social needs related with groups of patients, medical care, etc., avoiding any economic gain for the donor.