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Comments on the Consultation Document on T issue Engineered Products

This note is submitted in response to the public consultation on the future proposal for a harmonised regulatory framework on human tissue engineered products (TEPs). It provides suggestions for the definition of Tissue Engineered Products and related terms , and for the concept of placing on the market.

Core definitions

The following contains suggestions to the text on page 7 of the consultation document (presented in "track changes" mode).

• "Human tissue engineered product" means any autologous or allogeneic product which:

- contains, consists of, or results in engineered human cells or tissues; and

- has properties for, or is presented as having properti es for, the regeneration, repair or replacement of a human tissue or human cells, where the new tissue or the new cells, in whole or in part, are structurally and functionally analogous to the tissue or the cells that are being regenerated, repaire d, or replaced, or to comparable tissue or cells. *[There may be applications where the TEP perf orms a typical tissue or cell function but in a place where there is no such original tissue or cell, or at least not to a similar degree .]*

Human tissue engineered prod ucts are derived from living cells or tissues, with the final product containing viable or non-viable cells or derivatives thereof. They may, for their function, also contain cellular products, bio-molecules ~~and~~ biomaterials, and other components (including chemical substances, scaffolds and matrices).

For the purpose of the Regulation, human tissue engi neered products can be produced as standardised products, for a limited number of patients or for a single patient. In all three cases, the products propos ed in the Community will be covered by the definition of "placing on the market" (see section 3 b) below) also when they are prepared in the facility in which they are administered to the patient.

• *Engineering* means any process whereby cells and tissues removed from a human donor (source materials) are substantially manipulated, so that their ~~normal~~ physiological functions or other biological characteristics are affected.

• *Autologous product*: product derived from cells and tissues removed from one person and used in/on the same person.

• *Allogeneic product*: product derived from cells or tissues removed from one person and used in/on another person, also when it in addition contains autologous tissue or cells . *[Clarifies that in case of mixed autolog ous and allogeneic material, the TEP is considered allogeneic.]*

It is also advisable to allow a definition of key terms to be adopted , and where needed, amended by the Commission via the comitology procedure, especially in light of technical progress.

Placing on the market

The definition of "placing on the market" is inspired by the Medical Devices Directive 93/42 but does not clearly cover all use of in-house preparations. This follows from the experience with the medical devices regime. Community guidance is provided in the MEDDEV 2.1/1 document , which states:

> "1.3 Definition of "manufacturer"
> **Users in-house manufacturing**
> The Directive defines a manufacturer as the natural or legal person responsible for defined manufacturing activities related t o a device with a view to its being placed on the market under the manufacturer's own name.
> The reason for this link with the placing on the market is that the directive aims to subject to its protection requirements the transaction of a device from the sphere of a manufacturer towards the public. The directive does not provide any specific provisions for the case where a device is manufactured by the user (for example, a hospital) without being transferred to another person. The decision to which extent su ch in-house manufacturing activities by hospitals are subjected to legal requirements, belongs therefore to the national legislator. This relates however exclusively to such in-house manufacturing activities where a device remains within the users, but not to cases where, for example, a hospital produces orthopaedic devices for use with patients." (original underlining)

In the United Kingdom, the MHRA advised as follows:

> "… The Commission's view as set out in their guide to new approach Directives is tha t "making available" means the transfer of the product by way of transfer of ownership or the passing of the product to the final consumer or user in a commercial transaction , for payment or free of charge regardless of the legal instrument on which the tr ansfer is based (sale, loan, hire, leasing, gift, or any other type of commercial or legal instrument). For all definitions unless otherwise stated, see Regulation 2(1) of the Medical Devices Regulations 2002 (SI 2002 No 618).
>
> If a device is made by one l egal entity for use on or by the patients of that same entity, there is no placing on the market and the Regulations do not apply. It makes no difference that the device is transferred between parts of the entity under separate management or parts of the entity housed on different premises. For example, a device developed in a physics laboratory which is a constituent part of an NHS trust hospital for use on that hospital's patients would not be placed on the market when passed from the laboratory to anoth er part of the hospital."

> (MHRA Directive Bulletin 18, The Medical Devices Regulations: Implications on Healthcare and other Related Establishments ; original underlining).)

In Germany, specific rules for medical devices that are prepared in -house are contained in the *Medizinproduktegesetz* (in sections 3.21 and 12), requiring compliance with the essential requirements but not CE-marking.

These principles may in many instances not be easy to apply to the use of Tissue Engineered Products. Some TEPs may, for instance, be principally or exclusively used in a hospital facility (for instance for dialysis). Many others may be used in patients without there being a clea r "commercial transaction", the use being embedded in a more general relationship of medical treatment that is typically not of a commercial nature. Finally, some TEPs may very well be biologically transformed during the period the patient remains in treatment in the hospital, which makes them more difficult to compare with orthopaedic implants.

In order to avoid problems of interpretation, it is suggested to amend the definition of "placing on the market" as follows:

> "For the purpose of the Regulation, "placing on the market" mea ns the making available of a tissue engineered product, with a view to distribut ion and/or use in the Community, or, in the absence of the foregoing, use in or on a human person."

Obviously, allowance should be made for use in clinical trials , but this is most appropriately done as an exception to the marketing authorisation requirement .

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