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Natural implant

COMMENTS ON THE FUTURE PROPOSAL FOR A HARMONIZED REGULATORY FRAMEWORK ON HUMAN TISSUE ENGINEERED PRODUCTS (HTEP)

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1. Presentation of the company and Ligaplant, the product developed

Natural Implant, SME created in 1998, is based in France. The product developed by the company , Ligaplant®, is a dental implant made of titanium with living autologous periodontal ligament cells around its surface.

Ligaplant® is indicated for use to treat patients that have one or more missing teeth.

A small sample of the patient's periodontal ligament is extracted and put in culture in order to reconstitute the ligament around a titanium implant. The titanium implant and the autologous periodontal ligament cells are fully integrated in the finished so called "Ligaplant®" product. Ligaplant® is maintained inside its conditioning box (filled with culture medium) by a special holder which is used by the dentist to bring Ligaplant® into the mouth of the patient. The dentist will have to open the box just before the implantation. There is no manipulation of the Ligaplant® once outside the box and prior to implantation.

Ligaplant® is currently used in a **first human pilot clinical trial** in France.

Ligaplant® is a permanent artificial "tooth" for replacing a compromised natural tooth, with more anatomic and physiologic equivalence than any other techniques currently available. It is the only solution that allows the reconstruction of a functional periodontal ligament, whose role is critical.

Ligaplant® is a solution that eliminates the inconveniences of existing solutions for the replacement of lost teeth:

a) Benefits compared to bridges

The procedure respects the buccal-dental environment better, because it is less iatrogenic than current prostheses.

b) Benefits compared to osseo-integrated implants

Ligaplant® recreates the normal link between the root (artificial) and the bone. Its attached tissue layer is capable of regenerating the desmodont and the alveolar bone. It restores the periodontal membrane to a normal physiology: its relationship to growth and to the absorption and redistribution of loads.

2. Discussion on the future regulatory framework

a. Scope of definition

Scope

- We would like to insist that the new hTEP regulation should include in its scope the clinical trials, considering that the Clinical trial Directive(2001/20/EC) cannot be to the full extent applicable to TEP products (in particular, in terms of timelines of agreements)

- We disagree that xenogeneic products should be totally excluded from the final products and insists that it is very difficult to make sure that xenogeneic products used during the TEP manufacturing do not remain at the end (for instance PBS)

Definition

- We would like to stress that, where an hTEP is used in combination with a Medical Device, the Medical Device may need to comply with certain relevant requirements of Directive 93/42/EC (i.e. Annex 1 Essential Requirements [ERs]), but not all ERs would be applicable and there should be no requirement for CE marking. For example, in our product, the titanium implant (in particular its surface) has been designed for an optimal combination with the autologous ligament cells. The titanium implant used alone is not adapted to fulfil the intended use of teeth replacement.

- We would expect that a new Guidelines on the Borderline between hTEP/ medical devices (such as what was done for Medicinal Products and Medical Devices: MEDDEV 2.1/3 rev 2 July 2001) will be issued. This should include the Consultation Procedures between Competent Authorities and Notified Bodies for products on the hTEP/Medical Devices Borderline.

b. Authorisation procedure

- We think that the authorisation procedure should be based on the level of risks of the product and not according to the origin of the product (allogeneic/autologous). Level of risks could be determined according to the functionality of the tissue and related risks (for example, hTEPs aimed for replacement of heart vessels are linked with higher risks as hTEPs aimed for tooth replacement)
- If however a two-tier approach is maintained (allogeneic/autologous), the non-clinical and clinical evidence that would be required in the authorization dossier should be dependant on the risks analysis of the product.
- It should be certain that the same requirements will be required for autologous TEPs in all Member States and if a manufacturer prefers to use the central procedure as in the Member State level (necessary provision of solid guidelines).
- The EU commission suggests 210 days evaluation time. This is based on medicinal products authorization procedures. As the report of IPTS has clearly showed: only 8% of the companies involved in the development of hTEPs are from the pharmaceutical field while 71% are Small or Medium Biotech companies and 21% are medical devices companies, mainly SMEs as well. SMEs can not afford such a long evaluation time of 210 days, which could put in danger the development of the product and the company. Rather we suggest that 60 days (identical to the current evaluation time for clinical trials) would be an acceptable time. We would like the EU commission to consider the possibility of conditional and fast track approvals for hTEPs and reduction of licensing fees particularly for SMEs .
- Natural Implant is developing a dental implant. At this time, majority of the dental implants are implanted in dental practices by experienced surgeon. Many hospitals do not have experience and do not have adapted environment for dental application. In order to include human tissue engineered dental implants, we would ask the EU commission to include dental practices as possible implantation sites of hTEP. Experience and training of the surgeon could be a pre-requisite to allow hTEP implantation.

c. Authorization requirements

We would like to insist:

- That non-clinical testing is limited by availability and relevance of animal models – especially for Autologous treatment
- On the need to include the Clinical Trial Approval procedures in the hTEP regulation. We would suggest to make the clinical trial authorization at a centralized level (either the Competent Authority, who will evaluate the market authorization dossier or

EMEA) and not at each national level (what happens today), which might lead to discrepancies and difficulties in maintenance of confidentiality.

- That Risk /benefit assessment approach is a key precursor already in early development and could be indicative of the type of non-clinical and clinical evidence that would/could be required.
- On the possibility of 'Conditional Approval'
- On the need to shorten the evaluation time to obtain authorization : proposed evaluation time are too long to be supported by SMEs