Superior Health Council

PUBLIC CONSULTATION PAPER ON THE REGULATION ON ADVANCED THERAPY MEDICINAL PRODUCTS.

Reaction of the working group on cells tissues and organs of the Superior Health Council, Belgium No. 8924

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The Superior Health Council advocates adequate regulation of cells and tissues. The implementation of the directive 2004/23/EC and its daughter directives, already guarantees a number of aspects, such as donor selection, traceability and qualitative preparation and preservation when the human material is distributed as a tissue or as cells.

Some types of human material, substantially manipulated or used for another purpose than the original tissue, are considered as advanced therapy medicinal products (ATMP's). These products should not only comply with the Cell and Tissue Directives, but also with the Advanced Therapy Regulation.

1. Classification

Up till now it remains unclear which products are considered as ATMP's and which products remain entirely under the Cell and Tissue Directive. Moreover, in some cases it is not clear whether the product can be seen as a somatic cell therapy medicinal product or a tissue engineered product.

Some of the products which might be considered as ATMP's, do not necessarily comply with (all) the definitions of medicinal products as stipulated in directive 2001/83/EG (eg. "placement on the market", "prepared industrially or manufactured by a method involving an industrial process", "exerting principally a pharmacological, immunological or metabolic action").

Although some indications are given in the European regulation, and irrespective of the published decisions of the CAT, it remains difficult to classify a number of cells and tissues, which undergo a more or less substantial manipulation or which are released for a non-homologous use.

This uncertain classification might result in material that is considered as a tissue or cells in one country and as an ATMP in another country.

These problems are indicative of difficulties related to the "concept" and as such should raise some afterthoughts An European flow chart to determine the regulation that applies for a certain product, analogous to the one developed at a national level in a number of countries, could be useful to classify the cell and tissue products.

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2. Market authorisation application

The advanced therapy regulation includes central market authorisation, which is quite complex and hardly feasible, not only for (university) hospital based tissue establishments, but also for small and medium size enterprises.

- The laboratory or company should have performed a multicenter randomized controlled study, proving the effectiveness of the product. Such studies are difficult to organise and are very expensive.
- The current financial context makes it even more difficult.
- For some types of cell therapy the interest from the industry is minimal or non-existing, because of a limited number of patients involved, or because of the complex and expensive preparation process (eg. keratinocyte grafts).

The extremely low number of market authorisation applications, compared to the high number of laboratories and small enterprises involved in innovative medicinal products, might be, at least partly, due to the still too complex and too expensive application procedure.

3. Hospital exemption

The European advanced therapy regulation empowers member states to authorise the use of ATMP's in hospitals for individual patients in the absence of a marketing authorisation. The hospital exemption which is organised at a national level, and hence diverging in the different countries, might however provide flexibility and might allow application of older non-commerciable as well as newer innovative treatments in selected patients, and under strict conditions.

There are important differences between countries concerning the concrete criteria for hospital exemption. Some countries are still awaiting a specific regulation.

- Definitions such as "non-routine", "innovative" are interpreted differently in the different countries.
- There might be a co-existence of market authorised products and analogous products which are not authorised at the European level.

Some treatments, which have a proven and stable therapeutic effect and have been applied in patients for many years, are now considered to be ATMPs, but are likely to fall outside the scope of hospital exemption because they have been applied for many years. If these treatments (e.g. keratinocyte grafts) have low or no potential for further commercialization, they are likely to become outlawed. This situation may become detrimental to patients if no suitable alternative is available. Therefore, hospital exemption should not be perceived as limited in time or an "interim measure". Hospital exemption was aimed at solving the problems created by splitting the tissues and cells in tissues and cells and ATMPs, and should not be interpreted as such.

4. Clinical trial

The requirements for the production of ATMP in hospital exemption are different (cfr. other directive) from the (more severe) requirements for the production of a medicinal product for use in a clinical study.
Consequently, hospital exemption is not applicable for advanced therapy products intended for application in clinical studies, at this moment. A solution for this would be to include an exemption in the Directive on clinical studies to allow the use of ATMP in hospital exemption. This would allow to conduct proof of concept studies.

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5. Conclusion

There is need for advanced therapies as treatment modalities at the cutting edge of innovation. The Advanced therapy regulation has foreseen a number of incentives to support the development of these products. But these measures do not seem to enhance the development of new ATMP's. The distinction between ATMPs and non-ATMP cell and tissue products needs further clarification. There is no doubt that efficient quality systems should guarantee the quality of the therapeutic product. On the other hand, the current strict regulation seems to discourage university labs and small enterprises to create new tissue-and-cell-based therapeutic products. Application of (extended) hospital extension should allow to start early stage clinical trials (prior to further development in an industrial setting) and should guarantee the availability of treatments with limited or non-existent chance of commercialisation.

There is a need for a logical equilibrium between quality and feasibility and last but not least availability for the patients. An adequate risk assessment might serve as a tool.

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