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COLLEGE
TER BEOORDELING VAN
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Public consultation 'implementation of the advanced therapies regulation'.

Introduction

The new Regulation on the Advanced Therapies introduced a divergent approach on gene, somatic and advanced cell therapies and laid down specific rules on authorization, supervision and pharmacovigilance for those 3 types of therapies.
The National Institute for Public Health and the Environment (RIVM) and the Medicines Evaluation Board (MEB) have cooperated in this national reaction on the public consultation on the amendments of Annex I of the Regulation 1394/2007/EC.

Comment on the the consultation

In general

Progress in cellular and molecular biotechnology has led and in the future will lead to rapid development of new technologies at tissue, cellular or/and genetic level. The Netherlands underlines the notion that these modern technologies require a specialized regulation, because of their continuous and swift development at a complex level. Therefore Annex I should be set up in a flexible way to leave room for new complex developments and progress in this field. Essential requirements need to be set out in the Annex, however in a way that no review has to be adopted every time a new development comes along. The Annex needs flexibility in regard to future developments and consequently guidelines, although not legally binding, should be more detailed instead of the proposed Annex I.

In general the proposal laid down in the public consultation is in line with the previous suggestions made by different Working Party of the EMEA, however some points differ. It is felt that that definition for *gene therapy medicinal product* is too wide and would include, for example, synthetic oligonucleotides, which should not fall under the scope of ATMPs. Except for regulating, repairing or replacing a targeted genetic sequence, a fully new genetic sequence should in our opinion be added to the definition.

The definition of cell therapy is not fully correct. In this definition a reference is made to article 2(1)(c) of regulation 1394/2007. However in this article the words intended regeneration, repair or replacement are used while in the second part of the definition of a cell therapy product "treating, preventing or diagnosing a disease" is used. This may be similar, but is not the same. Maybe it is legally better to incorporate a separate definition of engineered cells and tissues specific for somatic cell therapy in Annex I (derived from but not referring to article 2(1)(c) of regulation 1394/2007).

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Characteristics in terms of quality, non-clinical and clinical data

Technical requirements regarding Module 3 (quality data)

- In section 2.3, it appears that the gene therapy medicinal product may also contain genetically modified cells, but this is apparently not included in the definition of a gene therapy medicinal product.
- Basic requirements for gene therapy medicinal products are not included such as the need for providing full information on oligonucleotide sequence, regulating codons genetic stability.
- It is unclear why the principles of GMP are specifically mentioned for the genetically modified cells as this would apply to all other types of cell bank system.
- In section 2.3.3. 6a It should be mentioned that donation, procurement and testing should be done in accordance with Directive 2004/23.
- In paragraph 2.3.4, bullet point 2 (a), first line, the word "active" should be added in order to make a reference to the specific directive for active implantable medical devices. It would read as follows: "*. ..... of the medical device / **active** implantable medical device ...*".
- In paragraph 2.3.4, bullet point 2 (b), the following text should be add at the end: "*If applicable, evidence of conformity of the device part with the requirements laid down in Directive 2003/32/EC shall be provided.*"

Technical requirements regarding Module 4 (non-clinical data)

- There are linguistic inconsistencies between the requirements (i.e. terminology) for gene therapy (GT) products and those for cell therapy (CT) products (e.g. tumorigenicity vs oncogenicity).
- For CT no specific remark on the choice of an animal model is made for use in immunogenicity and immunotoxicity studies, while for GT the use of homologous models is specifically requested.
- Safety pharmacology studies should be specifically mentioned as part of the secondary pharmacology studies.

Technical requirements regarding Module 5 (clinical data)

The Netherlands subscribes requirements as laid down in module 5 and moreover the specific requirements for gene therapy, somatic cell therapy and the tissue engineered products.
In paragraph 2.5.1 general requirements the Netherlands supports the last point, namely that a strategy for long term safety and efficacy follow-up should be included in the Risk Management Plan. However in Module 4 the same kind of follow-up in the Risk Management Plan should be also included. The preclinical phase is not included in the scope of this public consultation, however a follow-up in the RMP should be added in Module 1.
The point in relation to 'proposed indications should be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use' is essential. Important is that the clinical relativeness is assessed in line with the clinical benefit of the patient.

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