Response document Academic AMTP Working Party The Netherlands and Belgium (Flanders) on the IMI consultation 'Facilitating the translation of advanced therapies to patients in Europe'

Within this document we provide a response on the IMI consultation '*Facilitating the translation of advanced therapies to patients in Europe*' on behalf of the Academic ATMP Working Party The Netherlands and Belgium (Flanders). This working party consists of all academic ATMP manufactures in the Netherlands and Belgium (Flanders).

To our opinion, one important issue has not been highlighted in this consultation, namely the early clinical development performed largely by academic institutions. Regarding this issue, we would like to refer to a study we performed in the Netherlands entitled '*ATMPs to regular clinical care: hurdles and opportunities*'. The aim of this study was to investigate the current situation of ATMP development and to assess whether ATMPs become available for regular clinical care in the Netherlands. Recommendations were defined on how ATMPs may become more efficiently available for regular clinical care. The results of this study are presented in a report and in *Cytotherapy*, de Wilde *et al* [1, 2]. Hurdles and actions necessary to promote/boost the development of ATMP in the Netherlands identified in this study are very similar to the issues defined in this consultation document.

1. ***Have key challenges that can be addressed through collaborative, public private initiatives been properly identified?***

Overall

- To our opinion one important key challenge is missing. Since the major product development occurs at the academic institutes [3 -5], we think that the focus not only should be on commercialization but also on improving academic product development (i.e. the translation from bench to bed). Furthermore, the cooperation with industry and other stakeholders in the field with academia should be improved to facilitate the translation of ATMPs to regular clinical care in Europe.

Clinical development

- Next to enhancing the awareness of the general public it is also important to enhance the awareness of the clinicians and patients.

Manufacturing

- A missing issue is the actual translation of the manufacturing of the preclinical batches to a product which can be used for the first clinical trial /'first in man' studies. Issues like availability and qualification of reagents or specific equipment

and development and validation of specialized QC assays are hampering effective product development already in this stage.

- A very important issue that is not clearly addressed is the lack of solid potency testing for ATMPs. Reliable potency tests are very important in product development. However, the development of reliable and meaningful potency tests for AMTP has struggled many researchers in the field. Potency testing for ATMPs seems much more complicated compared to potency testing for biologicals, due to multitude in functions, like migration, proliferation, cytokine production, functional activity etc.
- Concerning the supply of materials, we think that next to supplier reliability the qualification of new suppliers of *new* materials needed for production of ATMPs is often a hurdle in ATMP development. In addition, there is a lack of pharmaceutical grade raw materials available for production and in addition a lack of availability of pharmacopoeial monographs for these raw materials (which would be a useful tool in defining material specifications towards suppliers). Establishment of (academic) networks for qualification of suppliers can be beneficial in terms of standardization and efficacy. This approach has been started within in our working party.
- The high degree of variability introduced by the starting material itself is a major point for consideration which should be added to the manufacturing issues.

Pricing, reimbursement and access

- It is important to realize that not all ATMPs developed will be suitable for commercialization. For these products, the hospital exemption could provide a framework to make these therapies available for patients (when safe and effective). However, HE harmonization within the EU is crucial.

2. Which of the prosed potential initiatives should be prioritized

- Better interaction between the public institutions, especially academic institutions, and the industry and other stakeholders in the field (like regulatory authorities, clinicians, patients and HTA) for co-development of AMTPs. This can for example be established in the pre-competitive platforms as mentioned in the consultation and which could be aimed at tackling problems related to the manufacturing of ATMPs (such as starting material, raw materials, QC testing, etc.) .
- Improving the translation from bench to bedside of ATMPs in a cost effective manner
- Develop health systems provisions for innovative reimbursement. This also includes reimbursement of products applied within the HE, especially for the commercially not interesting ATMPs.

3. Are any areas missing?

The area of the translation of the preclinical development to the first clinical study (often '*first in man'*). See also question one.

4. What are the key European or national initiatives that IMI shall synergize with

As an academic working party on AMTP manufactures we think it would be very valuable when academia will be involved in this project. Since we are a working party representing all academic manufactures in The Netherlands and Flemish Belgium, we think we will be a valuable partner in this project to synergize with.
Other initiatives to synergize with are the EBMT, ISCT Europe and EBA.

Minor comments to the consultation

- Not only reimbursement of ATMP granted a MA is a problem, but also funding of clinical studies, especially large phase II or phase III trials.
- Unregulated application of HE should not be possible, since application of HE should be regulated by national law. Important to realize that HE can only be obtained for one member state.
- The purpose of paragraph 2 of section 3.4 is not completely clear to us. We would like to emphasize that clarification and equalization of the national regulations on HE is essential.

On behalf of the ATMP working party,

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