

Public consultation of IMI ‘Facilitating the translation of advanced therapies to patients in Europe’

Introduction

Pharmaceutical products form the pillars of any health care system. Therefore measures that stimulate innovation in this sector have great influence on the level of public health. Especially the search for treatments for diseases with high-unmet medical need has become of particular interest. The last decade the Advanced Therapy Medicinal Products Regulation (Regulation EC 1394/2007) has been playing a large role in this search. At this moment several initiatives have been launched to evaluate the effects of this regulation on patients’ access to medicinal products. Many aspects of this dossier are addressed in the Dutch Medicines Policy Plan (29 January 2016) and the Council conclusions of the Dutch EU-Presidency on strengthening the checks-and-balances in the EU pharmaceutical system (PRESS RELEASE, 350/16, 17/06/2016).

In the Netherlands an expert group is created by the MEB to deliver answers, on a consultative basis, to specific questions addressed to them and to give advice on issues that pertain to the work of the MEB. In this expert group both governmental organisations (Ministry of Health, Health Care Inspectorate, Medicines Evaluation Board, and Central Committee on Research involving Human Subjects) as academic researchers and delegates from the innovative industry are present. At a national level the main stakeholders are represented by this expert group and from the side of the MEB the member of the CAT, chair of the Board and clinical experts are member.

The Netherlands welcomes the possibility of IMI consultation on ‘*Facilitating the translation of advanced therapies to patients in Europe*’. This means that the expertise available at a national level and also in the field can be addressed via this consultation. The Netherlands wishes to have contact with experts to further improve the assessment of the risk management of medicinal products, to improve the understanding of ATMP development and use to facilitate communication with the field and this IMI consultation fits in this approach.

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

Overall

To solve the issues, scientific guidelines were developed as to facilitate the applicants to submit their marketing-authorisation applications for ATMPs. However the situation should be avoided of a culmination of legislation with ever more single items which will make the registration of an ATMP in the end even more complex.

Preclinical development

Model systems for PoC and safety are indeed one of the key challenges in pre-clinical development. Referring to social discussions on the use of animals as testing models in general it is however suggested to be critical about using large animals for experiments related to non-specific toxicity and safety, expressed in overall survival or general health

damage. In addition human organoids as models for safety (and efficacy) evaluations are not yet in a satisfactory stage. It should be noted that alongside human organoids new types of arrays are explored as well.

Furthermore the IMI paper explicitly mentions targeted gene editing as important issue during preclinical development. We would like to add specifically immunogenicity as gentherapeutic treatment for monogenetic diseases like sickle-cell disorder and haemophilia as of great interest. Therefore we suggest to pursue the ABIRISK project. Another, strongly related issue, to draw your attention to is the development of innovative strategies to induce tolerance preceding gentherapy treatment.

Clinical development

During the ATMP development it is extremely difficult to collect sufficient data for a small non homogenous patient population. To demonstrate efficacy for a small cohort will be difficult as well as to demonstrate the benefit risk ratio.

An important step are the trials in 2nd and 3rd phase of the ATMP development as they will show if there is efficacy demonstrated. In addition, taking in to account “real life data” generated from treatment when processing registration and reimbursement dossiers would be of great importance for access of patients to ATMPs.

Pricing and development costs

In general, the costs of developing an ATMP will be high as there will not be a ‘production’ at a large/substantial scale which could reduce the costs in the end. Not only the amount of data that must be generated for a small group of patients (many ATMPs are orphan drugs) is problematic. Many ATMPs are currently being developed within academic hospitals and the development of second/third generation ATMPs is essential for innovative treatments. The treatments of patients with these new ATMPs are hospital-based and less international than the traditional pharmaceutical product that can be exported throughout the EU. In the clinical trial setting, where one small hospital based production facility cultures cells for use in the same hospital, treatments are often successful. But successful upscaling to the European scale is rarely seen. For those cases the development of a business cases for the development of ATMP within the IMI framework is important to explore. In this respect it is of great importance to involve the HTA bodies in an early stage to arrange a reimbursement-scheme in the future.

Concerning the GMP requirements in the phase of development and later on the costs, are often a hurdle in the ATMP development. The GMP requirements for the development of an ATMP are extremely expensive, whereas in most cases it is only a designed product for an individual patient (in most cases it will not be possible to develop as stock for a cohort of patients). In brief there need to be more reflection on how much cost of quality versus the GMP standards.

GMP requires testing at several fixed points in the preparation process. Because preparation of ATMPs differs substantially from medicinal products in general at certain stages, efforts could be put in for reducing the requirements for testing during preparation of ATMPs, e.g.

sterility testing of cell preparation. This could result in reduction of costs and saving of a delicate and scarce product.

Hospital exemption and end result access for patients

In order to harmonize the development, registration and distribution of pharmaceutical products in the European Union several Directives and Regulations were initiated by the European Commission and approved by the Council . The final legal structure of all legislation is consolidated in the current Directive 2001/83/EC. Whereas a detailed structure is well suited for the development and registration of small organic molecules, it is less optimal for ATMPs. After all, ATMPs often resemble more closely medical procedures being performed in a hospital, than pharmaceutical products being produced, tested, released and shipped to a pharmacy to be stored before use. In the end not all ATMPs will be submitted for a centralized procedure as in some cases an ATMP will remain an individual treatment in a hospital. As the regulation does not provide the possibility of a decentralized or national procedure for a registration of an ATMP the hospital exemption (HE) is crucial in all Member States. If there is no possibility of a national procedure within 1 Member States and legally only a centralized procedure foreseen, the HE needs room for flexibility at a national level. To harmonies the HE throughout the EU would result in less or no access for patients to ATMPs within the EU.

2. Which of the proposed potential initiatives should be prioritized

Both pharmaceutical companies and academic centers involved in development of ATMPs do struggle with assessing the pro's and cons of registration. Giving more clarity in the effects of registration for data and structural finances would benefit all relevant parties, including the patients.

3. Are any areas missing?

See above the proposed suggestions.

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

- National level and including the scientific advice at national level/scientific expertise including the members of the CAT to involve the expertise from the National Competent Authorities;
- EMA initiative (ATMP: exploring solutions to foster development and expand patient access in Europe; report EMA/345874/2016);
- Dutch Medicines Policy Plan (29 January 2016);
- Council conclusions of the Dutch EU-Presidency on strengthening the checks-and-balances in the EU pharmaceutical system;
- Research program of ZonMW (stem cells, gene therapy): <http://www.zonmw.nl/en/>

Conclusion

The high costs to develop an ATMP are mainly caused by the small production scale and it concerns designed product for an individual patient. There is a need to develop a business innovation and development to ensure sustainable funding and make ATMP available to the patients. Beside the business model to develop an ATMP, it is of great importance to take to involve the HTA bodies already in an early stage.

Within the EU regulation there is only the possibility to register an ATMP via the centralized procedure which make it rather difficult to register for 'local' treatments of ATMP. The Netherlands would like to underline that the HE foresees in unmet medical need for patients in the different Member States. Currently not many ATMP are registered and HE can be seen as a transition tool. The problem will of only a few registered ATMPs will not be solve by harmonization of the HE, however the focus should be on monitoring HE in order to determine the evidence base.

On behalf of the national expert group on ATMPs in the Netherlands,



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