Innovative Medicines Initiative (IMI) consultation

Facilitating the translation of advanced therapies to patients in Europe

Response of the European Association of Hospital Pharmacists (EAHP)

www.eahp.eu *July 2016*

Introduction

The European Association of Hospital Pharmacists (EAHP) welcomes the opportunity to respond to the IMI consultation relating to the translation of advanced therapies to patients in Europe.

The mission of the hospital pharmacy profession will always be connected to ensuring patients can receive the treatments they require. The consultation is therefore timely and needed as it is clear, as outlined in the consultation paper, that the translation of advanced therapy medicinal products (ATMPs) is not yet occurring at the rate that society would ideally hope for.

We applaud the initiative to examine some of the factors complicating translation from research into patient access, and offer commentary on the key questions posed from the perspective of the hospital pharmacy profession.

Hospital pharmacists are conducting a crucial role in supporting present use of ATMPs, including taking responsibility for the governance of their safe use in the hospital sectors. As such, we trust that the hospital pharmacy profession can be kept in mind as key stakeholders as IMI further develops projects and activities in this important area of public interest.

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

From review of the document, it appears that a mostly creditable analysis of primary challenges to overcome has been made. EAHP makes further suggestions however in response to question 2 and 3.

In respect to "communication to the general public" (p3) it is important that this is conducted via independent, unbiased and creditable sources. This will avoid any unintended undermining of public confidence.

EAHP would, however, like to make comment to one particular remark within the document "Nevertheless the growing number of unregulated application of Hospital Exemption (which

does not require long and costly safety, quality and efficacy demonstrations) acts as a disincentive to small and big companies."

The authors of the document should have understanding that hospitals across Europe operate to strict governance and supervision arrangements in respect to the oversight of medicines supply and use. In addition to this, Article 28 of the ATMP regulation sets out numerous conditions for operation of the hospital exemption, for example, in respect to professional supervision, traceability, pharmacovigilance and quality standards.

For these reasons the term "unregulated application of Hospital Exemption" could give a false impression to a lay reader in respect to patient safety, which we do not believe the authors intended to convey. The term "unregulated" should therefore be removed as it does not provide an accurate representation of the manner in which the hospital exemption operates.

In respect to the second supposition within the sentence, the hospital exemption is acting as "a disincentive to small and big companies", this is a subjective point of view, with opinions collected within our hospital pharmacy indicating both agreement and disagreement with the statement. Without the evidence to support the statement being well set out in the document, the sentence would be better termed in the conditional i.e. "has been suggested by some within the ATMP stakeholder community as acting as an unintended disincentive".

Otherwise, it should be understood that the hospital exemption exists for sound reasons, to authorise the use of custom-made ATMPs prepared on non-routine basis in the absence of a marketing authorisation, provided that the product is used for individual patients in a hospital and under the professional responsibility of a medical practitioner. The exemption exists as a tool for providing access to ATMPs where otherwise full marketing authorization requirement may have made the access unfeasible. As tangible evidence of this, the 5 currently marketed ATMPs, such as ChondroCelect, began within the hospital exemption regulatory bracket.

Useful discussion and debate can of course be had on how the operation of the exemption might be improved. This could include learning from best practices (and indeed any identified poor practices) within certain EU member states in respect to oversight of the exemption, and how best to insure maintenance of manufacturing standards when operating the hospital exemption.

Question 2: Which of the proposed potential initiatives should be prioritized?

Aside from the areas EAHP considers missing from the consultation document (see answer to question 3 below), of those initiatives mentioned within the consultation document, EAHP suggests prioritization of:

1. Addressing manufacturing knowhow;

EAHP agrees with the statement in the consultation document: *"In general there is a lack of manufacturing knowhow, regulatory sciences and Current Good Manufacturing Practice (CGMP) related to ATMP usage."*

However, the document goes on to state: "Besides that, there is a shortage of well-trained engineers that understand the manufacturing processes and are capable to develop automated/robotic methods and common platforms."

Understanding that what is in scope is medicinal products, it is incorrect to focus the manufacturing knowhow needs on the engineering profession alone. ATMP manufacturing knowledge is also a great need for the pharmacist profession, in hospitals and academia. This reality should be better represented within this particular IMI reflection.

2. Access to early regulatory consultation

Further to this, there is a need to make regulatory considerations in relation to the potential marketing authorization application as early in the process as possible, ideally at the preclinical development stage should be prioritized. Innovators / researchers need to understand the importance of Quality by Design thinking to develop their product in such a way that it facilitate an easier pathway through the regulatory pathway later.

Pharmacy Quality Assurance and Regulatory colleagues may be able to help if innovation is occurring in a healthcare / academic setting.

Question 3: Are any areas missing?

EAHP identify the following areas as missing, or capable of further elaboration:

1. Hospital facility needs/clinical site development
2. Healthcare professional education needs in general
3. Regulatory requirements enabling Hospital Pharmacists to engage in reconstitution/preparation of ATMPs in different clinical settings
4. Patient engagement

1. Hospital facility needs/clinical site development

Research and Development Teams within potential clinical sites for clinical trials should be prioritised. Clinicians in a variety of specialisms could be interested in being an investigator. Therefore, the Research and Development Teams in such prospective sites, including those clinicians, research nurses and clinical trial coordinators as well as pharmacy clinical trial staff, need to be trained.

Attention must also be paid to any required upgrade to hospital site facilities, such as pharmacy production areas (and accompanying staff training).

2. Healthcare Professional education needs in general

Another area of challenge from the hospital pharmacist perspective, not well represented within the document, is the need to address healthcare professional education needs in respect to ATMPs.

In very practical terms, if ATMPs are to be translated into patient access, healthcare professionals (prescribers, nurses, pharmacists) will be critical intermediaries, and must be knowledgeable enough about ATMPs to prescribe with confidence, advise the patient on use, and ensure correct governance around use and administration to underpin safe access. This challenge should be included within the priorities.

EAHP would be pleased to be involved with IMI deliberations on how best to meet these educational needs. Principles around achievement of the goal include ensuring education materials and provision comes from unbiased, independent and credible sources e.g. medicines information services.

3. Regulatory requirements enabling Hospital Pharmacists to engage in reconstitution/preparation of ATMPs in different clinical settings

Reconstitution of an investigational medicinal product (IMP) is not considered manufacturing and therefore may be carried out in hospitals, health centers or clinics, by pharmacists or other persons legally authorized in the Member States to carry out such processes and if the investigational medicinal products are intended to be used exclusively in those institutions (Commission Directive 2005/28/EC, Art. 9 (2)). This will obviously remain unchanged by the Commission Guidelines pursuant to the CT Regulation No. 536/2014, as will the definition of the term “reconstitution” which remains the same as in Eudralex Vol. 4, Annex 13.

By German law defined preparation processes of Advanced Therapy Medicinal Products (ATMPs) which do not meet the definition of reconstitution as it is stated in Eudralex Vol. 4, Annex 13 (especially the criteria of several preparation steps) require therefore per se a manufacturing authorization for any activity concerning ATMPs (§ 13 (2b) AMG). It is not clearly defined whether the reconstitution of an ATMP may be carried out in hospitals without manufacturing authorization and the decision on that matter is currently made by the German regional commissions, not by the national competent authorities.

This jeopardises the feasibility of therapy with ATMPs in Germany, and possibly Europe, since only very few hospitals and clinical trial centers in Germany have an appropriate manufacturing authorization and the diversity of ATMP products renders a general authorization for these products quite impossible. Hospital pharmacists in other European countries are facing similar problems.

The general requirement for a manufacturing authorization regarding any activity concerning ATMPs should be subject to discussion. A risk-based approach adapted to the

specific characteristics of an ATMP should not only be applicable regarding the GMP requirements, but also regarding the permission to reconstitute ATMPs at hospital pharmacies, especially for clinical trials, but also for approved drugs without manufacturing authorization.

For instance, a genetically modified organism (GMO) falls under the definition of an ATMP, but not the categorization as ATMP alone should be the decisive factor whether the reconstitution is subject to an manufacturing authorization or not. But rather the respective ATMP-specific process of reconstitution, the single steps involved and possible risks arising during that process and whether these can be appropriately handled should be the determining factors.

The environment, training and expertise found in a hospital pharmacy offers the ideal setting for patient individual reconstitution of ATMPs used in the clinical setting. A high standard of safety is implemented for the handling and preparations of CMR substances, but also biological. This provides a solid basis for the handling of biologically hazardous materials like GMOs, as well as any other cell therapies. Any aseptic preparation processes are clearly defined and regularly validated, the specialist staff carrying out the preparation is well trained and highly experienced. Equipment and environmental conditions are kept to the appropriate technical standard.

In order to keep the performance of clinical trials and the regular treatment with new and innovative ATMPs feasible in Europe, the handling of ATMPs and their preparation for administration should be possible in hospital pharmacies without a special authorization, if a favorable product-specific risk-assessment is provided by the Sponsor and/or Hospital Pharmacy.

4. Patient engagement

The reflection paper currently comes across as light in description in respect to patient engagement with ATMP take up. Yet it must be recognized that great scope for development in posed in this area, for example, in respect to patient preferences, patient reported outcomes, reporting of side effects, to name just a few aspects.

Question 4: What are the key European or national initiatives that IMI shall synergise with?

EAHP identify the following initiatives for IMI awareness and potential linkage:

1. Efforts being undertaken by the European Medicines Agency (EMA) to facilitate greater uptake of ATMPs
2. Projects underway to support the implementation of the European Statements of Hospital Pharmacy
3. A forthcoming elaboration at the European level of a common training framework for the hospital pharmacy profession

1. Linkage with the European Medicines Agency

It is unclear the extent to which IMI initiatives on ATMPs are in linkage with similar reflections on ATMP uptake being facilitated by the European Medicines Agency. For example, an EMA stakeholder meeting on the subject was recently with the report of that meeting published in June.

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/06/WC500208080.pdf

Close linkage between IMI and EMA on this subject would seem sensible and appropriate, as goals appear similar if not the same. Furthermore, via its healthcare professional and patient and consumer working parties, EMA enjoys excellent connection to stakeholder organisations that may benefit IMI initiatives.

2. European Statements of Hospital Pharmacy, and their implementation

In respect to the development of hospital pharmacist services across Europe, a guiding initiative in this area, with some synergy to ATMP translation to patient access, are the European Statements of Hospital Pharmacy. These express commonly agreed objectives that every European health system should aim for.

Relevant statements in this respect include: "*Hospital pharmacists should have responsibility for all medicines logistics in hospitals. This includes proper storage, preparation, dispensing, distribution and disposal conditions for all medicines, including investigational medicines*" and "*Hospital pharmacists should be actively involved in clinical trials of medicines."*

More information here: http://ejhp.bmj.com/content/21/5/256.full.pdf+html

EAHP is now fully engaged with its membership in achieving the realization of these statement aspirations across Europe, and potential for synergy in respect to ATMP takeup (e.g. addressing healthcare professional education needs) may therefore exist.

3. Common Training Framework for hospital pharmacy in Europe

Another European initiative in the area of hospital pharmacy, with potential synergy to ATMP translation, is the current development of a common training framework for advanced practice in hospital pharmacy. The content of a draft framework will be consulted on later in 2016. More information here: www.hospitalpharmacy.eu

Question 5: Further comment

In respect to the consultation paper's reflection on pricing and reimbursement for ATMPs, consideration is required to how the early investment made by hospital sites and academic centres into ATMPs, can be returned within pricing and reimbursement systems. This does not appear well explored within the paper.