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Response by the European Society of Blood and Marrow Transplantation (EBMT) to the IMI consultation on Advanced Therapies Concept Paper*

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The European Society for Blood and Marrow Transplantation (EBMT†) is a not-for-profit medical and scientific organisation established in 1974 dedicated to fighting life-threatening blood cancers and diseases and improving patients' lives.

EBMT members – more than 4,000 physicians, nurses, scientists and other healthcare professionals from over 600 centres in more than 60 countries in and beyond Europe – participate in a unique collaborative network of peers involved in haematopoietic stem cell transplantation (HSCT) and cellular therapy research. The EBMT plays a central role in performing co-operative studies and disseminating state-of-the-art knowledge with the aim to increase survival rates and enhance the quality of life of patients with life-threatening blood cancers and diseases. EBMT maintains a unique registry of transplants with data on over 500,000 transplants with over 30,000 being reported annually. Preparations are currently underway to upgrade and modernize this registry.

The EBMT through its structure of committees and working parties, continues to promote basic and clinical research, education, harmonisation of medical practices and standardisation of cellular therapy products, quality improvement and accreditation for transplant procedures.

Bone marrow transplantation (BMT) has been described as a "legacy therapy". As a legacy therapy BMT counts on over 50 years of experience in collecting and manipulating cells and tens of thousands of patients have been successfully treated.[1 2] Many established BMT practices (e.g. donor lymphocyte infusions) are now being adapted to new therapies (e.g. CAR-T cells).

* http://www.imi.europa.eu/content/advanced-therapies-consultation
† www.ebmt.org

EBMT's participation in this consultation on the Innovative Medicines Initiative (IMI) on Advanced Therapy Medicinal Products (ATMPs) concept paper is based on our interest in the following areas:

1. Safety, quality and efficacy of treatments provided to EU citizens with blood cancers and corresponding regulatory frameworks
2. Equitable access to these treatments by EU citizens and questions of affordability and sustainability by public health systems
3. Patient and donor follow-up based on an effective registry tool
4. Advancing research into new treatments

The EBMT response is based on the four questions posed by the IMI for this consultation:

1. Have the key challenges that can be addressed through collaborative, public-private initiatives been properly identified?
2. Which of the proposed potential initiatives should be prioritised?
3. Are any areas missing?
4. What are the key European or national initiatives that IMI shall synergise with?

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

Note: We understand that the wording of this question restricts key challenges only to those that can be addressed through public-private initiatives. EBMT is very supportive of such collaborations in the interest of advancing treatments for blood cancers and delivering care to patients. Our response also includes aspects where public-private initiatives may not necessarily be a solution.

Logistics of delivery of care

There are examples of the development of new therapies that were made possible through robust collaborations between industry and academic centres whose strong basic and translational science background provided expertise in cell biology and cell engineering e.g. suicide gene therapy and CART cells. This experience has shown that while some, although probably not all, future cell therapies may be manufactured and delivered by central manufacturing facilities operated by pharmaceutical companies, development and validation still require the participation of academia, including academic cell processing facilities.[3] Since hospital pharmacies – at least in the short term - are likely to lack experience in managing such living products, preparation of these products will also still require the collection facility of the clinical centre and also the storage capacity of the cell processing laboratory

For therapies not suitable for central production and delivery, the site of administration will form part of a complex manufacturing chain. This raises the possibility that all sites including the hospital would need a manufacturing license which is unrealistic to expect.[4] To illustrate this, administration to the patient of these expensive, extensively engineered, functionally complex cellular therapies could be performed after bedside thawing in a water bath. This step will most typically be carried out by nurses and clinicians - rather than by technologists or pharmacists - in an uncontrolled environment

with low-tech equipment and risk of microbial contaminations. Fortunately large-scale experience with minimally-manipulated cell products e.g. BMT has amply demonstrated that better controlled procedures allowing for the final evaluation of the infused cell product can effectively substitute these rudimentary techniques while achieving the necessary levels of quality and safety.

Companies working with this logistical complexity will need to form partnerships with established clinical centres to procure, deliver and assess the performance of their ATMPs. The Joint Accreditation Committee for ISCT & EBMT[‡] (JACIE)-accredited centres are well positioned to enter these partnerships as centres of excellence. Professional societies like EBMT and their extensive international networks can contribute by (i) helping identify those clinical centres via accreditation/designation (ii) educating healthcare professionals in applying these new therapies and (iii) disseminating treatment and favour access to these treatments after initial validation by large numbers of patients. The incoming European Reference Networks[§] for rare diseases will also constitute an important channel for developing and delivering novel therapies.

A further development could lie in the design of point-of-care cell manufacturing devices which could reduce the needs, costs and risks related to long-distance shipping of living cells, tissues and medicinal products while addressing the need for harmonization and standardization, as prescribed in various regulations and standards. There could be scope for the joint development by industry and academia of automated and closed processes/platforms that standardise and make reproducible products produced in hospital-based facilities.

Need to adapt patient pathways

Related to the logistical issues outlined above, healthcare providers will need to review their current processes and adapt them to new therapies. This may have a financial impact on the providers as they adapt infrastructure and human resources to the new pathways and enter into unfamiliar and potentially complex relationships with third parties in providing care to their patients.

Resources needed for clinical trials and development process including financial, intellectual and human

The need for well-designed clinical trials to demonstrate safety and efficacy is often beyond the financial capacity of academic centres.[5] The lack of sufficient financial and human resources may limit the number of institutions capable of participating in development and testing processes. Consequently, other options (including merging, acquisitions, and out-licensing) will have to be considered as a strategy by academic hospitals[5] [6] and collaboration with private companies maybe provide a solution to this, for selected products.

Reimbursement of treatments

[‡] JACIE is an accreditation initiative of the EBMT and International Society for Cellular Therapy (ISCT). See www.jacie.org.

[§] http://ec.europa.eu/health/ern/policy/index_en.htm. Consulted 22/07/2016

It seems reasonable to expect that only very few products that are or will be developed will have a commercially-viable demand because their target population is too small to be attractive to companies. At the same time there is a view that it may be precisely these small populations that are most ideal for introducing such therapies as they help reduce payers' budget impact concerns by delimiting the potential costs to health systems.[7] However it is likely that for these small population settings, public-private collaborations e.g. GSK & SR-TIGET joint venture[**] working with specific incentives will be critical. Whatever the model, the question of reimbursement has to be considered alongside medical factors when developing novel therapies, especially in the context of blood diseases, already estimated to cost two times higher than average cancer costs even before new therapies are taken into account.[8,9]

It is less clear to see how public-private initiatives will resolve the following issues:

There appears to be an assumption underlying this consultation that there is always a market for these products. We consider this to be an unsafe assumption given the history of ATMPs authorised so far with only 5 products authorised since regulations came into place and with little if any commercial success.

When a product is obliged for regulatory reasons to be developed via a commercial collaboration, the authorisation route unsurprisingly increases the costs significantly without necessarily adding any therapeutic value. It is unreasonable that public health systems, the origin of many products developed at a relatively low cost, would have to purchase the same product at higher prices with the consequence of restricting or even blocking provision of this therapy to citizens.[10]

2. Which of the proposed potential initiatives should be prioritised?

Hospital Exemption: harmonise and develop as complementary to market authorisation route

The AGORA GMP project reported that "EMA data show that more than 85%[††] of clinical trials of ATMPs are academic-led", significantly more than the 60% indicated in this consultation document. Much of this development is carried out under the Hospital Exemption (HE) clause.

HE needs to be harmonised across the member states. It is implemented at national levels, does not resolve the lack of procedural harmonization associated with the existence of multiple cell processing/ manufacturing facilities that operate on a relatively small scale, does not provide an appropriate setting for medium-scale manufacturing and includes some worrisome limitations such as restrictions on exports that hamper the conduct of multicentre and multinational clinical trials, particularly critical for rare diseases. Also of concern is the proposal made at the recent EMA advanced therapies meeting of restricting the hospital exemption to situations of high unmet medical needs and termination of the exemption when authorised products for that indication reach the market.[4] HE should be considered as complementing rather

[**] GSK press release 18/10/2010 https://us.gsk.com/en-us/media/press-releases/2010/gsk-fondazione-telethon-and-fondazione-san-raffaele-to-collaborate-on-gene-therapy-for-rare-diseases/. Consulted 21/07/2016

[††] AGORA project http://agora-gmp.org/about-agora/. Consulted 15/06/2016

than competing with centralized marketing authorisation[11] and subject to controls of safety and quality in the interest of the patient. A mapping exercise should be performed across all member states to establish the current national interpretations and applications of this clause.

Data: Follow-up and Health Technology Assessment (HTA) support

Patient follow-up will become increasingly important in the future especially for new therapies. This is a practical challenge which will require a significant reorganisation of the way in which healthcare providers and industry work and which would benefit from a harmonised solution. Future cellular therapies will require good quality data captured in a harmonized and reliable registries, in order to assess short-term and long-term safety and efficacy. EBMT is developing a common dataset for cellular therapies that will address these needs. HTA will need reliable bodies of data to help when determining the impact of new therapies.

Reimbursement

See above.

3. Are any areas missing?

Alternative to GMP

In many of these instances, the current need is not so much for full implementation of GMP for the manufacturing step as that there is a robust preclinical demonstration of the validity of the proposed approach. Also agreement is necessary on the definition of novelty. We note that this issue will be tackled under the Euro GTP II project under Work Package 5 where it is termed 'threshold of novelty'.

Starting materials and ethical concerns

Starting materials for ATMPs – the primary or starting materials (living cells) - are regulated under the Tissues and Cells directives. In many countries procurement is performed by public healthcare providers for specific altruistic ends which may conflict with commercial manufacturers' need to gain access to these starting materials.[12] This leads to two concerns:

1. There is a need to determine the extent of the responsibility of the collection institution to the manufacturer. Since hospital- and blood-based collection facilities will remain in charge of providing the primary biological material (human cells and tissues) to be engineered at a central manufacturing facility for a significant proportion of cellular therapies that are currently being developed, there is an urgent need to delineate responsibilities and define liabilities in case of error, incident or adverse effects for the donors and recipients.
2. Ethical considerations must not be dismissed. Patients' perception of the commercialization of "their own cells or tissues" by for-profit pharma companies (in contrast to historical practices where cell transplantation mostly involved not-for-profit institutions) should be discussed with patients associations, in the context of national and European regulations. A consensus is necessary on how

to preserve the principle of Voluntary Unpaid Donation (VUD) and meeting the donor's expectations while ensuring that manufacturers can access quality starting materials.

Definition of non-homologous use

Agreement is necessary on the concept of "same essential function" / "non-homologous use" by taking a common sense attitude in the interest of patient care and based on demonstration of safety and quality.[13]

Import/Export

Regulatory aspects in relation with exporting / importing human cells and tissues must be clarified and harmonized in view of arising new practices and activities and the need to recruit a meaningful number of patients in trials which for rare conditions is not always possible within a single country.

Education/Training

Need for education of the academic sector in ATMP development.[4] [5] We welcome that the EMA Committee for Advanced Therapies (CAT) has included this aspect in their work plan for 2016.[14]

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

- EMA consultation on GMP for ATMPs
- EMA CAT Work Plan 2016
- EMA patient registries initiative‡‡
- DG SANTÉ evaluation of the need to revise the Tissues and Cells Directors 2004 and 2006 – due to open in Q3-2016
- Conclusions of the EUCelLex§§, AGORA-GMP and EuroGTP-II*** projects
- European Reference Networks (ERN)

Conclusion

The EBMT supports robust interaction and collaboration between industry and academia in the pursuit of the shared goal of optimal patient care. We view the IMI initiative on as a positive contribution with the potential to combine expertise and resources towards achieving this goal.

We are concerned that a solely market-driven approach could create a situation whereby academia-developed therapies are displaced by new commercial treatment options with all of the safety and quality guarantees of a pharmaceutical product at the manufacturing stage but overlooking the specificities associated with human cell procurement and at such a cost that

‡‡ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000658.jsp&mid=WC0b01ac0580961211. Consulted 20/07/2016

§§ https://www.eucellex.eu/. Consulted 22/07/2016

*** http://ec.europa.eu/chafea/projects/database.html?prjno=709567 consulted 22/07/2016

patient care becomes unsustainable by public healthcare systems and access to care is restricted or blocked as a result.

An ongoing and open dialogue between all parties – academia, industry, European Union, EMA, IMI, national authorities, HTA authorities, patient associations – is required to reach this shared goal of giving the patient the best care possible.

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