Innovative Medicines Initiative (IMI) consultation

Facilitating the translation of advanced therapies to patients in Europe

Response from Newcastle Cellular Therapies Facility (NCTF).

Introduction

Newcastle Cellular Therapies Facility is a collaboration between Newcastle University and The Newcastle upon Tyne Hospitals NHS Foundation Trust. NCTF aims to ensure that Newcastle patients are able to access available advanced therapy medicinal products (ATMPs) through ensuring appropriate governance for these advanced products manufactured elsewhere and sourced for our patients for use in clinical trials or as unlicensed or licensed medicines. NCTF also operates as a site on the manufacturing authorizations to allow the translation of researched ATMPs through to IMP manufacture or to manufacture based on individual patient need as unlicensed medicines.

The consultation is timely and needed as it is clear, as outlined in the consultation paper, that translation of ATMPs is a rate limiting step in realising their therapeutic promise to society.

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

NCTF agrees that the challenges have been explored fully in the document.

We feel that it should be emphasized that the term "unregulated" relates to the manufacturing facility for sites operating under the hospital exemption. We understand that use of the hospital exemption (HE) is unregulated by the Competent Authority in most EU member states. In the UK, however, the MHRA favours the use of our Specials regulations which ensures that the facilities and quality systems in which the unlicensed medicines are made are compliant with EU GMP.

NCTF agrees that the HE can disincentivise the progression of ATMPs to marketing authorisation in member states other than the UK. In the UK, MHRA Guidance Note 14 prohibits the use of an unlicensed medicine where a medicine with a marketing authorisation exists. This is not the case for other member states. Hence if a manufacturer gains a centralised EU MA for an ATMP there is nothing to stop individual member states continuing to manufacture an equivalent product under the HE. Hence there is effectively no guaranteed market for the authorised product. This is especially the case for autologous products and is most certainly disincentivising companies from investing in the marketing authorisation process. Even where companies are willing to progress to MA the potential threat is that companies fail to raise funding (as the investors recognise this issue as an obstacle to commercialising the product) - end result is that innovation is stifled and

patients don't realise the benefit OR for companies who don't go down the MA route, they end up working outside the regulatory framework at greater risk for patients.

Whilst central authorisation (EMA) allows the expertise required for assessment to be collected in one place, and is therefore useful, the granting of an EU wide MA carries logistical problems. Many ATMPs have short shelf lives and are very vulnerable and therefore susceptible to quality deviations during transport. Manufacture in one member state and transport to all others is therefore not always realistic. This may prevent MA applications which would be possible to service one country or an easily accessible geographical area but cannot logistically satisfy the entire EU (without extreme circumstances being required for users). This encourages the use of the Hospital Exemption and disincentives a MA application.

NCTF would **recommend** HE sites should be inspected by the GMP competent authority in the member state and hospital exemption manufacture should not be permitted where an equivalent product with a MA exists but that consideration is given to granting an MA for a limited geographical area if that is what the manufacturer prefers or to encourage applicants to collaborate with /subcontract to manufacturers in local regions of the EU to ease these logistical problems.

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

NCTF believes that the use of registries should be prioritized. If ATMP usage, safety and efficacy data is available it would help the field to advance by facilitating the targeting of ATMPs to go through to marketing authorization that have a chance of being funded due to their having big impact on patients (i.e. will be curative for rare diseases or will offer a significant benefit to quality of life for common diseases.) Currently NCTF believes that there is no overarching strategy to target funding and grants to develop products which will have such an impact. The market is largely being driven by the interests of individual innovative researching clinicians who may have a niche interest only.

NCTF 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 ATMPs are medicinal products, it is incorrect to focus the manufacturing knowhow needs on the engineering profession alone. ATMP manufacturing knowledge exists in hospitals via the haematopoietic stem cell transplant (HSCT) laboratory teams who are experts in handling cell and tissue products. When combining this practical expertise with GMP and GLP expertise, which is available in pharmacy (as pharmacists in hospitals and academia often have manufacturing sites for traditional pharmaceuticals), then HSCT stem

cell laboratories offer perhaps the most suitable environment in which to manufacture ATMPs for early phase trials or under the HE. This should be better represented within this particular IMI reflection.

NCTF recommends that access to early regulatory consultation should also be prioritized. There is a need to make regulatory considerations in relation to the potential marketing authorisation application as early in the process as possible, ideally at the preclinical development stage. Innovators / researchers need to understand the importance of Quality by Design thinking to develop their product in such a way that it facilitates an easier pathway through the transition to a GMP product suitable for a marketing application.

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?

There is a need to focus more on the lack of education around the field of ATMPs. Staff involved in research and development should be prioritized.

Clinicians in a variety of specialisms are interested in being an investigator using ATMPs as they are innovative and may offer tangible patient benefit. As a result, healthcare settings participating in clinical trials need to have a Research and Development Team with an understanding of ATMPs and that can develop a streamlined pathway to introduce these trials whichever clinical speciality that they occur in. Clinicians, research nurses and clinical trial coordinators as well as pharmacy clinical trial staff need to be trained in relation to ATMPs.

It should also be recognised that segregated facilities for ATMPs will be required in many cases and that sites for preparation prior to administration will need to be considered and provided by pharmacy aseptic teams going forward. NCTF would recommend that hospitals consider the use of facilities and staff from HSCT laboratories due to their expertise in this area, with appropriate oversight and governance from the pharmacy department.

As ATMPs become more embedded in routine use as licensed and unlicensed medicines then 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.

NCTF feel that the document would benefit from the addition of a recommendation to include teaching about ATMPs on a variety of university syllabuses so that medical, pharmaceutical and biomedical undergraduates become aware from an early stage in their career about this group of medicines which, whilst currently in their infancy, are likely to feature heavily during their careers.

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

NCTF recommends that IMI synergise with regulatory bodies including

1. European Medicines Agency (EMA).
   A stakeholder meeting on the subject of promoting easier access to ATMPs was recently held by the Agency with the report of that meeting published in June.

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

   Goals of the IMI appear to be similar to the EMA goals therefore collaboration would be sensible.

2. JACIE (Joint accreditation committee of ISCT and EBMT).

   JACIE's primary aim is to promote high quality patient care and laboratory performance in haematopoietic stem cell collection, processing and transplantation centres through the development of global standards and an internationally recognised system of accreditation. This is relevant to ATMP manufacturing centres and clinical sites where harvesting for autologous and allogeneic treatments occurs

In addition HSCT networks including the European Bone Marrow Transplantation Group (EBMT) and its working parties already engage in cellular therapies activities and networking with in this group would be beneficial to the further development of ATIMP's.

NCTF strongly believes that there is a need for IMI to synergise with national funding schemes such as the Medical Research Council and British Biotechnology Science Research Council, and European funding such as Horizon 2020 initiatives. This linkage could lead to the funding of, for example, training programmes through the Marie Curie Initial Training Networks and collaborative networking via COST networking proposals

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.

Within section 3.4 it is important to make note that when comparing traditional therapies, lifetime cost should be considered. ATMPs are often curative and therefore represent a one

off cost (albeit large), but when compared with a lifetime cost it may be seen to more cost effective.

In Newcastle we have developed an optimal way of handling ATMPs. Hospital pharmacists are conducting an appropriate role in supporting the use of ATMPs, including taking responsibility for the governance of their safe use in the hospital sector whilst HSCT laboratory staff are using their existing expertise to handle and manipulate the products as required for individual studies. As such, we believe that we have developed a system in which ATMPS can be safely and efficiently introduced to bring maximum benefit for our patients.