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DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety and innovation

Meeting between European Society for Blood and Marrow Transplantation (EBMT) and DG SANTE B4

21 June 2016

Summary Minutes

Participants:

EBMT: C. Chabannon, J. Halter, R. Saccardi and E. McGrath

DG SANTE (Unit B4 Medical products: quality, safety, innovation): D. Schnichels, D. Fehily, I. Pucinskaite-Kubik and S. Van der Spiegel

The European Society for Blood and Marrow Transplantation (EBMT)[1] represents over 4700 physicians and scientists in 568 centres in 55 countries in the EU and beyond. Through a structure of committees and working parties, EBMT promotes research, education, harmonisation of practices and quality improvement through standards and accreditation. The society is funded through membership fees and corporate sponsorship. More information is available at www.ebmt.org and in the 2015 Annual Report online[2].

Following a short introduction of participants, the following topics were addressed:

1. EBMT noted that registry data shows a steadily increasing rate of haematopoietic stem cell (HPC) transplantation and predicted that this therapy is likely to remain a key treatment well into the future. EBMT considers that the introduction of Directive 2004/23/EC has allowed for ensuring safety and quality without bringing any implementation issues/disruption in medical practice in the field of transplantation.

2. However, they have noted that, in the period since 2004, practice has changed significantly and there is now a need to update legislation appropriately. The representatives noted that there is still room for harmonization in practices across EU Member States, for example regarding the nature and number of tests performed on donors. Some countries have national regulations that go beyond the Directive requirements, and creating challenges for

[2] http://www.ebmt.org/Contents/Resources/Library/Annualreport/Documents/EBMT_AnnualRep_2015.pdf.

cross-border distribution. Significant changes since the adoption of the legislation include the threat of emerging infectious diseases including some that were considered controlled but that have been 'reactivated' through increased intercontinental travel and climate change. Furthermore, the field now shows more diversity/complexity with different categories of donors, more specific preparations customised for specific patients, single patients receiving multiple products etc. The EBMT considered that "traditional" HSC transplantation serves as a model for the development of cellular therapies – whether minimally-manipulated or substantially manufactured – for other categories of disease. For these developing and promising therapies, they consider that the main challenge is rather in the preclinical and clinical demonstration of utility of these approaches than in obtaining full compliance with any set of standards (GMP) for processing / manufacturing.

3. EBMT note that the recent emergence of cellular therapies provided by industrial for-profit manufacturers is generating a shift in the relationship between industry and academia. The field is very much academia- and public sector-led but EBMT welcomes the contribution of companies that, through investment, can accelerate the delivery of novel and effective therapies. The development of CAR-T cells was provided as an example of the result of a strong collaboration between academia and industry. They consider that academic facilities and public sector tissue establishments will continue to be the locations where the primary development takes place although these organisations have no mandate or intention to put products on the market. EBMT underlines the following key points:

   - While there is so far limited experience of these new cellular therapies, growth in industrial demand for starting materials is expected. As a result, tissue establishments may come under pressure to serve not only the needs of their traditional customers, usually public or not-for-profit institutions, but also new commercial customers manufacturing therapeutic products. The EBMT experts considered that this may lead to initiatives aimed at easing restrictions on donors as a means to cut costs and improve profits.

   - Academia-based tissue establishments often need upgrading of facilities towards GMP, in order to develop and provide substantially manipulated products. This requires significant financial investment. As a result, consolidation of suitably equipped establishments is occurring and is regarded as a positive trend as experience and capacity is concentrated in fewer centres. That said, EBMT remarked that typically academia is only able to conduct early clinical trials. Industry participation or control is necessary to progress to phase II/III trials and achieve marketing authorisation of a product. This is financially unsustainable for academia and the public sector organisations that could provide these therapies.

   - EBMT commented that along with intellectual property (IP), a team's know-how should also be taken into account. Know-how represents the cumulative experience gained by individuals or teams as a result of extensive practice and management. Their production may not include sufficient novelty to be granted a patent and thus is difficult to commercialize other than as a service. IP is considered to apply to new products or

reagents or constructs that can be patented and licenses that can be sold to industry partners for further development and commercialization.

- EBMT is concerned about the eventual availability of ATMPs for patients. There is so far very limited commercial availability of ATMPs. They consider that most cell-therapies will not be commercially interesting to industry. This applies in particular when they do not have intellectual property (IP) rights, they involve simple processes and are of value for small numbers of patients. The CORDIS-funded AGORA-GMO project indicated that 85% of ATMP's are developed by tissue establishments in a hospital setting.

- The experts noted that for industry to commercialise a product, there needs to be a high degree of standardisation, although the respective contributions of inter-individual variability in the starting material collected from patients and donors, and procedural variations in cell engineering to this lack of harmonization remain difficult to measure. For many developing therapies there is the need to continuously improve and adapt the process. Tissue establishments in clinical or academic settings, being close to the clinicians and having access to patient cells, are uniquely positioned to do this development.

4. EBMT noted that much is expected of CAR-T cell therapies which might further change the landscape as from 2017. CAR-T cells are a gene-therapy that might serve as a bridge to HSC transplant or possibly as an alternative. It is forecast that these products will cost several hundreds of thousands of dollars per patient. The technology beyond CAR-T cell therapies is patented by several US-based universities, and not-for profit institutions (University of Pennsylvania, Memorial Sloan Kettering Cancer Centre, Ohio State, Fred Hutchinson Cancer Research Centre, National Cancer Institute and others). Nowadays, CAR-T Cells are individually and extemporaneously produced for each individual in need of this treatment. It is expected that in the future, off-the-shelf CAR-T cells will be produced from allogeneic starting materials becoming readily available for those patients who need them. This might create a pressure on donors or on cord blood banks to provide cells and potentially put at risk the principle of Voluntary Unpaid Donation (VUD) as established in the Tissue and Cells Directive.

5. EBMT explained that it runs a well-developed database with outcome data on HSC transplants, including follow up on around 16,000 allogeneic HSC transplants per year. Approximately 80% of HSC transplant centres in the EU actively provide transplant data to the EBMT at no cost to EBMT. These data allow for studies as well as for individual feedback to the centres. Given the large scale of this data-register, it is also possible to gather data on patients with rare diseases and in that context EBMT outlined the small but increasing activity in the use of HSC transplantation in severe Autoimmune Diseases. The data-collection could also allow providing vigilance data as requested by authorities.

EBMT is currently harmonizing this data collection with CIMBTR[3], its US-based counterpart. CIBMTR pays centres for delivering data and also is collecting data from some EU-based centres. Corporate members of EBMT (commercial companies) can access EBMT anonymised registry data. EBMT already provides this service to companies for the follow-up of patients treated with commercial products to meet post-marketing requirements and consideration would be given to extending this facility to ATMPs via the cellular therapy registry that is currently being developed.

6. In recent years the EBMT register also collects data on donor follow-up, delivered by about 60 centres (mandatory in Switzerland, but voluntary in the EU). This donor register also includes related donors (>50% of the donor data) which it considers particularly important given the higher risks often posed to related donors. The society aims to assess follow-up at 30 days, 1, 5 and 10 years after donation.

7. EBMT has noted a reduction in use of cord blood, since the uptake of haplo-identical bone marrow or peripheral blood stem cell transplants. Cord blood does offer some advantages in that it allows HSC transplants with less matching and less rejection/relapse. There is also the potential to expand cord blood before transplantation. However, haplo-identical donations from adults allow for identification of one or several potential donors for virtually every candidate for HSC transplantation, provide high numbers of cells that have full characterisation and have proven effective with appropriate immunosuppression. In order to optimize the use of cord blood, a full characterisation is needed, which is not the case for the majority of cord blood units in storage currently. There are over 100 public cord blood banks worldwide jointly containing 700,000 units with many accredited to international standards e.g. FACT-Netcord[4], AABB[5]. A consolidation might be needed for economic reasons but it will be important to maintain banks to provide highly characterised units as sources of cells for the manufacture of other products.

8. The Commission thanked EBMT for the meeting and all the information provided. They informed EBMT that it is likely that an Evaluation of the tissue and cell legislation will begin during 2016 and that there will be ample opportunities for EBMT to submit comments and feedback in the associated consultations.

[3] Centre for International Blood and Marrow Transplant Research, a research collaboration between The National Marrow Donor Program and the Medical College of Wisconsin www.cibmtr.org. CIBMTR collects outcomes data on every allogeneic transplantation performed in the U.S. (for the SCTOD, as required by U.S. law).
[4] http://www.factwebsite.org/CordSearch.aspx?&type=CordBloodBank&country=&state=
[5] http://www.aabb.org/sa/facilities/celltherapy/Pages/CordBloodAccrFac.aspx