EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

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

Brussels, SANTÉ/DF

Workshop with Stakeholders and Tissue and Cell Competent Authorities Substances of Human Origin Expert Group (CASoHO E01718)

5 May 2021, 09:30-13:00

By teleconference

WORKSHOP TOPIC: Regulating for Sufficiency – tissues and cells

Participants: All EU blood competent authorities attended. Liechtenstein, Montenegro, Norway, Republic of North Macedonia, Serbia and Turkey also attended as well as representatives of the Council of Europe (EDQM), ECDC and EMA.

The following stakeholder organisations attended: European Association of Tissue and Cell Banks, European Eye Bank Association, European Society for Blood and Marrow Transplantation, World Marrow Donors Association, European Society for Human Reproduction and Embryology, Fertility Europe, Cryos and the European Sperm Bank, European Hospital and Healthcare Federation.

1 Welcome and Introduction of stakeholders present

DG SANTE opened the workshop, welcoming all of the authorities and stakeholders. He explained that the event was organised in the context of the Impact Assessment for the revision of the BTC legislation. The objective was to provide an opportunity for key stakeholders in the tissue and cell fields to present, to the national blood competent authorities and the Commission, their positions on the topic of ensuring a sustainable supply of tissues and cells. It was explained that the format would be that of a ‘hearing’ rather than an interactive discussion. The views expressed would form part of the evidence gathering process for the Impact Assessment.

It was explained that the authorities would have the opportunity to ask questions, to clarify their understanding and to indicate, in an anonymous manner (using online polling), their initial reactions to the proposals made by stakeholders.

Authorities were informed that closed meetings of each competent authority group (blood and tissues & cells) were scheduled for June. These would provide the opportunity to discuss openly the topics that will have been explored in all three hearings being organised by the Commission. They would also provide the opportunity to review the 11 stakeholder workshops being organised by the company, ICF, contracted by the Commission to conduct a study to support the BTC Impact Assessment.

2 INTRODUCTION TO THE WORKSHOP – DG SANTE

DG Santé summarised the topic of the hearing, explaining that it addressed one of the key five shortcomings identified in the BTC evaluation, i.e. the lack of legislative measures to support the achievement of a sufficient and sustainable BTC supply. It was noted that the key legislative measures identified were (i) the introduction of regular supply monitoring at a national and EU level and (ii) the introduction of requirements to have emergency plans in place. It had been noted also that having the possibility for more regulatory flexibility could support increased supplies during crises that threaten sufficiency. It was noted also that non-legislative measures such as increased collection and improved utilization could be supported by the European Commission in other ways. It was underlined that this workshop would focus on the possible legislative measures.

DG Sante informed the participants that there had been a high level of response to the public and targeted online consultations, with submissions from across the EU and from all affected sectors and stakeholder groups. It was notable that a majority of respondents were working across the blood and tissue and cell fields and many worked also in related fields, particularly pharmaceuticals. Some preliminary results were presented for those consultation questions that touched on the topic of this hearing. Stakeholders had indicated that obligations for both mandatory routine reporting of sufficiency data (donations, distribution numbers, exchanges between Member States and import/export, clinical use) and for rapid notification in the case of sudden drops in supply, would positively impact on the information available to policy makers and on transparency for citizens. However, they also considered that it would result in significant additional costs and administrative burden for blood and tissue establishments and for authorities. A majority had also considered that mandatory emergency plan requirements would bring some, or many, improvements towards ensuring sufficiency during crises. Improved inter-Member State trust and BTC exchange (with digital tool support), more appropriate clinical use, reduced wastage, donation promotion campaigns and economic investment were all seen by stakeholders as actions that would support achieving sufficiency of supply.

3 ACTIVITY DATA MONITORING AS A TOOL TO SUPPORT POLICIES FOR SUFFICIENCY – EDQM

EDQM presented work carried out in the context of the grant agreement between the European Commission and Council of Europe on the topic of tissue and cell activity data monitoring. This work was completed and published recently and authorities had been provided with links to the data sets proposed and the recommendations made. The expert group that carried out the work with EDQM had representatives from the major tissue and cells professional associations and from a number of EU tissue and cell competent authorities.

The group had developed an agreed data set that, in their view, should be considered for mandatory reporting by tissue establishments to their competent authorities, and by the authorities to the European Commission. This data would allow visibility to citizens for transparency purposes, would allow policy makers to take action when certain dependencies or trends raised concerns and would provide denominators for vigilance.

The key recommendations of the group were presented as follows:

1. Legislative changes at EU level will be required in order to enforce the collection of activity data in the field of tissues and cells for the purpose of transparency for citizens

and as denominators for vigilance exercises, in accordance with the minimum data set elaborated (and ideally to be continuously updated) by the EDQM in cooperation with the EU (Health Authorities) and data-collecting professional societies and registries.

2. Governance and data collection and curation should be under the responsibility of the national Competent Authority(ies) designated bodies.

3. All parties performing any activities covered under the EUTC legislation (i.e. tissue establishments, donation/collection centres, MAR clinics, tissue establishments handling reproductive tissues and/or cells, independent professionals/practices performing any MAR procedures, etc.) must be authorised by their competent authority. This authorisation must be conditional, among other factors, on activity and biovigilance data reporting. This would ensure accurate and complete data reporting.

4. End users must ensure traceability and report all clinical applications and SARE. Each country can decide how to organise and ensure this reporting.

5. If CA delegate some of their data collection duties to professional societies they would have to enforce rules to ensure adequate and mandatory transmission of data from these registries to them (i.e. to their national registry(ies)), in good quality and in a timely manner.

6. CA must qualify those registries providing data to them. This could be done through inspections. In the case of international registries, inspections could be performed by one CA (mutual recognition by other CA) or by multinational groups of inspectors, or alternatively CA could rely on qualifications performed by EU authorities.

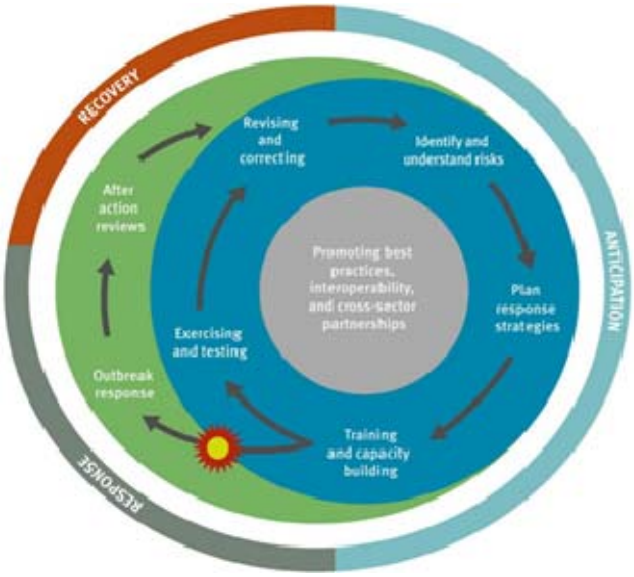
An online poll of participants indicated wide support for the future EU legislation to enforce the collection of activity data in accordance with the proposed minimum data set. Most supported the other proposals presented although a significant number considered that more discussion on this would be needed on the details. The most significant challenges for implementing the proposals were seen by the participants as cost and administrative burden. Harmonisation of terminology, obtaining information from hospitals, technical expertise and GDPR were seen as important but lesser challenges.

4 MAINTAINING SUPPLY DURING EPIDEMIC CRISES – ECDC

The discussion moved from routine supply monitoring to measures that address sudden changes due to crises caused by disease outbreaks. ECDC presented relevant experience from the Covid-19 pandemic.

ECDC described the global experience during the pandemic. In this case, it was clear early in the pandemic that transmission of the virus via clinical use of substances of human origin (SoHO) was not a concern. The focus, therefore, moved quickly to the impact of the crisis in general on the possibility of donors to donate, establishments to continue to collect, process and supply and hospitals to use the substances. A number of case studies from across the world were presented, demonstrating the risks to supply that had emerged in the different sub-sectors of substances of human origin.

The experience had underlined that preparedness and response are essential for maintaining and safeguarding BTC supply during epidemics. The preparedness cycle includes planning, identification and prioritisation of risks; training and simulation exercises; after action reviews; evaluation of lessons learned and implementation of the organisational change identified.



The approach presented had been promoted also by WHO. It was noted that in its guidance documents developed during the pandemic, ECDC had differentiated between three categories of substance of human origin: critical SoHO, essential SoHO and common SoHO. Critical SoHO included blood and blood components, organs and haematopoietic stem cells as there are usually no alternative therapies, they are often lifesaving and there are limited possibilities for storage. Plasma for the manufacture of medicinal products and tissues for lifesaving transplantation (e.g. heart valves, skin in some cases etc.), and plasma for fractionation, are considered to be 'essential SoHO' as they can be stored; and other types of cells and tissues used to enhance the quality of life were considered to be 'common SoHO'.

Finally, ECDC noted the key importance of the SoHO sector during infectious disease outbreaks. The sector was seen as key as a source of big data of relevance to public health. In particular, this related to monitor, including by sentinel event surveillance, the spread of the infection in the population and to following its trend. Important tools include sero-epidemiological studies and investigation of the association of immunogenetic parameters. Data might be sourced from donor registries and could provide information on the severity of the disease course. The sector might also detect the first occurrence of a disease in a previously disease-free population.

An online poll indicated strong support among the participants for a requirement to report to an authority whenever allogeneic donations, unrelated donations, third party donation, or stocks fall below a certain level, although some participants needed more specific details to be able to decide on this. When asked which would be the critical tissues and cells that should be the subject of such crisis notification, the most common substances mentioned were haematopoietic stem cells, heart valves and corneas. The participants also indicated strong

support for a requirement on tissue establishments to have contingency or preparedness plans in place to address crises.

5 A SERIES OF SHORT PRESENTATIONS BY TISSUE AND CELL ASSOCIATIONS

A series of short presentations were given by professional associations to share their views on how EU legislation could support a sustainable supply of tissues and cells in the EU. The key proposals were the following:

EBMT presented their views on this topic as follows:

1. EBMT favours Policy Option 2
2. HSCT are directed donations so supply is generally not an issue except for patients from minority communities
3. Approximately 75% of patients of European descent are likely to identify a matched donor*. Rate is much lower for ethnic minority and mixed-race patients e.g. 20-25% for patients of African descent
4. Approximately 50% of the patients that find a donor find his or her perfectly matched donor in another country±
5. VUD: Unrelated donors act voluntarily and altruistically; their availability varies due to medical and personal reasons but this principle should be maintained and strengthened.
6. EBMT cautions against setting very rigid rules - donors are considered on a risk-benefit basis so should be left to clinicians' judgement based on professional guidelines; HSCT is affected by disruption to travel and transport e.g. pandemic, Islandic volcanic ash cloud, bad weather but clinical decision-making e.g., donor age
7. EBMT would welcome legislative measures to improve donor follow-up, particularly for related donors
8. Since 2017, the numbers of family donors continues to rise with HLA identical sibling and syngeneic twin donors increased by 6% and haploidentical donors by 16.3%¥
9. EBMT would welcome support for donor registries e.g. quality via certification/accreditation - Registries perform a critical role and contribute to research, enhancing services and extending the range of cell products provided
10. EBMT would welcome measures that ensure that testing and other requirements are the same across member states to facilitate cross-border movement of cells
11. ECDC could contribute by recommending testing requirements including test kits in order to harmonise requirements
12. EBMT would welcome any measures to recruit donors to national bone marrow donor registries, particularly younger donors

WMDA described their experiences during the Covid-19 pandemic. Despite the fact that the European Commission confirmed that haematopoietic stem cells are considered as critical goods, with free circulation within the European Union, transporting these substances was a major challenge. Fourteen products (bone marrow, peripheral blood stem cells or cord blood) crossed an EU border every day, each for a specific patient. The numbers of bone marrow transplants decreased although this was partially because some less urgent transplants were postponed. Different national regulations lead to additional coordination hours to organise collection and transport, and caused additional work to understand quarantine, vaccination policies etc. A central role for professional societies to facilitate and inform emerged.

WMDA would welcome measures that ensure testing and other requirements are the same across EU Member States during crises. ECDC in collaboration with professional societies could recommend these requirements. They questioned the rationale for Covid-19 testing when there is no evidence of transmission via blood.

In general, HPC would be more available if certain technical rules were kept up to date in line with the scientific evidence (e.g. donor exclusion for endoscopy, tattoo, acupuncture, travel history to regions with similar epidemiologic situation) and they consider some of the required deferral periods after exposure to be unreasonably long.

An online poll indicated significant support for future EU legislation should to ensure common testing rules during epidemic situations. There was strong support for allowing HPC donor eligibility to be decided on a case-by-case basis.

EATCB

The association clarified the difference as they see it between the concepts of sustainability and self-sufficiency. They consider that sustainability is 'the ability to maintain supply at a certain rate or level (the quality of being able to continue over a period of time)' while they see self-sufficiency as 'the quality or state of being able to provide everything you need without the help of other people or countries'.

In their view, the EU legislation should reinforce the requirements of activity report, establishing common indicators. The number of donations should be monitored and the EU should promote donation and monitor indicators. Tissue establishment activity monitoring should address the availability of tissues and should monitor the sources (other Member State, non-EU, distributors etc.) and promote local programmes over commercial suppliers for greater sustainability. Data should be harmonised, based on the proposals from the EDQM exercise. Mutual recognition of authorisations between Member States would facilitate tissue exchange in case of high demand in one country. It was suggested that an EU mechanism to support tissue exchange between Member States be established.

EATCB also made a number of recommendations for actions at the national level.

An internet poll showed strong support for EU legislation differentiating between the concepts of sufficiency and sustainability and significant support for greater transparency on import. The proposal on establishing an EU structure for tissue exchange was seen by many participants as needing more discussion. Just over half of the participants considered that the EU should discourage or limit commercial activities in the supply of tissues.

EEBA expressed their view that the revised BTC legislation should:

1. Include provisions to regulate the quality of imported SoHO
2. Reduce diversity of interpretation and implementation of technical rules to ensure mutual recognition between Member State competent authorities
3. Remove barriers to BTC exchanges by certified & qualified establishments to guarantee accessibility and sufficiency
4. Include provisions for emergency preparedness, especially important for BTC with short clinical expiration date (e.g. matter of weeks for corneas)
5. Support improvements to optimize usage through (scientific) investments and legal regulation for tissues used for research and innovation.

On online poll of participants showed that there was considerable support for EU legislation ensuring that tissue export be limited if local patient need has not been met. There was some support for abolishing administrative barriers for the distribution of tissues and cells into another Member State but many participants indicated that this would need further discussion and a high level of support for consensus terminology.

ESHRE noted a significant shortfall in gamete donations compared to demand. They called for differentiation between rules for "within-couple use" and "third-party donation" with a move away from the current terminology (partner vs non-partner). Data on third-party donation (EIM report 2016) indicated that 23.2% of all reported assisted reproduction deliveries result from oocyte donation (22497/97011) and that 38.2% of all reported deliveries after intra-uterine insemination with donor sperm (5705/14946). There is an increasing gap between the supply and demand of cryopreserved donor oocytes and a growing number of people in need of donor gametes.

The key shortcomings in the current legislation are seen by ESHRE as the lack of any provision on donor anonymity for the supply gametes (sperm or oocytes) and the failure to provide recommendations for national robust and harmonized data collection that can be shared between countries.

Their key proposal was to establish a pan-European registration of assisted reproduction activity with compulsory reporting to improve traceability and avoid the risk of bypassing quality and safety measures in the context of cross-border care. In an online poll of participants, most fully or partially agreed that a pan-European registration of ART activity and compulsory reporting would improve traceability, quality and safety of ART.

6 ROUND TABLE WITH A PANEL OF OTHER PARTICIPATING ASSOCIATIONS

The associations that had not presented were specifically invited to add comments. Fertility Europe stated their position as patient representatives. Fertility Europe said that they see many issues that have to be clarified. The main concern of the organization recently has been that two countries within the "force" embryo donation when the patient does not want to donate.

The 2 largest sperm banks in the EU - Cryos and the European Sperm Bank also added comments. Cryos support the suggestion to give more mandates to international organizations (policy option 2) as a means to increase standardisation, trust and collaboration between Member States.

European sperm bank noted that it is aligned with Cryos and stated that supply would be easier if there were standardized rules on registration of donors.

The European Hospital and Healthcare Federation (HOPE) noted that the Covid-19 crisis showed how important standardization is across the EU in this sector.

7 THREE BREAKOUT GROUPS – REPLACEMENT TISSUES, HAEMATOPOIETIC STEM CELLS AND MEDICALLY ASSISTED REPRODUCTION – DISCUSSION OF PROPOSALS.

Three breakout groups were asked to discuss the benefits and the challenges of introducing reporting requirements for monitoring of donations/supplies at national and EU levels and to consider what other measure in EU legislation could support achieving sufficiency of supply.

Group 1 – Replacement tissues

The benefits of monitoring activity such as donations, use, inter-Member State exchanges and exchanges with third countries were seen as (i) increased transparency – particularly for authorities and professionals and (ii) the facilitation of activity indicator mapping (iii) the promotion of learning from others to improve the supply situation locally.

The challenges were seen as a need for IT tools to support this; concerns regarding the personnel resources and infrastructure needed; GDPR; engagement of the clinical hospital staff; access to data on tissues imported from third countries (in real time) and delays from data collection to publication. A view was expressed that data collection should be frequent but reporting to authorities/the Commission should be annual. It was also mentioned that tissue establishments should have some kind of stock/donation rate targets, based on the demand in the area supplied, that could be used as indicators of supply sufficiency.

With regards to other measures that could support achieving a sustainable supply, it was suggested that health authorities and BTC authorities should promote activities in public establishments and hospitals as this would be more resilient than relying on the private sector or on imports. There should also be increased pubic awareness activities and clear visibility on all imported tissues, as well as on wasted/unused donations.

Group 2 – HPC

In this field, international exchange is not an indicator of local shortage but is essential for matching of donors to recipients. The benefits of monitoring activity such as donations, use, inter-Member State exchanges and exchanges with third countries were seen as a means to mentoring/good practice sharing as is possible/already happening through WMDA. This should also lead to encouragement for setting up more registries/recruitment schemes in countries that are still lacking these. It was noted that WMDA accreditation as a facilitator for imports as currently existing alternative accreditations have much higher administrative burden.

The challenges were seen as needing a case-by-case assessment rather than having standardized criteria for allowing import. There could be standardized criteria as the basis of case-by-case basis as well – e.g. separation of related/unrelated donors. It was noted that no donors/recipients should be subjected to additional risks. The EDQM guides (developed by experts, physicians, CA representation) support case-by-case decisions and should remain that way. On the topic of accreditation of national donor registries, it was noted that the WMDA programme can be used a model (already existing) that focuses on donor care.

The following additional points were raised:

- It was noted that transported HPC need to be used immediately (risk to the recipient if there is a failure in transport) or cryopreserved at arrival before the patient is

conditioned (risk to the recipient if there is cell loss. There need to be rules donor/recipient protection in cryopreservation.

- There is a key need for response measures/plans for closed borders at times of crisis.
- To ensure supply, changing demographics need to be taken into account in donor recruitment (ageing, immigration).
- There is a lack of harmonization for viral pathogen testing, particularly during seasonal outbreaks. The group discussed whether there should be harmonisation of testing or whether authorities should be responsible for assessing where tests are needed based on the case. There could be a role for ECDC to help authorities decide on viral testing requirements.
- Initiatives to increase the HPC donor base should be more targeted, particularly at minority groups that are not well represented in donor registries.
- There was a discussion on the accountability of large actors, such as donor registries, and on the robustness of supply when those actors are public or private.
- It was noted that ongoing research on donor motivation could provide beneficial results for more global exchange/improved access.

Group 3 – MAR

The benefits of monitoring activity such as donations, use, inter-Member State exchanges and exchanges with third countries were seen as:

- Providing the possibility for registries to follow up donors or donations that move across borders;
- Increased traceability leading to increased safety of donors and recipients, as well as monitoring offspring.
- Supporting consistent safety and quality across Member States.

It was noted that, for this field, there is not an EU-wide sufficiency problem – the access problems relate to local issues in individual countries. However, improved standardisation can prevent future shortages through facilitating exchanges.

The challenges were seen as:

- How to monitor patients and donors moving for treatments;
- How to balance the rights and protection of patients/offspring, with improving the reporting system;
- Inevitable differences of national rules regarding ethics, such as anonymity;
- Resources for IT systems for data collection and monitoring.

The following additional points were raised:

- If an EU level gamete registry is established, tissue establishments, as well as existing registries, should be consulted when defining common datasets/ develop registries
- There is a need to improve the standardisation of rules of compensation for donors
- There is a need for increased transparency regarding donor adverse reactions

- There should be mandatory follow up of oocyte donors, to ensure necessary care in case of need
- There should be agreed rules or recommendations on technical issues such as the number of donations permitted per woman
- There should be education campaigns on the long term outcomes for donor treatment
- There were calls for standardise parental rights in the EU and for increased transparency on anonymity rules and a need for recruiting donors from a wide ethnic pool to address the needs in smaller populations.

8 FEEDBACK FROM BREAKOUT GROUPS

The facilitators of the three breakout groups summarised the points above to the participants in plenary session.

9 WORKSHOP CLOSE

The Chair thanked all participants for the fruitful and rich discussions. It was noted that all presentations were provided to the competent authorities and would be shared with all stakeholders after the meeting. It was explained that the information provided and views expressed will feed into the BTC Impact Assessment process.