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SANTE B4/IPK ARES (2019)

Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718)

Meeting of the Competent Authorities for Tissues and Cells

13-14 May 2019

Summary Minutes

The meeting of the tissues and cells competent authorities (CA) took place on 13 and 14 May 2019. The previous meeting took place on 20 and 21 June 2018.

PARTICIPATION:

- Competent authorities from all Member States (MS) participated in the meeting, with the exception of Bulgaria, Greece, Hungary, Romania, Luxembourg and Slovenia.
- All candidate countries except Albania, Montenegro and Republic of North Macedonia attended the meeting.
- In addition, the representatives of the Consumer, Health and Food Executive Agency (CHAFEA), the European Centre for Disease Prevention and Control (ECDC) and the Council of Europe (EDQM) were present as observers.
- The World Health Organisation (WHO) representative could not attend the meeting.
- Private experts attended for specific agenda topics, as detailed below.

The representatives of the European Commission/DG SANTE unit B4 chaired the meeting.

1. WELCOME AND ADOPTION OF THE AGENDA

The chair welcomed the participants. Those representatives attending for the first time were asked to present themselves. Following this, the SoHO team members introduced themselves to the new representatives and they informed the meeting about the usual house rules.

2. ADOPTION OF THE AGENDA

The participants adopted the agenda without major modification.

DG SANTE invited the participants to declare any conflicts of interest. None were declared.

The Summary Minutes of the previous meeting had been approved by email and published on the DG SANTE website.

3. LEGAL MATTERS

3.1. Transposition and implementation of Tissues and Cells Directives (DG SANTE)

The Commission updated the group on the transposition of the EU tissues and cells legislation. The overall transposition check is finalised for all MS. There remains one on-going infringement proceeding which has been referred to the Court for failure to notify transposition of Directive 2012/39/EU.

3.2. Update on implementation of coding and import legislation (DG SANTE)

On the 2015 Directives on coding (Directive (EU) 2015/565) and import (Directive (EU) 2015/566), the Commission reported that all Member States had notified their transpositions. DG SANTE has begun the conformity check and MS may be requested to fill in tables of correspondence.

3.3. Danish non-partner donor testing protocol – update with regards to changing the national legislation (DK)

As discussed in previous CA meetings, ECDC assessed the risks associated with the donor testing protocol for non-partner donations being applied in Denmark. The ECDC concluded that the Danish protocol largely ensures an equivalent level of safety.¹ Commission legal services were consulted following the previous meeting of this expert group. They concluded that the Danish serological testing protocol can be considered as a more stringent national requirement as permitted in Article 4 of Directive 2004/23/EC and Article 168 (4)(a) of the Treaty.

With regard to the Danish NAT testing protocol, this could also be considered as a more stringent national requirement provided that the Danish national legislation is changed in line with the recommendation of ECDC to defer release of the donated sperm until the longest window period has lapsed.

The Danish representative confirmed that, since the previous meeting, this change had been implemented in the Danish legislation.

This concluded the discussion on this topic, with a confirmation that the Danish sperm donor testing protocol can be considered a more stringent requirement with respect to the non-partner donor testing provisions in EU legislation, and is therefore in line with EU legislation.

3.4. New Medical Device Regulation: interaction with TC competent authorities (DG GROW)

¹ However, under certain circumstances, i.e. when sperm donations are released by NAT for HIV, HBV and HCV, a minor increased risk of missing a window period infection remains (as it does for all tissues and cells released by NAT), which could be mitigated by restricting release for a specified period. In other respects, particularly if the delayed release by serological testing is implemented, the protocol could be considered as more stringent than the Directive requirement.

The Commission (DG GROW) gave an overview of the revised Medical Devices legislation (Regulation EU 2017/745 on medical devices (MDR) and Regulation EU 2017/746 on in vitro diagnostic medical devices).² According to MDR³, Member States shall share expertise in the fields of medical devices, in vitro diagnostic medical devices, medicinal products, human tissues and cells, cosmetics, biocides, food and if necessary, other products, in order to determine the appropriate regulatory status of a product, or category or group of products.

DG GROW informed the authorities regarding the set-up of a MD/Tissues and Cells task force, working under the Medical Device Coordination Group (MDCG). To date, CAs on MD/IVD from five MS had indicated their interest to participate. The Tissue and Cell authorities were invited to volunteer to join the group to work on borderlines and issues related to SoHO/MD combination products.

The competent authorities welcomed this initiative and highlighted a need of interaction between different bodies concerning classification of borderline products. CAs agreed on the need to strengthen the communication between SoHO and medical device sectors. At the end of the discussion, IT, NL, DK, SE, UK, ES, and DE responded positively to GROW's call for working with MD CAs in the taskforce. It was suggested that this taskforce also looks into new bedside devices and into supply dependency of the SoHO sector on MD/IVD. These two issues have been discussed repeatedly in this forum, and are considered of increasing importance for the sector.

DG SANTE mentioned that in the evaluation of the blood, tissues and cells (BTC) legislation, different stakeholder's highlighted issues on the coherence of the BTC legislation with other regulatory frameworks including the borderline with medical devices manufactured from human tissues and cells, or their derivatives. In the report on the BTC evaluation, to be published by the Commission in 2019, the summary of the findings on coherence will form a constituent part of the report.

On the subject of coherence with other legislative frameworks, it was also mentioned that the pharmaceutical committee is currently reflecting on the application of the 'hospital exemption' in the field of Advanced Therapy Medicinal Products (ATMPs). One participant asked for the relevant documentation to be circulated also to the tissue and cell authorities. The Chair agreed to check this internally and invited participants to liaise with their national counterparts in the pharma sector as appropriate.

4. EVALUATION OF THE EU BLOOD, TISSUE AND CELL LEGISLATION (DG SANTE)

DG SANTE summarised the state of play of the Blood, Tissues and Cells Evaluation (BTC Evaluation), explaining that the Commission's Evaluation Report was expected to be published in 2019.

The key issues coming forward from the Commission stakeholder consultation activities, focusing on activities and messages emerging since the previous tissue and cells authorities meeting were outlined.

The key findings emerging out from the evaluation are the following:

² <https://ec.europa.eu/growth/sectors/medical-devices>

³ Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance.) See Article 4. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745> «

- Technical provisions of the legislation are out-of-date in a rapidly changing sector;
- Oversight provisions are not adequate to regulate today's BTC landscape;
- Some citizens groups are not adequately protected (donors, children born from medically assisted reproduction);
- Innovation in BTC is not optimally facilitated;
- Limited provisions to ensure BTC sufficiency.

These findings come from the Open Public Consultation conducted by the Commission⁴, including submissions from a broad spectrum of stakeholders from different sub-sectors, multilateral meetings between stakeholders, the Commission and MS authorities⁵ and an external study. The group of NCAs recognised and supported these findings.

A number of CAs urged that there is a need to revise the BTC legislation.

In the context of the BTC evaluation, DG SANTE had circulated a short survey to the authorities to gather data on three topics, where evaluation data was incomplete. The topics concerned:

- i) the situation in Member States prior to the adoption of the tissue and cell legislation (the BTC evaluation 'baseline')
- ii) the classification mechanisms in Member States for substances/products with tissues and cells
- iii) the classification of certain BTC at Member State level.

The results of the survey, to which 21 MS had responded, were presented. On the first topic, over a third of respondents indicated that binding legislation to define safety and quality rules were not in place in their countries before the adoption of Directive 2004/23/EC or prior to their accession to the EU. This applied for each of the sub-sectors (replacement tissues, haematopoietic stem cells and medically assisted reproduction). There was no regulatory oversight for replacement tissues or haematopoietic stem cells in the same proportion of Member States and in more than half; there was no regulatory oversight of medically assisted reproduction.

Almost all tissue and cell authorities are involved in the classification process in their MS. The most common criteria used for classification (and the number of MS using the criteria) were the following:

- Degree of consolidation of a therapy (i.e. is there retrospective history of safe use) (8)
- Mode of action (15)
- Autologous/allogeneic use (11)
- Same/different essential function as in the donor (17)
- Substantial/non-substantial manipulation (17)
- Intention to place on the commercial market (9)
- Industrial nature of processing (11).

⁴ https://ec.europa.eu/health/blood_tissues_organ_consultations/implementation_legislation_en

⁵ The key messages emerging from those meeting were summarised and the meeting participants were referred to the webpage where summary minutes are published here https://ec.europa.eu/health/blood_tissues_organ_events_en#anchor1.

On the classification of a range of specific substances/products, the survey indicated that in some cases Member States apply divergent regulatory frameworks for identical therapies, or, in some cases, no regulation. Specifically, Faecal microbiota transplants (FMT), human breast milk, platelet-rich plasma prepared in the hospital, autologous adipose tissue prepared in the hospital, cells separated by enzymatic digestion without expansion (e.g. keratinocytes and hepatocytes), serum eye drops, demineralised bone combined with gel or putty, decellularised dermis and decellularised heart valves are being regulated in divergent ways across the MS.

One participant suggested that any product obtained from blood and intended for a purpose other than transfusion (e.g. non-homologous use) falls outside any regulatory framework at EU level as blood cells are completely excluded from the Medicinal Products Directive (2001/83/EC), and blood and blood components are excluded from the Tissue and cells Directive (2004/23/EC), except haematopoietic stem cells and donor lymphocyte infusions that do fall under the tissue and cell framework.

In the general discussion, many participants highlighted the need for the BTC NCA to be more involved in classification matters also at EU level, e.g. through an advisory BTC subgroup/body. The Danish delegation referred to its recent submission to the REFIT platform calling for more clarity, and for more common EU views, on the applicable legal frameworks for innovative therapies and asking for closer cross-sector discussions and advice at EU level on classification matters⁶. This message was supported by other authorities since it can provide clarity for developmental programmes and ensure the availability and access for therapeutic products, where regulatory controls applied are proportionate for ensuring quality and safety.

The chair summarised the next steps and the planned timing for publication, noting that it would be up to the new Commission, in place after the 2019 elections, to consider how to address the shortcomings and gaps identified during the process. She thanked Member States for all their contributions to the process so far and urged them to inform DG SANTE if they had any concerns regarding the findings outlined to date. In addition, they were invited to submit any additional data/evidence they considered important and encouraged to disseminate the report once published. Outputs are available on the DG SANTE website.⁷

5. OVERSIGHT FUNCTIONS

DG SANTE, ECDC, EDQM and the rapporteurs of SoHO expert sub-groups presented and discussed the activities related to oversight functions including the extensive progress in the subgroups on vigilance, traceability and inspections. This work is recognised as very valuable to increase common level of knowledge/skills in national authorities.

⁶ Proposals for simplification of EU-Legislation prepared jointly by the Danish Minister for Business, Industry and Financial Affairs and the Danish Business Forum for Better regulation March 2019, p. 4.

https://ec.europa.eu/info/sites/info/files/proposals-simplification-eu-legislation-danish-ministry-industry_en.pdf

⁷ Summary of the Stakeholder consultation on the BTC Evaluation;

https://ec.europa.eu/health/blood_tissues_organs/consultations/implementation_legislation_en https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/2018_consultation_evaluationbtc_report_en.pdf

Summary of the Blood, Tissues and Cells Stakeholder Event of 20/9/2017:

https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/ev_20170920_sr_en.pdf

5.1. INSPECTION AND AUTHORISATION

The Group were given a debrief on the work of the recently established expert sub-group on inspections (IES). The representatives were reminded that a proposal to establish such a sub-group was first made in the October 2018 CASoHO Expert Group meeting (Blood CAs). Terms of Reference were then agreed in writing by both sets of blood, tissues, and cells competent authorities. DG SANTE called for nominations at the end of 2018. 28 competent authorities nominated 45 representatives. The first IES meeting took place in January 2019.

The IES involves both blood and tissues and cells CAs, the meetings take place at least twice a year. The IES focus its work on the following areas:

- (i) review of existing guidance documents on inspections and inspections systems and the development of new guidance documents;
- (ii) development and coordination of training courses on inspection and the audit of inspection systems;
- (iii) coordination of inspection-related activities between competent authorities and audits of inspection systems⁸;
- (iv) dissemination of the results of its work and the monitoring of uptake of its work.

The rapporteurs of the IES presented the work carried out and outlined next steps, which include the development of the 2019 work. The plan is being finalised. The ultimate objective is to move to a more operational IES by 2020. This work of IES is recognised as valuable to increase common level of knowledge/skills in national authorities.

5.2. TRACEABILITY

Update on the work of the Coding Expert Subgroup (CES)

The Coding Platform that supports the Single European Code for tissues and cells is in place since April 2017. The Tissue Establishment compendium on the Coding platform includes information from 28 Member States and Norway and Iceland.

There are over 4000⁹ tissue establishments in the compendium, with the activities and authorisation status shown. 60 national and 29 regional authorities have been registered in the coding platform and are responsible for updating the information contained there.

To clarify implementation questions brought forward by the CA on the implementation of the Single European Code, the Commission organised a dedicated meeting of the Coding Expert Sub-group on 3 October 2018. The questions brought forward in the discussion focused on the necessity to define/clarify so-called split numbers, to add new definitions, to display the SEC, to provide clarifications on tissues and cells prepared before April 2017 etc. It was announced that next CES meeting will take place on 15 May 2019 and focus on the clarifying of the open issues and technical improvements and new features of the EU Coding platform.

The work of CES is recognised as valuable to increase common level of knowledge/skills in national authorities.

More information about SEC for tissues and cells is available at DG SANTE website.¹⁰

⁸ Point iii covers joint inspections and the CESIP work.

Overall, IES has been divided into five work clusters: Inspection Guidelines, Coordination of Training Courses, Coordination of Joint Inspections, Oversight of inspection systems, Dissemination and Monitoring.

⁹ April 2019

5.3. SURVEILLANCE AND VIGILANCE

5.3.1. Update on infectious disease risks

a) Epidemiological - general update (ECDC)

The ECDC representative gave an epidemiological update informing the group of recent infectious disease transmissions that pose potential threats to safety of tissues and cells.

The presentation focused on Ebola virus disease outbreak in Democratic Republic of Congo, Zika virus transmission worldwide (ECDC Rapid Risk Assessment), West-Nile Virus and Usutu Virus viruses, as challenges for blood safety in the EU and ECDC SoHO activities in 2019.

In the next meeting of the CAs, ECDC will update about their work on the projects such as “Assessing the risk of bacterial infections transmission through SoHO”, “Assessing the risk and prevention of fungal and parasitic infections transmission through SoHO”, ECDC Risk Assessment on TBE transmission through SoHO, recommendations on Ebola virus disease and SoHO safety and planned expert meeting on “Pathogen inactivation of blood and blood components”

Participants highly appreciated the update provided by ECDC.

b) Other - Member State updates

No Member State had specific national surveillance information to report.

5.3.2. Rapid alerts

DG SANTE provided the participants with a summary of alerts posted in the RAB and RATC platforms up to May 2019. A number of alerts (epidemiological alerts, Quality and Safety defects, information notices, bilateral enquiries and illegal/fraud cases) had been reported via the platform. In total, 37 rapid alerts for tissues and cells (RATC) were reported for 2018. In January-May 2019, there were 14 alerts uploaded for tissues and cells by the CAs.

Although the number of rapid alerts for RATC reported each year were generally decreasing, 2018 showed an increase.

DG SANTE also noted that a link between RATC and the EU Coding Platform for Tissues and Cells is ready to be tested.

The Commission informed delegates that the 2018 RAB and RATC activities were summarised in one single report for publication which was published in March 2019¹¹.

5.3.3. Serious Adverse Reaction and Events reporting exercise (EDQM)

SARE 2018 exercise (2017 data)

¹⁰ https://ec.europa.eu/health/blood_tissues_organ/tissues/single_european_code_en

¹¹ https://ec.europa.eu/health/sites/health/files/blood_tissues_organ/docs/2018_ra_soho_summary_en.pdf

The Council of Europe (EDQM) debriefed the participants on the final analysis of the 2018 SARE reporting exercise for Tissues and Cells. The numbers and types of SAR and SAE reported were presented, along with denominators and the EDQM team highlighted areas where improvements could be made.

A total of 756 serious adverse events (SAE) and 231 serious adverse reactions (SAR) were reported to have occurred in 2017. Importantly, SAR in non-reproductive TC transplantation led to 13 recipient deaths and, in reproductive TC application in ART, to 2 recipient death. EDQM reported that the country data submitted revealed there were 10 SAR in non-reproductive TC donors and 17 SAR in reproductive TC donors.

EDQM noted that some countries still do not report any SAE, SAR or a complete set of denominators. SARE reporting continues to be subject to inconsistencies and heterogeneity but the data quality has gradually improved.

The SARE report for the 2018 exercise will be shared with CAs for comments before publication. The Commission thanked EDQM for the professional way they have carried out this work.

Launch of 2019 exercise (2018 data)

The Commission reminded all participants that the new SARE reporting exercise had been launched in April 2019 with a deadline for submission of July 19th 2019. The Commission highlighted the need for Member States to submit their country reports on time.

The MS were invited to carefully consider the SARE Common Approach document and pay special attention to the changes in the reporting template. If there are two or more CAs in a MS, the representatives were asked to coordinate and send a single submission.

5.3.4. Update from the Vigilance Expert Subgroup

A sub-group to the expert group CASoHO E01718 working on vigilance across blood, tissues and cells with the aim of improving the Commission's vigilance related activities, particularly the SARE and rapid alerts programmes.

One of the Vigilance Expert Sub-group's (VES) rapporteurs provided an update of the work of the VES. The VES had compiled a list of issues that might/should be addressed to improve the quality and usefulness of the SARE exercise and categorised them as 'quick fixes' involving changes that do not impact on how data is currently collected, changes which will involve advance notice because of changes in the way data will be collected at MS level, possible future improvements that would imply a revision of EU legislation.

Several priority proposals for implementation in the 2018 and 2019 reporting exercises had been proposed and implemented. The VES proposed improvements for 2019 were elaborated by three vigilance experts working groups focusing on (i) TC SARE definitions and categories, (ii) BTC SAR and (iii) BTC SAE. A meeting of those working groups had been held on 7 May 2019.

A full VES meeting is scheduled for 19-20 November 2019 where a new wave of proposals for improvement will be discussed and prioritised there for possible implementation in the 2020 exercise or beyond. It was reported that the VES would also start to address vigilance issues for organs.

In the context of vigilance work, DK gave a presentation on the result of a neighbour check about the Danish Implementation of the EUTCD. The purpose was to determine whether the definition in the Danish Tissue Act of genetic disease in donor children as a SAR could be

considered unnecessary. The Danish Patient Safety Authority concluded that the Neighbour check did not give any causes to change the implementation of the definition of serious adverse reactions, including genetic disease /hereditary genes in gamete donors. The final decision was taken at a ministerial meeting 30th of January. DK asked the representatives from other MS to avoid sending RATC to non-affected clinics.

The VES rapporteur noted that the VES would like to send a questionnaire to the TC Competent Authorities about the current procedures for collecting data for the EU vigilance reports.

DG SANTE supported this initiative and thanked the VES for their work and noted that this expert sub-group is providing an excellent bridge to the vigilance officers in Member States that are completing the SARE submissions each year. The level of activity in the group was clearly high and the results should bring significant improvements.

5.4. CLINICAL OUTCOME DATA

5.4.1. Good Practices for demonstrating safety and quality through recipient follow up (EURO GTP II)

EURO GTP II is an EU funded project on good practices applied to T&C preparation, processes and patient follow-up procedures, to ensure safety and support the evaluation of clinical efficacy. This three-year project started in 2016 and was led by the Blood and Tissue Bank of Barcelona. It brought together 14 associated and 13 collaborating partners. The final outcomes of the project were presented, and a particular call was made on CAs to make their tissue establishments aware and use the important outputs of the project.

The objectives of the project were to determine

- (i) methodologies for assessing the risks associated to novel tissues/cells,
- (ii) methodologies for assessing the extent of the studies needed to provide enough quality, safety and efficacy data for the use of tissues/cells and
- (iii) the follow up programs, according to the inputs of (i) and (ii), to ensure safety and support the evaluation of clinical efficacy.

The EURO GTP II project linked to topics that are also covered by other EU-funded initiatives (Joint Action VISTART and the new Joint Action GAPP) and are relevant for CA when authorising preparation processes.

A representative of EURO GTP II presented as outcomes the EuroGTP II guide, an interactive assessment tool created, a TC database and GTP management.

- The EuroGTP II guide focuses on Good Practices for evaluating quality, safety and efficacy of novel tissue and cellular therapies and projects was issued;
- The interactive assessment tool allows for a practical assessment to determine the extent of studies and follow-up programs needed to implement, evaluate and authorise a novel T&C product, process or therapy;
- The TC database collates references and evidence relating to safety and efficacy data; it allows stakeholders/CAs to accept the validity of data and promote collaboration amongst TEs;
- The GTP management tool allows to define technical requirements and to identify organisations with relevant knowledge and resources.

DG SANTE encouraged the CAs to disseminate the outputs, and to use them as input to help understand risks of novel TC therapies, a.o. through the GAPP joint action. The CA expressed an appreciation for the work done by EURO GTP II. The work of the project can be found at www.goodtissuepractices.eu.

5.4.2. Update on the work of GAPP WP 8 on assessing clinical data as part of a preparation process authorization (FIMEA)

This three-year EU funded Joint Action GAPP started in June 2018 and aims to support the development of a common and optimal approach to both assess and authorise preparation processes in blood, tissues and cells establishments. The Joint Action is led by Italy and the project consortium has 28 associated partners from 24 Member States and a large number of collaborating organisations.

FIMEA (FI) presented one of the work packages (WP8) which aims to introduce systematic methodologies for the evaluation of clinical data, as part of the CAs authorisation of processing activities. Together with WP9 leader Paul-Ehrlich-Institut (DE) it will build a data model that will bring together dependencies of preparation methods, preparation steps, test results and specifications of the final product, clinical outcome data demonstrating efficacy and safety of the product upon application to a patient. At the next CAs meeting a further update on the work carried out will be given, including first views on how and which clinical data can be utilized by authorities to assess and (pre-)authorize (novel) TC therapies.

5.4.3. Use of registries for clinical follow-up (ECCTR)

The three-year ECCTR project started in 2016. Within the project eye banks, universities and professional associations from Italy, United Kingdom, Sweden, Netherlands and Ireland collaborate.

The main objective was to build an EU web-based registry where ocular tissue transplant outcome data will be registered and shared. The objective was to assess and verify the safety, quality and efficacy of human tissue transplantations in ophthalmic surgery and to build a common outcome assessment methodology for corneal transplantation.

Significant milestones have been achieved: a European quality registry has been set-up for corneal transplant surgery. It incorporates one of the largest web-based databases in the field. ECCTR offers surgeons a tool for quality improvement by comparison and benchmarking with state-of-the-art epidemiological data and patient reported outcomes.

The online platform of the registry is now live and provides information on donor cornea origin, recipient and surgical procedure to allow for evidence-based decisions in the future. This registry is maintained by the European Society of Cataract and Refractive Surgeons (ESCRS).

The registry provides a unique opportunity to monitor and compare results and to promote quality improvement in cornea transplantation.

5.4.4. SoHO Registries meetings (SANTE)

DG SANTE debriefed others about the SoHO registries meetings. The objective was to raise awareness of SoHO registries and their possible future role in the work of the authorities.

Triggered by requests for advice regarding the implications of the General Data Protection

Regulation (GDPR) for SoHO Registries, the Commission had convened a meeting of registries to discuss data protection and other topics of shared interest in 2018-2019. The meetings were attended by representatives from different organisations that host and maintain registries in the fields of bone marrow transplantation, organ transplantation, IVF etc. The key topics addressed were compliance with the GDPR, ensuring quality of data in SoHO registries, registry governance, registry sustainability and funding and the potential for the secondary use of data from SoHO registries. A discussion that came up in the registry meetings was on whether the data should be collected by authorities or by professional societies, including the pros and cons of each approach. Participants did agree that data then needs to be shared and recycled to keep the collection workload as efficient as possible for the clinicians (collect once, use often). The participants had appreciated the opportunity to share experiences with each other and to discuss the GDPR with Commission experts working on that legislation. A GDPR specific Q&A was prepared for the registry meeting and shared amongst the NCA's.

6. THERAPY SPECIFIC TOPICS

Overviews on some therapy specific developments were presented, including skin cell suspensions, faecal microbiota transplants (FMT) and germline editing, covering science, preparation and (potential) use. The experts expressed some concerns about the regulation of these substances/products.

6.1. Epidermal cell suspensions (EATCB)

A representative from the European Association of Tissue and Cell Banks (EATCB) gave a presentation on epidermal cell suspensions.

In the context of the ongoing evaluation of the BTC legislation, (cf. agenda item 4), the representative expressed their concerns on the inter-MS differences in classification of some skin preparations (e.g. non-cultured autologous epidermal cell keratinocytes and melanocytes) and their regulation. These differences in national approaches in regulating the skin products have triggered the EATCB to present their position to the group of NCA's.

The results of the survey¹² (cf. ref. in point 4 of the summary above) confirm that these products (non-cultured keratinocytes and hepatocytes) are differently classified across the EU: in 9 Member States - Tissue and Cells safety and quality requirements apply, 7 Member states – Advanced Therapy Medicinal Products (ATMP), 5 Member States – other or no specific regulation.

The association described the processing and use of non-cultured epidermal cell suspensions in tissue establishments, explaining that they are recognised as the standard treatment for stable vitiligo and other forms of leukoderma. They consider that the cells, and their processing, meet the criteria for regulation under Directive 2004/23/EC and should be regulated in that way across the EU. They noted that there is extensive experience using the T&C legal framework with good (documented) safety and quality outcomes. They agreed to share a paper outlining their reasoning on this subject with the competent authorities and the Commission following the meeting. The representatives of the CA noted the variation among the MS on classification of such products and some emphasised the need to ensure a common approach across the EU.

¹² These survey results are updated and include receipt of further MS responses submitted after the CA meeting.

6.2. Faecal Microbiota Transplants (FMT)

DK gave a presentation on classification/regulation of FMT at the national level.

The results of the survey (cf. ref. in point 4 of the summary above) revealed that FMT fall under different regulatory frameworks in the Member States: in 2 MS Tissue and Cells safety and quality requirements apply, 4 Member states – Medicinal product requirements (non-ATMP), 13 – no regulation and in 2 Member States – other.

Although the Commission had previously advised the CAs that FMT does not meet the definitions of ‘tissues and cells’ in Directive 2004/23/EC, they are considered substances of human origin and, therefore, competence is granted in the Treaty to regulate at EU level. DK noted that MS are free to apply a regulatory framework at a national level with requirements based on the tissue and cell framework.

In DK, FMT are currently performed at several local hospitals in the framework of research projects. DK explained that in 2017, they received an application for authorizing a Tissue Establishment to provide FMT for treatment of recurrent *Clostridium difficile* (rCDI). DK CA recommended to the TE to follow the standards included in the EU tissue and cells regulatory framework and laid down in the Danish Tissue Act. Over 250 patients were treated and useful research findings were published. There have since been discussions on the classification and whether it should be a medicinal product. The current DK approach is that the tissue and cell framework is the appropriate one for hospitalized patients with rCDI treated with FMT, applied in cryobags or in capsules, and receiving a transplant from one donor.

Other CAs echoed that the classification of FMT is also a concern in their MS. Many CAs agreed that there is need for increased cooperation on classification and expressed the willingness to be more involved in interactions between different sectors.

University Hospital Ghent (BE)

A private expert from University Hospital in Ghent (BE) complemented the discussion on FMT regulation, by sharing technical insights on how FMT is organised from donor to recipient, what benefits and risks FMT might bring and what measures are considered appropriate to manage these risks (donor screening, testing, etc.). The expert explained the underlining processes of collecting and transplanting faecal microbiota. He noted good (documented) safety and quality outcomes.

Following the presentations, the participants concluded that in terms of regulatory oversight, MS classification varied from human tissue and cell regulation, medicinal product (non-ATMPs) regulation to no regulation. DG SANTE acknowledged the ongoing discussions concerning FMT. The concerns on divergent classifications will be taken into consideration in the BTC Evaluation report to be published by the Commission in 2019.

6.3. Germ line editing (ESHRE)

In the light of the high level of recent media attention given to germ line editing of embryos, a representative of the European Society for Human Reproduction and Embryology (ESHRE)¹³

¹³ ESHRE is a pan European/ OECD professional organisation of 6,000 members that are clinicians, embryologists, psychologists, nurses, midwives and lab technicians. It also supports a European Patients Association. Its aims are to promote interest in, and understanding of, reproductive science and medicine by teaching and training, development and maintenance of data registries and research and dissemination.

was invited to give a presentation on the subject.

The presentation informed the authorities what germline editing would entail in terms of techniques and processes, what risks this would bring to the field of SoHO and the type of measures that would be appropriate to manage these risks.

The presentation raised an issue on the legal perspective of such research. CA's from UK, Sweden and Belgium emphasized that in their Member States it is possible to use human embryos in this way for research purposes only.

Overall, the discussion on therapy specific products showed that there are efforts at the national level to increase understanding and management of risks inherent to new SoHO therapies. However, there was a consensus among the CAs arguing that there is a legal gap in the BTC legislation to be addressed by putting adequate regulatory provisions in place for SoHO that do not meet the current definitions of 'tissues' and 'cells'.

7. PRESENTATION OF ACTIONS UNDER THE PUBLIC HEALTH PROGRAMME

7.1. TRANSPOSE (TRANSfusion and transplantation: PrOtection and SElection of donors)

This project, TRANSfusion and transplantation: PrOtection and SElection of donors, is led by Sanquin in the Netherlands. The aim of the project is to build risk-based guidelines and a standard Donor History Questionnaire for the procedures followed for collection of substances of human origin, including blood, plasma, gametes, haematopoietic stem cells and replacement tissues. The objective of this action is:

- (i) to collect and compare EU and national donor selection and protection criteria;
- (ii) to identify the information needed from donors or their families to allow the application of appropriate donor deferral or exclusion criteria for the protection of recipients;
- (iii) to propose approaches to control and minimise these risks.

Few questionnaires were developed for Blood, Plasma, Tissues, ART, Stem cells and were shared with 130 experts in the various SoHO sub-sectors to collect feedback. Results were compiled in a database and were the topic of a focus group during a meeting in Copenhagen in September with WP5 and WP6 leaders. The results of these expert opinion reviews were being documented for submission to scientific journals. In parallel, risks were listed and categorized. These will be scored according to severity and level of evidence according to expert estimates and compared with actual reported adverse incidents.

The outcome of these activities formed the basis for the development of the common Donor Health Questionnaire (DHQ). The DHQ was reviewed during the TRANSPOSE April 2019 meeting in Amsterdam and steps are being taken to validate it. Currently, WP5 on Development of Donor Selection & Protection Guidelines is advancing. Next Transpose meeting will take place on 25 and 26 September in Amsterdam and will focus on DHQ and education and dissemination.

TRANSPOSE final results are due in February 2020. The CAs acknowledged the work undertaken within Transpose project and noted that donor selection criteria were established 18 years ago and is now outdated and evidence lacking.

7.2. WMDA - S(P)EAR (Serious (Product) Events and Adverse Reactions) for blood stem cell donation and transplantation registries

The World Marrow Donor Association (WMDA)¹⁴ representative gave a presentation on SPEAR in blood stem cell donation and transplantation registries.

This WMDA vigilance work is supported by the HP operational grant. WMDA is supported by the EU Health Program to prepare a necessary digital update of the registry of bone marrow donor registries and also launch a HSC donor SAR system.

The representative noted that WMDA strives for collaboration with Competent Authorities. The aim is to reduce administrative burden for reporters and to work towards one time reporting for adverse events occurring in the hematopoietic stem cell transplantation chain.

The participants agreed that the experiences in vigilance should be exchanged between the Commission and WMDA in the future.

8. INTERNATIONAL DEVELOPMENTS

8.1. Council of Europe (EDQM) update

EDQM presented their work on contributing to ensuring a high level of quality and safety standards in tissues and cells field and harmonising the activities among European countries, facilitating uniform standards and practices.

In the context of the ongoing BTC Evaluation, EDQM noted that the EU tissues and cells directives have some limitations because technical standards as set out in the Directives cannot keep pace with ongoing scientific and medical advances. They cannot provide the level of details required by TE or CA to respectively deliver safe and effective products or to underpin an effective inspection process.

The CA were reminded about the latest edition of the Tissues and Cells Guide published in July 2017. The guide is available at the EDQM website¹⁵ where it can be downloaded free of charge.

The work on the 4th edition of the Guide on TC was presented. A number of important updates were implemented in particular, the elaboration of Good Practice Guidelines for TE to support inspections, and TC monographs to facilitate mutual recognition.

EDQM then summarised other activities of relevance to this meeting, including the Newsletter Transplant, the ongoing projects in the field of TC such as Women's Guide To Informed Choices Regarding Oocyte Preservation, Donation And Treatment; Impact On Patient Access To Therapy In Different Member States Of Ambiguous/Differing Regulatory Status Of Certain Substances Of Human Origin and Donor Protection in HPC.

EDQM also gave details about the EU grant agreement with EDQM which includes projects on Serious Adverse Reactions Events (SARE) TC and Blood; Trainings on reporting SARE in the field of Tissues and Cells and Blood; Harmonisation of activity data collection exercises

¹⁴ WMDA provides access to the global database to search for potentially matched bone marrow or peripheral blood haematopoietic stem cell donors or cord blood products. Their focus is on unrelated volunteer donors and they maintain standards, run accreditation, and training programmes. The Bone Marrow Donors Worldwide registry included 94 organisations listing 30,168,410 donors and cord blood products for international search on February 17th, 2016 www.bmdw.org

¹⁵ <https://register.edqm.eu/freepub>

in the field of Tissues and Cells in Europe; Understanding post-mortem blood testing practices for tissue donation; Quality Management systems for Tissue Establishments and Country assessments in Blood & TC sectors.

The Commission and the representatives acknowledged EDQM work in the field.

8.2. World Health Organisation

The WHO representative could not attend the meeting on this occasion.

9. ANY OTHER BUSINESS

DG SANTE gave presentation on media related issues in the field of tissues and cells, i.e. the recent cases found in public domain.

CHAFEA representative provided information on their relevant activities in the field.

DG RTD (Research and Development) presented Horizon Europe and the possibilities for funding research in the area of SoHO. The representative asked the authorities to participate in deciding what research topics they would suggest for the future to move the T&C field forward in a survey that will be disseminated.

IT suggested the need to explore the possibility for a common exchange platform for surplus tissues and cells. In particular, IT suggested setting up a working group to investigate if there is an interest for sharing programme of surplus TC. This suggestion was positively received and might be further elaborated in future.

10. CONCLUSIONS OF THE MEETING

The Chair thanked the group for their active participation in the meeting.

All participants were thanked for their active and constructive interventions during the meeting and were reminded that all presentations and associated documents would remain accessible in the CIRCABC platform.

The next Tissues and Cells Competent Authorities meeting is planned for 22-23 October 2019 (tbc).