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## Meeting of the Competent Authorities for Tissues and Cells

2 - 3 June 2014

### Summary Report

The meeting of the Competent Authorities on Tissues and Cells was convened on 2 and 3 June 2014. The previous meeting of National Competent Authorities (CAs) took place on 2 and 3 December 2013.

#### PARTICIPATION:

All Member States (MS) except Greece and Romania were present at the meeting. In addition, Liechtenstein, Norway, the Former Yugoslav Republic of Macedonia and Turkey, as well as the European Directorate for the Quality of Medicines and Health Care (EDQM) of the Council of Europe (CoE) and the European Centre for Disease Prevention and Control (ECDC) attended the meeting.

European Commission (DG SANCO):

Chairs: Mr D. SCHNICHELS, Mr S. VAN DER SPIEGEL

Commission Representatives: Ms I. SISKI, Mr R. Mc GEEHAN, Mr P. CATALANI

Administrative Assistants: Ms G. CSOKA, Ms A. CORNEA

#### **1. ADOPTION OF THE AGENDA**

One new agenda point on the organisation of a training course for inspectors of Member States' Tissues and Cells CAs was proposed by PT and it was agreed to add this point to the agenda in the AOB section.

#### **2. RULES OF PROCEDURE FOR THE MEETINGS OF THE TISSUES AND CELLS COMPETENT AUTHORITIES**

No further comments were provided on the rules of procedure, which were in the meantime also presented to the national competent authorities for blood and for organs respectively. The rules are therefore considered adopted and will be uploaded on CIRCABC.

#### **3. LEGAL MATTERS**

##### **3.1. Update on the transposition of the Tissues and Cells Directives**

The Commission presented an overview on the current status of the transposition of the Tissues and Cells Directives. In December 2013 the Commission reported that 6 MS have sufficiently transposed all Directives, 15 MS have been recommended for follow-up in

the EU Pilot system, 6 MS responses were under final analysis, whereas 1 MS is the subject of infringement proceedings and have been referred to the Court for failure to fulfil its obligation to transpose the EU legislation in relation to certain reproductive cells. Of the 15 recommendations for follow-up in the EU Pilot system, 13 procedures have been launched. Concerning the latter, by June 2014 only 4 answers were received. After evaluation of replies, 1 pilot is now subject of infringement proceedings, whereas the other 3 are still under analysis. For 9 MS the replies are still pending.

The main issues to be clarified during the pilot procedures refer to the transposition of requirements related to the scope of the Directive, some definitions, supervision of human tissue and cell procurement, third party agreements, inspections and control measures, and publicly accessible report/register in the Directive 2004/23/EC.

It was also underlined that MS that provided information on their plans to amend national legislation in line with shortcomings raised in the transposition check, need also to inform the Commission once the amendments are officially adopted to bring to an end the transposition check.

### **3.2. Update on the implementation of the Tissues and Cells Directives – 2013 Survey**

Following a presentation in December 2013 which included a preliminary analysis of the first four sections of the 2013 survey on the implementation of the Tissues and Cells Directives, the Commission showed the results of the evaluation of the next sections of the survey (inspections, distribution, import-export, traceability, reporting, notification of SARE, consent and data protection). It was mentioned that the reply from one MS is still pending.

An overview of the replies concerning the last sections (quality management, responsible person and personnel; tissue and cell reception, processing, storage, labelling and packaging; relations between tissue establishments and third parties), together with the draft report on the implementation of the Tissues and Cells Directives should be presented by the Commission during the next meeting in December 2014. The draft shall be circulated by the Commission before the meeting allowing MS to both verify their replies and provide feedback regarding its conclusions.

### **3.3. Update on the third survey on the implementation of the principle of voluntary and unpaid donation (VUD) for tissues and cells**

The Commission gave a first presentation on the outcome of the survey regarding the implementation of the principle of VUD, which was launched in January 2014. The initial deadline was set for 18 March, but due to technical difficulties and requests from several MS was extended until 28 March. Twenty seven MS, as well as LI and NO submitted their replies. The Commission presented an overview of the provisional findings of the sections that have been examined so far (legislative provisions and guidelines, tissue and cell donation and anonymity, promotion and advertising and donation-related practices in the healthcare system.

The preliminary analysis showed that 28 of the 29 reporting countries reported that VUD is mandatory in their countries, with one MS allowing payment for the donation of reproductive cells. The legislative provisions for the voluntary and unpaid donation of tissues and cells have been subject to changes in a number of countries, with 5 MS reporting changes in their national legislation and 6 MS declaring that updates or changes in their legislative provisions, guidelines or administrative practices are envisaged. Moreover, 14 MS ensure the voluntary and unpaid character of tissues and cells donation by taking additional measures such as training of professionals to spot illegal and

fraudulent activities, inspection of the consent documentation for imported tissues or examination/inspection of advertising materials provided by tissue establishments.

Most of the reporting countries (27) have legislative provisions for tissues and cells regarding donor anonymity or non-anonymity. For non-reproductive tissues and cells the donation is predominantly anonymous (24 of 27 reporting countries), whereas for reproductive tissues 13 MS declared that anonymous donation is mandatory, 8 require non-anonymous donation, and 2 allow both anonymous and non-anonymous donations.

Twenty countries confirmed having taken measures to promote voluntary and unpaid donation of tissues and cells, such as awareness campaigns, events focusing on donation (e.g. donor days) and patient-specific donor drives. In terms of provisions providing restrictions or prohibitions on advertising the need for, or availability of particular tissue and cells with a view to offering or seeking financial gain or comparable advantages, 13 countries stated having such restrictions for human haematopoietic stem cells and 15 countries have relevant provisions for gametes and embryos.

In relation to supply, several countries reported that they experience regular shortages of tissues and cells at national level, mostly for corneas (10 MS), bone marrow and peripheral haematopoietic stem cells (10 MS), but also for other tissues and cells like skin and heart valves. Regarding improvement measures, 10 countries have policies in place to endeavour to promote self-sufficiency of tissues and cells and 25 countries reported having bilateral agreements or other forms of collaboration structures to ensure an appropriate national supply.

The analysis of the answers provided to section 3 of the questionnaire concerning practices vis-à-vis donors (e.g. compensation, incentive) shall be given in December 2014. The final report to be sent to the European Parliament and the Council should be available in the first half of 2015. Like the previous ones<sup>1</sup>, this third report shall be also published on the Europa website, together with the individual Member States' replies.

### **3.4. Debrief from the Import Working Group**

The Commission gave the group an update of progress in the Import Working Group and in particular the discussions which took place during the last 3 meetings of this working group subsequent to the December 2013 CA meeting. These meetings were held in December 2013, February 2014, and March 2014. The group currently includes 13 MS (AT, BE, DE, DK, ES, FR, HR, IE, IT, NL, PL, PT, UK) who have regularly attended the working group meetings. The Commission presented an overview of the contents of the draft measure and provided clarifications on a number of points following questions raised during the discussion which followed the presentation.

The Commission explained that considerable progress had been made since the previous CA meeting and during the course of the subsequent Working Group meetings towards finalising the draft text. The March meeting of the Working Group was thus considered to be the sixth and final meeting of the group and since this meeting. It was mentioned that between April and May 2014 bilateral consultations with the main professional associations were organised (EATB, EEBA, ESHRE, EBMT/JACIE and WMDA) and their input was also taken into consideration and included in the draft text discussed with the WG. The Commission had also undertaken an internal consultation process which was ongoing at the time of the June CA meeting. While the Commission expected further minor changes to the text following the conclusion of its internal consultations, it informed the group that it felt the draft text was sufficiently mature to take it forward for

<sup>1</sup> [http://ec.europa.eu/health/blood\\_tissues\\_organ/key\\_documents/index\\_en.htm#anchor7\\_more](http://ec.europa.eu/health/blood_tissues_organ/key_documents/index_en.htm#anchor7_more)

discussion in the Tissues and Cells Committee with a view to seeking an opinion on the draft text from the Committee.

The Commission informed the group that an overall consensus had been reached within the Working Group on the framework of the draft measure with authorisation and inspection requirements mirroring the approach to tissues and cells regulation within the EU. A second major requirement on importing tissue establishments is to have written agreements in place with their third country suppliers ensuring the availability of sufficient documentation allowing them to verify the equivalency of the quality and safety of imported tissues and cells. This approach was not questioned by the CA group and instead the discussion there focused on a number of issues relating mainly to clarifications concerning the scope of the draft measure and its definitions.

A question was raised as to how the draft measure would relate to any future import of 'starting materials' to be used in the manufacture of advanced therapy medicinal products (ATMPs). The Commission explained that substances considered as tissues and cells at the point of import would fall within the scope of the draft measure (unless considered to fall within the scope of any exclusions). Thus, as outlined in Directive 2004/23/EC such tissues and cells would need to be imported via an authorised importing tissue establishment although the verification of the equivalency of their quality and safety would be limited to the donation, procurement and testing of such tissues and cells which took place outside of the Union. Clarifications were also made concerning the types of tissues and cells covered by the definition of one-off imports and that where centres of application were importing tissues and cells themselves they would be considered to be an importing tissue establishment.

#### *3.4.1. Update of the Operational Manual for CAs on Inspections*

During the work of the Import Working Group it had originally been foreseen to create guidelines on the inspection of importing tissue establishments and third country suppliers which would accompany the Commission Directive on import verification procedures. FR, who was leading this work, had subsequently proposed that a better approach would be to update the Operational Manual on Inspections rather than have two separate sets of guidelines.

As the Import Working Group does not have a mandate to update the Operational Manual, a proposal was made to the CA group to form a specific sub-group to carry out this work. In effect FR, with support from other members of the Import WG will make a first proposal for this update over the summer months and the new Working Group would then meet to formalise this work in the autumn before presenting it to the competent authorities group in its December 2014 meeting. The CA group approved this approach and any member wishing to take part in this new Working Group is invited to inform the Commission of its desire to participate in writing.

### **3.5. Debrief from the Working Group for the implementation of the Single European Code for tissues and cells**

The Commission gave an update on the discussions in Working Group for the implementation of the Single European Code for tissues and cells, in particular on the outcome of the two last meetings which took place during in February and May 2014. It was mentioned that between April and May 2014 bilateral consultations with the main professional associations were organised (EATB, EEBA, ESHRE, EBMT/JACIE and WMDA) and their input was also taken into consideration and included in the draft text discussed with the WG.

The overview of the draft legal requirements given by the Commission included a clarification of several definitions (e.g. “EUTC” which replaces “EU Generic” code, “within the same centre”, “released for circulation”), explanations on the application and format of the SEC, as well as of the obligations of the tissue establishments, competent authorities and Commission regarding the application of the SEC and the hosting and maintenance of the tools for the implementation of the SEC (the EU TE Compendium, the EU tissues and cell product Compendium, and the code translator application as developed by the EURO CET128 contract). It was explained that particular situations are either excluded or may be exempted from the application of the SEC. For example, partner donation of reproductive cells, when such cells remain within the same centre from procurement to application, as well as direct distribution for immediate transplantation to the recipient (e.g. haematopoietic stem cells) are foreseen to be excluded from the application of the SEC. Additionally, exemptions from the requirement to apply a SEC were also foreseen (e.g. where tissues and cells remain within the same centre from procurement to application and/or for tissues and cells that are imported into the Union and applied within the centre an authorised importing tissue establishment).

The envisaged transposition (12-18 months) and transitional periods (tissues/cells in storage on the day when transposition deadline expires should be exempted from the application of the SEC provided they are released for circulation within 5 years following that date) were also presented.

During the subsequent discussions, the Commission clarified the queries of several MS on particular situations (e.g. new products developed at national level for which only temporary ISBT128 codes were allocated, but these are not globally recognised – the corresponding EUTC codes may be used; the code of the tissue establishment on the label of cord blood units collected by a procurement organisation in one MS, but stored in a tissue establishment in another MS – the TE code of the code receiving the cord blood unit for storage (i.e., the first TE in the chain) should be used when distributing the unit for human application; application of the full SEC versus the use of the donation identification sequence at least in the accompanying documentation). One Member State objected to limiting the exclusion from the application of the SEC to partner-donation of reproductive cells only remaining within the same centre from procurement to application. It was explained that this risk-based approach was introduced following a consultation with the relevant professional association.

The Commission confirmed that a 2014 adoption would require laying down a final text to the Parliament in July. The text was still undergoing internal consultations within the Commission with a view to holding a Regulatory Committee meeting in early July.

### **3.6. Interpretation questions**

#### *3.6.1. Breast Milk Banking*

The question of how to regulate the allogeneic 'application' of breast milk has been discussed during the meeting in December 2013 when it was agreed that the outcome of the Council of Europe work on this topic should be presented to the group in June 2014 and the Commission should verify the information regarding human breast milk banks and their regulatory framework with the European Food Safety Authority (EFSA).

The representative from the DE (PEI) gave an overview of the answers submitted by the 27 countries (mostly EU MS) who replied to the Council of Europe questionnaire distributed through the members of the CD-P-TO. Only one third of the countries declared having legislation that would cover the use of human breast milk for allogeneic use and in only 7 countries the Ministry of Health was responsible for these legal

requirements. Furthermore, 7 countries indicated that the use of allogeneic human milk is regulated as "other food" (although the concept of "other food" was not clearly defined) and 9 regulate the use of allogeneic breast milk as food. The survey also showed that in half of the reporting countries breast milk banks and procurement centres have been established and in these countries, standard operating procedures for the collection, processing, storage and use of breast milk have been put in place. Additionally, in one-third of the countries women are allowed to receive financial compensation for donating breast milk, and breast milk banks receive financial compensation for distribution of processed and stored breast milk.

In addition, the Commission provided data published by the European Milk Banks Association (EMBA) on their website and details on the regulatory framework in Canada and USA.

Representatives of the Directorate E in DG SANCO (Safety of the food chain) stated that based on the definition of food as provided in the Regulation 178/2002 banked human breast milk could in principle be covered by the EU food legislation. However it was mentioned that this issue was never brought to their attention or discussed during their regular meetings with the MS competent authorities. They expressed their interest to be informed about which EU MS currently regulate banked human breast milk under the food legislation and how (e.g. food or other foods). They also underlined that some aspects related to the selection, evaluation and testing of donors seem to be more appropriated to be covered by requirements similar to those laid down in the Tissues and Cells Directives.

Several MS representatives (DE, LU, NL, SK) questioned the nature and use of human breast milk (e.g. food vs. "tissue" containing stem cells with potential human application) and argued that it should be considered as food. The CoE/EDQM representatives stated that CD-P-TO considers that human breast milk should not be covered exclusively by the food legislation due to the donor-related safety issues and that banked human breast milk will be also included in the second edition of the CoE Guide for safety and quality of human tissues and cells. Additionally, FR representative informed that banked human breast milk is covered by a specific national legislation and offered to make this information available to the WG.

*Following discussions the group requested DG SANCO to consult the Commission Legal Service and ask for their views on the legal status of banked human milk. The group request DG SANCO to report back during the next meeting of the competent authorities in December 2014.*

### 3.6.2. Regulation of faecal microbiota transplants (FMT)

The issue of transplantation of faeces donated by partner/close relative as treatment for *Clostridium difficile* infections was already discussed by the group of tissues and cells CAs in June 2012 when the group concluded that bacterial flora does not fall under the provisions of the Directive 2004 /23/EC.

The topic was re-introduced by the UK CA (HTA) who referred to the UK's National Institute for Health and Care Excellence (NICE) assessment which states there is enough scientific evidence on the efficacy and safety of faecal microbiota transplant for recurrent *Clostridium difficile* infection and this procedure was supported by NICE, provided that normal arrangements are in place for clinical governance, consent and audit. Clinicians were recommended to ensure that a confidential record is kept of the donor and recipient of each FMT. It was underlined that in the FMT the active agent is the gut flora and not the human cells, but the latter are present in the donor sample and therefore potentially

delivered to recipient. HTA advised centres that have enquired about licensing and FMT to follow the requirements of the EU Tissues and Cells Directives, but respecting these requirements is voluntary and no license was granted until now. Therefore, taking into account the increased number of such procedures, the potential risk of disease transmission between donor and recipient, as well as lack of traceability and monitoring of SARE, HTA reiterated the question of the appropriate legal framework for faecal transplants.

Other MS representatives (DK, LU) agreed that a legal clarification is needed. The IT representative informed the group that this issue was already raised at national level and suggested drafting a position paper and/or guidelines including quality and safety principles for areas having similar concerns to those in the SoHO field (e.g. human breast milk banking, FMT); this suggestion was approved by the group and several MS representatives expressed interest in participating to a drafting WG (DK, IT, SK) as well as ECDC.

*The Commission agreed to consult the Legal Service and report back during the next meeting of the competent authorities in December 2014.*

*It was agreed to re-discuss both topics (e.g. human breast milk banking and FMT) in December 2014, when the Commission will present the conclusions of the consultation with the Legal Service.*

#### **4. SURVEILLANCE AND VIGILANCE**

##### **4.1. Update on infectious disease risks**

###### *4.1.1. Epidemiological update – ECDC*

ECDC presented an epidemiological update focused on MERS-CoV and Schistosomiasis and their current future activities relevant for the SoHO sector.

Concerning MERS coronavirus it was concluded that safety criteria for prospective donors presenting acute respiratory symptoms are sufficient to exclude from donation of blood, cells and tissues symptomatic MERS cases residing in or returning from affected countries. Organ donors should be assessed individually in combination with recipient taking into account current epidemiological situation. However, given that infection includes a viraemic phase, the possibility of asymptomatic viraemia and potential transmission through transfusion and transplantation cannot be excluded. The absence of reported transmission through blood transfusion or transplantation and the experiences with related SARS coronavirus viraemia, which seemed largely confined to the symptomatic patient, suggest that the current risk of donor derived MERS coronavirus transmission appears to be very low. Thus specific deferrals of donors returning from affected countries are not considered necessary at this stage of outbreak. However, the deferral of prospective blood, tissues and cells donors returning from affected countries including questions about close contacts with primary cases may become necessary upon an evidence of asymptomatic viraemia and continuous increase in the number of travel related cases.

Regarding the recent cases of schistosomiasis with origin in Corsica (France) and reported by 2 MS (FR – 6 cases and DE – 5 cases of uro-genital schistosomiasis) it was clarified that until now there are no reports of transmission through blood and cells.

ECDC representative informed the group that the risk assessments concerning the transmission of WNV, malaria and dengue through SoHO are expected to be delivered by the contractor in July 2014 and MS competent authorities shall be informed when these documents will be publicly available. It was also stated that the HTLV-I high prevalence

areas map required for the implementation of the Directive 2012/39/EU (deadline for transposition 17 June 2014) is expected only in September 2014 and the delay is due to technical/procedural issues on ECDC side.

The call for tender procedure for developing risk assessments on the transmission of *Trypanosoma cruzi*, Chikungunya and *Leishmania* through SoHO are in preparation and should be launched by the end of this year. Prioritisation of bacterial disease transmission through SoHO is foreseen for the beginning of 2015.

After a question from FR, it was clarified that no cases of Chikungunya transmission through blood or tissues and cells have been confirmed. Following queries from the MS, it was explained that ECDC shall inform the Commission about the onset of the 2014 transmission season of West Nile fever and this information shall be circulated to the SoHO Competent Authorities. *Additionally recent risk assessments will be made available by ECDC shall be also uploaded in CIRCABC SoHO Library.*

*4.1.2. Other – Member States will be asked whether they have additional information or updates to report*

Member States did not report any additional information on infectious diseases.

#### **4.2. Update on the development of the new European code for tissues and cells – EURO CET128 contract**

The coordinator of Eurocet128 (IT/CNT) gave an update on the good progress made since the last reporting in December 2013. The group was informed that a final complete check of the whole EU Tissue Establishment Compendium has been performed, and final EU TE codes have been assigned to all the TEs. Additionally, the data provided by DE were revised and manually uploaded due to differences in the data format provided. The group was reminded that seven MS requested to use their national TE number appropriately adjusted to fit the requirements of the SEC. It was also mentioned that the EU Tissue Establishment Compendium does not include all authorised TEs due to several objective reasons (e.g. no reply from one MS, inappropriate transposition/implementation of the EU legislation in the ART field in 3 MS). Regarding the EU Tissue and Cell Product Compendium it was reported that the mapping of the 3 coding systems EUTC, ISBT128 and Eurocode has been finalised. In addition the guidelines for competent authorities and tissues establishments were being updated taking into account the last developments in the draft coding requirements.

The results of the two pilot tests organised in February-March and April 2014 were also presented together with the feedback provided by both competent authorities and tissue establishments. It was clarified that the Compendia together with the guidelines and user manuals will be transferred to the European Commission at the end of the contract (August 2014).

Regarding the dissemination activities, updated materials were distributed at the 26th EEBA Annual Meeting (24-25 January 2014) and during the 2014 EBMT Annual meeting, where a presentation was also delivered by DG SANCO (JACIE session). The organisation of an e-learning course for all the MS Competent Authorities in June 2014 was also announced; this two weeks course would allow Competent Authorities to get familiar with the SEC (week 1) and provide a hands-on training on using and updating the Compendia (week 2). All Competent Authorities were asked to complete registration before the beginning of the course which was scheduled for 9 June. It was clarified that the learning sessions will be moderated only in June, whereas the materials will remain available for consultation until September 2014.



Both the Commission and the Tissues and Cells Competent Authorities congratulated the consortium for the excellent work.

In addition to the presentation of the Eurocet128 coordinator, the Commission explained its role and the support provided during the two pilot phases organised by the consortium. It was underlined that after the transfer of the Compendia and the code-translator application, the Commission shall be responsible for making the tools accessible to the public and ensuring their maintenance. Concerning updates the Commission shall be in charge of the EU Tissues and Cell Product Compendium updates, together with a group of experts, in particular experts nominated by the Member States Competent Authorities. It was also clarified that a link with RATC will be put in place (e.g. the EU Tissues and Cell Product codes shall be made available when encoding alerts), but this link shall be made available only to the members of the RATC platform. Member States will be responsible to update the list and status of their tissue establishments in the TE compendium. National Authorities in each Member State will therefore receive a login and password into the IT system.

#### *4.2.1. RATC Annual report – 02/2013-02/2014*

The Commission presented the report of the first year following the launch of the new RATC platform in February 2013. The group was informed that the platform includes users of 53 Competent Authorities with an average of two users per country. In addition to the training course provided by the Commission in 2013, in 4 MS Competent Authorities who attended these courses have given demonstrations and training courses to colleagues in their respective institutions. Regarding the number of alerts in 2013 it was emphasised that of the 13 alerts launched, 12 were quality and safety defects, and one was an information notice regarding a tissue establishment located in another Member State; additionally two bilateral inquiries concerning the authorization status of a tissue establishment in another Member State were recorded. The Commission informed the group that the RATC 2013 annual activity report will be soon ready for circulation in view of publication on the Commission website.

#### *4.2.2. Revised RATC SOP*

The Commission thanked the Competent Authorities who provided comments and suggestions to the first version of the RATC SOP, particularly to DK and IT representatives and informed the group that the revised SOP (version 1.1) was made available in CIRCABC. Additional input may be sent to the Commission by end of August 2014, when this version shall be uploaded in the RATC platform. After this date, all additional comments and suggestions will be discussed with the RATC WG and incorporated in the next version due for 2015.

It was also mentioned that comments/ideas have been collected from the users and a RATC WG meeting may be convened in 2015 to further discuss the improvement of the platform. This suggestion was appreciated by several MS who confirmed their interest to attend the RATC WG meetings (DE, DK, ES, IT).

#### *4.2.3. Follow-up of alerts launched in 2013 (FR alert launched in December 2013)*

DE authorities provided a state of play on the follow-up of the FR alert on Tutogen from December 2013 and on previous alerts regarding the same company.

PEI, the local authorities of Ober Franken (ROF), joined by an observer from IT, have re-inspected the concerned facility in December and uploaded their findings on RATC on 2/4/2014. The observations in the original alert were confirmed, however many were already addressed by the company. Three major deficiencies were still reported. The main deficiency, the absence of a class D environment for the pre-processing, was

temporarily addressed since 23 January 2014 by transferring pre-processing activities to another building. The definitive solution will however require construction works.

ROB has re-visited the site and confirms that substances leaving the facility since January 2014 can be considered of good quality and safety. ROB expects the construction works to be completed in July and will report back to the group through RATC. At that moment all corrective actions agreed will be in place and a final report can be uploaded in the rapid alert in order to close the alert. It was agreed that PEI would be assigned as rapporteur to upload this final report.

Overall the group expressed its satisfaction with the initial observations leading to the alert, and with the consequent follow-up by the company and local authorities which will lead to strengthened safety and quality of the substances processed in this facility.

Concerns were expressed regarding the safety and quality of substances manufactured and distributed prior to the corrective actions implemented in January 2014. ROB gave a summary of the risk assessment process undertaken by Tutogen and verified by PEI and ROB.

Participating National Competent Authorities overall agree that assessments by colleagues in other Member States can be relied upon. Due to the complex nature of this alert, several major affected Member States requested additional reassurances. These concerns were in particular driven by the high dependence on the final inactivation step in the processing of the tissues. There is a common understanding that inactivation steps cannot be considered as sufficient to compensate for deficiencies in the prior donation and processing steps. A correct implementation of all safety and quality measures, at least as laid down in Directive 2004/23, is therefore expected of all tissue establishments supplying tissues to the EU.

It was suggested to share the original Tutogen risk assessment. DE authorities will verify this possibility, and COMM could organise for a translation into English. It was also suggested to organise a broader sampling of batches by an independent laboratory, under oversight of DE authorities. DE authorities will discuss this possibility with the company and report back to the group.

The chair thanked the participants for the constructive exchange of views, and reiterated the need for a speedy follow-up and close collaboration between the affected NCAs.

### **4.3. Serious adverse reactions and events (SARE)**

#### *4.3.1. 2013 SARE Final Annual report (2012 data)*

The Commission presented the final report of the 2013 SARE reporting exercise (data recorded from 01/01/2012 to 31/12/2012). The data analysis showed that MS reported lower numbers for the SAR denominators (tissues and cell distributed and the number of recipients) compared to the previous two years when a similar reporting template was used. As in the previous two years, many Member States acknowledged that accurate data for certain types of tissues/cells were difficult to collect and chose to report not available data instead of incomplete/ imprecise numbers. On the other hand, the total number of tissues and cells processed, used as denominator for SAE evaluation, gradually improved reaching its highest value in 2013. While the SAR number is lower than the one reported in the previous two years, the number of SAEs reported in 2012 is higher than in the previous two years. Eleven countries reported that in 2012 there were no occurrences of SAR and SAE were reported only by 17 MS. The Commission encouraged MS to report also partial data and if needed to provide updates at a later stage. Regarding the voluntary reporting of SAR in donors, 10 MS provided data, with a large majority being recorded in

in oocyte donors (e.g. severe OHSS cases, other surgical complications). Even though the quality and data collection is improving, both the Commission and CAs acknowledged that there is still a high degree of under-reporting, which needs to be taken into account for the data interpretation.

Member States acknowledged the Commission's work and the good progress made.

#### 4.3.2. *Launch of the 2014 SARE Annual reporting exercise (2013 data)*

The Commission informed that the 2014 SARE reporting exercise should be launched by mid-June and the deadline envisaged is 31 July 2014. The groups were informed that the reporting template is identical with the one used in 2013 and consulted the group on a change in the Common Approach document regarding the reporting of OHSS cases under the category "SAR in donors". The group agreed with following the reporting guidelines proposed by the SoHO V&S project in the deliverable 8 "Communication and Investigation of Serious Adverse Events and Reactions associated with Human Tissues and Cells". It was also agreed that hospitalisation for more than 24 hours can be considered a criterion for establishing the severity of OHSS cases.

## 5. PROJECT PRESENTATIONS – HEALTH PROGRAMME

### 5.1. **2013 Joint Action on good practices on donation, collection, testing, processing, storage and distribution of gametes for assisted reproductive technologies (ART) and of haematopoietic stem cells for transplantation (HSCT)**

The new Joint action ARTHIQS (Assisted Reproductive Technologies and Haematopoietic stem cells Improvements for Quality and Safety throughout Europe) was introduced by a representative of the coordinator, the Biomedicine Agency (ABM) in Paris. ARTHIQS, which includes 17 partners and 9 collaborators from 18 different Member States, kicked-off in May 2014 and will last 3 years. The main objectives are to develop guidelines for key aspects of service provision and regulation in ART and HSCT sectors, notably by increasing donor and recipient / beneficiary safety, also tackling inspection of ART centres and cord blood banks. The role and tasks of the coordinator, as well as the WP leaders (WP2 Dissemination – SUKL/CZ; WP3 Evaluation – Health and Social Care Inspectorate/SE), WP3 ART – ABM/FR, WP4 HSCT – Ministry of Health/HR and CNT/IT) were introduced. Updates on ARTHIQS progress shall be reported during the next Competent Authorities meetings.

### 5.2. **Introduction of the study on the economic landscape of the tissues and cells sector (Rathenau Institute)**

A representative of the Rathenau Institute representing the consortium who was awarded the contract for the call for tender EAHC/2012/Health/19<sup>2</sup> introduced the members of the consortium, together with the objectives of the study and the activities foreseen to achieve them. It was clarified that the study should identify the characteristics of the EU tissue and cell markets and key players for broader understanding of economic dynamics of these markets, their regulatory and reimbursement context, ethical and socio-legal issues involved, and forecast of trends in future markets for tissues and cells and should provide information and identify the gaps and opportunities for regulatory decision making and policy development. It was emphasised that for some of the tasks the contribution of the MS Competent Authorities is essential, therefore a questionnaire will be sent in the coming weeks. The survey will be submitted to an NCA for testing first.

<sup>2</sup> [http://ec.europa.eu/eahc/documents/health/tenders/2012/EN/EAHC\\_2012\\_19\\_contract\\_notice.pdf](http://ec.europa.eu/eahc/documents/health/tenders/2012/EN/EAHC_2012_19_contract_notice.pdf)

The Commission reiterated the importance of the study for the decision making process and encouraged the Competent Authorities to collaborate with the contractor. In reply to some data provided to the contractor by tissue establishments in different MS, one CA requested more details. It was therefore overall considered important to continue data collection as good as possible, following which CA's can address specific questions. The terms of reference of the study will be uploaded on CIRCABC.

### **5.3. The 2014 call of the Third Health Programme 2014-2020 - Updates on procedures (Chafea)**

The representative of Chafea gave a presentation focused on the Joint Actions included in the 2014 Annual work plan for which 18.6 million € were allocated. It was emphasized that a Joint Action aiming strengthening the MS capacity of monitoring and control in the field of blood transfusion and tissue and cell transplantation is planned. The novelties regarding the procedure which requires nomination of participants by the relevant Competent Authorities as well as details regarding the electronic submission of the proposals were also presented.

The Commission clarified that training of inspectors and vigilance measures should be addressed for both blood and tissues and cells sectors, whereas coding (e.g. the implementation of the upcoming requirements for the implementation of the SEC) refers only to the tissues and cells sector.

The IT representative stated that a discussion is expected at national level with colleagues from the Blood CA which are part of the same institution (Superior Health Institute) and expressed interest in coordinating the Joint Action.

## **6. UPDATE FROM COUNCIL OF EUROPE – OVERVIEW OF ACTIVITIES**

The Council of Europe representative provided an update on the tissues and cells activities at the EDQM. The current activities of the European Committee on Organ Transplantation (CD-P-TO) were presented.

A survey to address compliance with Recommendation (2004)<sup>8</sup> on autologous cord blood banks was performed and an information booklet for parents on cord blood donation and transplantation (indications, options, state of the art, etc.) should be made available by the end of 2014. This brochure is developed based on the most recent and reliable scientific and medical data on cord blood donation and transplantation and could be used at national level by Health Authorities in the Council of Europe Member States. Additionally, a new project proposal to clarify the role, competencies and limits of health authorities in preventing commercial advertising of for profit cord blood banks has been submitted to the CD-P-TO.

A survey to address status of human breast milk banks across member states has been finalised and due to the safety and quality issues associated with the use of this SOHO (risk of infections, traceability issues, reporting of SARE, substances that can be unwittingly passed to the infant such as alcohol and medications, etc.) CD-P-TO representatives decided including human breast milk in the 2nd edition of the Guide for the Quality and Safety of Tissues and Cells for Human Application.

It was underlined that the Council of Europe Committee on Bioethics (DH-BIO) was re-examining the Recommendation (2006)<sup>4</sup> on research on biological materials of human origin by DH-BIO and Competent Authorities were encouraged to respond to the public consultation<sup>3</sup> until 15 August 2014.

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<sup>3</sup> <http://bit.ly/1nIZO6W>

An update on the use of the first edition of the Guide for the Quality and Safety of Tissues and Cells for Human Application was given together with a brief report on the on-going work of the drafting group working on the second edition of the Guide. The EU-funding, the contribution of the EU-funded projects, as well as the alignment of the Guide to the EU Tissue and Cells Directives were highlighted. The second edition of the Guide should be published by mid- 2015 and should be updated every 2 years thereafter.

## **7. RESULTS OF THE PUBLIC CONSULTATION ON THE ATMP REGULATION**

The Commission presented the main points of a report published in March 2014<sup>4</sup>. This report was written in follow-up of a public consultation early 2013<sup>5</sup>. To date 4 ATMPs marketing authorisations have been granted. However the high number of other EMA/CAT activities suggests a lot of ongoing research at earlier stages. In parallel over 60 hospital exemptions authorisations are reported and over 30 therapies were provided prior to entry into force of the ATMP legislation. Most ATMPs are developed by SME's, academia and hospitals.

Overall the report highlights the need find a balance between ensuring safety and quality on the one hand and allowing sufficient innovations to reach patients at the other hand.

The report focuses on difficulties and different views regarding the scope of hospital exemptions, the need to clarify definitions, the need for flexible requirements to obtain a marketing authorisation, and the need for incentives and fee-discounts to allow SMEs to bring innovation.

Participants welcomed the presentation and showed a lot of interest, pointing to the many related agenda points on borderline issues within these meetings of NCA's on Tissues and Cells. Participants asked the Commission for more information on 2 points:

- The anticipated next steps and timeline for the potential revision of a new Regulation. The Commission responded indicatively that such a procedure would take at least 2.5 years, but will contact the colleagues in charge of the file to get more info.
- How the Commission would ensure in future mutual consultation and collaboration between national authorities in charge of pharmaceuticals, medical devices, blood, tissues and cells.

## **8. AOB**

### **8.1. Update on direct distribution of reproductive cells to users (DK)**

The DK representative stated that under the Danish legislation sperm banks are not prevented or hindered from distributing directly to individuals for application at home. Following a question addressed by the group during the previous CAs meeting on the extent of distributing sperm cells directly to end users, it was explained that such type of distribution is significant in particular in 2 MS, possibly due to their national legislation with more restrictive provisions regarding access to fertility treatment. It was also mentioned that direct distribution of sperm to end users seem to be a trend not only in Europe, but also at global level.

Several MS expressed concerns regarding vigilance and traceability of cells in such situations. The DK reiterated that reporting reactions and ensuring traceability are included in the contract between the individual and the sperm bank. One MS representative suggested developing a standardised information document for sperm buyers similar to the information booklet for parents on cord blood donation currently under preparation by Council of Europe. The IE representative informed that such a document, highlighting the regulatory framework, the benefits and shortcomings of

<sup>4</sup> [http://ec.europa.eu/health/files/advtherapies/2014\\_atmp/atmp\\_en.pdf](http://ec.europa.eu/health/files/advtherapies/2014_atmp/atmp_en.pdf)

<sup>5</sup> [http://ec.europa.eu/health/files/advtherapies/2013\\_05\\_pc\\_atmp/2013\\_04\\_03\\_pc\\_summary.pdf](http://ec.europa.eu/health/files/advtherapies/2013_05_pc_atmp/2013_04_03_pc_summary.pdf)

tissues and cells internet sales has been drafted and is currently reviewed by the Irish Ministry of Health and could be shared with the group after its approval at national level. It was also agreed that MS interested in getting more information on direct distribution to individuals in their countries may request it from the DK CA.

### **8.2. Liquid Nitrogen - a CE marked medical device? (DK)**

This issue was brought up to the attention of the group by DK following a question raised within the medical devices sector by the IT CA in April 2014, when the regulatory status of liquid nitrogen for the cryopreservation of cells of human origin based on the Manual on Borderline and Classification in the Community Regulatory Framework For Medical Devices was questioned. During the discussion the group agreed that CE-marked liquid nitrogen for storing organs or body tissues and cells is not available. It was also mentioned that there is no difference in the quality of the liquid nitrogen used for research and medical applications, and the fact that GMP regulation require CE-marked certified liquid nitrogen during the ATMP manufacturing does not provide for additional quality.

### **8.3. Training course for inspectors of tissue establishments (EUSTITE) (PT)**

The group was reminded that the very successful EUSTITE project which ended in 2009 organised 5 courses (2008, 2009 and 2011) which were attended by 99 inspectors from all EU MS. The group was informed that, due to the interest expressed by some MS, a new EUSTITE course is organised. The course will include an e-learning stage (27 October 2014 - 1 March 2015) followed by a residential stage (16-20 March 2015). The tutors and the main topics of the e-learning phase were introduced. It was mentioned that travel, accommodation and daily subsistence during the face-to-face course need to be covered by the participants and that a certificate will be awarded at the end of the course.

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