EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Directorate D - Health Systems and Products
D4 – Substances of Human Origin and Tobacco Control

Brussels,
SANCO D4/IS/ac ARES(2013)

Meeting of the Competent Authorities for Tissues and Cells

5 and 6 June 2013

Summary Report

The meeting of the Competent Authorities on Tissues and Cells was convened on 5 and 6 June 2013. The previous meeting of National Competent Authorities (CAs) took place on 3 and 4 December 2012.

PARTICIPATION:

All Member States (MS), except Romania, were present at the meeting of the CAs. Croatia, Liechtenstein, Norway, Serbia 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):

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

Ms I. SISKA, Ms H. LE BORGNE, Mr P. CATALANI, Mr R. MCGEEHAN

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

1. ADOPTION OF THE AGENDA

No new points were suggested. Participants were reminded about the conflict of interest rules. The publication of the minutes of the last two CA meetings in June and December 2012 was discussed. It was agreed that if there are no further comments, the documents will be published on the Europa website in the coming weeks.

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

A draft proposal for a set of specific Rules of Procedures (RoP) for the meetings of the Tissues and Cells CAs prepared by DE and AT was presented by the DE representative. The proposal was prepared based on the standard rules of procedure which are currently used and the accompanying document to the Commission Communication C(2010)7649 and already included comments from the Commission services/DG SANCO.

It was clarified that the group of Tissues and Cells CAs is part of the Substances of Human Origin Expert Group (E01718), therefore the RoP proposed by this group should also be adopted by the Blood and Organs CAs. The Commission also mentioned that the mandate of the Tissues and Cells CAs group could be clarified in case of a potential revision of the Directive 2004/23/EC.

Following discussions, it was agreed to include in the RoP an Article on conflicts of interest and a voting procedure, to be used exceptionally when issues of considerable political importance are discussed. The technical subjects should be debated and agreed without any voting. It was decided that the Commission will consult the Blood and Organs CAs and will circulate an updated version of the RoP to be considered for potential adoption during the next meeting in December 2013.

The Commission will also align the public register of Committees accordingly.

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. Six MS had sufficiently transposed all Directives. One EU Pilot procedure was on-going and, in at least 11 cases, further clarification was required. Six replies were either under analysis or awaiting translation. Three MS were still to reply to clarification requests sent in the second half 2012 or January 2013 respectively. Among all MS with unsatisfactory transposition, seven MS already informed the Commission about draft legislation which should lead to further transposition of the Directives.

The analysis showed that the transposition was insufficient especially in the areas related to the tissue establishments' annual reports, definitions, third party agreements, procedures, and some inspections and control measures.

MS were requested to react as soon as possible on questions and requests from the Commission. The Commission notified the MS that any further follow-up needed would be done in the form of EU Pilot procedures.

3.2. Implementation of the Tissues and Cells Directive – 2013 Survey

The Commission informed the MS that the second survey on the implementation of the EU Tissues and Cells Directives has been launched on 2 May 2013. The deadline for submitting replies is 3 August 2013. The Commission emphasised that this legal obligation should also provide an overview of the EU sector, allowing the identification of shortcomings with a view to a potential revision of the Tissues and Cells Directives. It was also mentioned that when analysing the answers to the implementation survey, the Commission will also take into consideration the results of the transposition check.

Several MS noted that the survey seems a good opportunity to itemise topics which require clarification during a potential revision (e.g. definition of the "homologous use", borderline with advanced therapy medicinal products/medical devices, etc.).

The Commission mentioned that a draft report should be presented during the Tissues and Cells CAs meeting in December 2013. The full implementation report is expected to be published in March-April 2014.

3.3. Debrief from the second meeting of the Import Working Group. Current practices in MS

The Commission informed the MS about the second meeting of the Import Working Group (WG) which took place on 28 February 2013. The group currently includes 13 MS (AT, BE, DE, DK, ES, FR, HR, IE, IT, NL, PL, PT, UK). During this second meeting, the WG unanimously agreed that legally binding requirements (likely in the form of a Commission Implementing Directive) are needed. These requirements should ensure that imported tissues and cells respect equivalent quality and safety standards, that a parallel approach to authorising imports across the EU MS is introduced and that the import authorisation procedure is harmonised. The WG members had been asked to send to the NL representative relevant information on their national practices for authorising and inspecting importing tissue establishments with a view to coming up with common authorisation forms and, potentially, a common inspection checklist.

The NL representative presented the replies received from ES, FR, IE and the UK, as well as the current practices in NL. The NL made suggestions concerning definitions (e.g. "import", "non-routine import" of tissues and cells) and a cross reference table for import authorisation applications. The issue of the donor's country of origin vs. country of residence was also addressed.

ES congratulated the WG for its work and made clear that harmonisation of import authorisations is crucial because imported tissues and cells are often subject to onward distribution across the EU. Furthermore, the ES representative considered that the donor's country of origin should be included in the application form.

During discussions other topics were addressed by the group: authorisations for "brokers" which only buy and sell tissues/cells, provisions for the import of large quantities of raw tissues and cells for processing within the EU, data protection issues and inspections of procurement sites/tissue establishments in third countries. It was emphasised that appropriate definitions should be put in place (e.g. brokers, import, transit, etc.). The DE representative suggested having a cross reference table also for EU countries with the more stringent quality and safety requirements. For cases falling under Article 9.3 of Directive 2004/23/EC, DE suggested having a batch or certificate attached to the product. AT representative was in favour of an approach similar to the plasma master file and of mutual recognition of licenses.

Concerning the ART sector, the UK(HFEA) representative pleaded for appropriate, requirements for the persons who want to import their own gametes and embryos. Furthermore, an authorisation/license should not be required for ART centres in third countries, as in most non-EU countries these are not authorised/licensed as tissue establishments. The DK representative agreed with the UK's point of view and considered that an authorisation for the importing tissue establishment would be sufficient. The Commission confirmed that all particular cases should be taken into account when drafting the new legal requirements.

The IE representative informed the group of the good collaboration between the Tissue and Cells authorities and the customs officials at national level, which allows an improved control of tissues/cells entering customs.

The Commission informed the group that the third WG meeting will take place on 3 July 2013 and that a draft legal text would be prepared and should be made available to all CAs in the second half of 2013.

3.4. Donor Registries

The issues surrounding the activities of private bone marrow donor registries were initially debated in the Tissues and Cells CA meeting in June 2012. Following these discussions the Commission was asked to provide legal clarifications in terms of the

compatibility of such activities with the requirements of the EU tissue and cells legislation, and also on the compatibility of national measures linked to donor drives with EU Treaty provisions.

The Commission presented the answers its Legal Service gave on the questions surrounding the activities of private donor registries. According to the Legal Service:

- Activities prior to donation, including the initial screening of the potential donors fall outside the scope of EU legislation on tissues and cells.

- Activities from actual donation onwards fall under the EU Tissues and Cells legislation. It would depend on an organisation's involvement and particularly their contractual relations as to whether they would require an authorisation under EU Tissues and Cells legislation.

- Concerning donor drives, these are considered promotional activities and, as such, fall under Article 12(2) 2004/23/EC, and are thus regulated at Member State level.

- Such activities should be considered as economic activities as they entail a mutual exchange of services and reimbursement for the services provided is made at a later stage. To answer to a request of clarification, the Commission pointed out that in this specific context:
  - The "services" referred to are those such as the fees entailed by a donor's registration on the donors registry (biological and clinical selection, medical interview which includes the information given about donation etc..);
  - The "reimbursement" thus covers the costs of these services by the centre in charge of the transplantation or health insurance scheme of the recipient.

It was underlined that national laws for regulating donor drives need to comply with EU Treaty provisions and relevant secondary legislation. The freedom to provide services and right of establishment are enshrined in Articles 56 and 49 of the Treaty on the Functioning of the European Union (TFEU) and national laws should be compatible with these provisions. In particular national law must not render the exercise of these rights obsolete.

In this regard, a prior authorisation scheme would be considered a restriction of Articles 56 and 49 of the Treaty rights. Any such restriction, in order to be permitted, would have to be necessary, justified on public health grounds or grounds of public policy, proportionate and non-discriminatory.

The ES representative clarified that such promotional activities are not prohibited, but that prior authorisation is considered as very important. It was emphasised that activities such as donor drives should also comply with the national strategy developed by ONT in collaboration with REDMO. Furthermore, ES agreed that the organisation of donor drives was a national competence. The Commission indicated that it is analysing the national plan submitted by ES.

The UK representative agreed with the Commission's Legal Service's assessment and informed the group that HTA had provisionally licensed a private donor registry called DKMS at the beginning of 2013, but the organisation has not started their activity yet.

The PL representative updated the group on the position of DKMS Poland, who have agreed to transfer their data into the Polish registry. The importance of a broad international collaboration in the area of bone marrow transplantation was also underscored. Several MS confirmed that more than 50% of the donors for patients in their countries are provided by other registries (e.g. DE, DKMS-DE, USA).

The group was informed that IT, FR and ES are aiming to develop a common approach on this issue. These countries expressed concerns that private registries are incompatible with the necessity to have in this field national health policies with strategic and clear choices with the aim to respect the rights of the donors and to meet the needs of the patients at a national and international level.
The main points raised by these countries were:

- registration of potential donors not only in private registries, but also in the national ones (which in some MS include mandatory requirements on donors' data protection and on their follow-up) and not only in private registries;

- donor data' updates after the initial registration; and

- compliance with national strategies in the field of HSC for transplantation (which in some MS may refer to the use of various sources of HSC – bone marrow, PBSC and cord blood stem cells – according to the patient's needs and providing the best HLA compatibility between donor and recipient).

It was also highlighted that the national registries carry out their activities in the frame of national public health programs, depending on the budget allocated to this particular healthcare sector by each Member State.

The Commission was asked to clarify with the Legal Service on the issue of data protection.

3.5. Interpretation questions

3.5.1. Therapeutic applications of blood cellular components separated by cytapheresis (NL)

The NL representative asked the Commission and the group of Tissues and Cells CA whether blood cellular components separated by cytapheresis are covered by the Blood or Tissues and Cells legislation. This clarification would be needed to decide whether a blood establishment performing such procedures may also require an authorisation as a tissue establishment.

Several MS (DE, PT) considered that such activities are covered by the Blood legislation. The BE representative recalled previous discussions in which the Tissues and Cells CA group agreed that donor lymphocytes infusion and mononuclear cells should be covered by the Tissues and Cells legislation (cf. minutes of the Tissues and Cells CA meetings held on 8 February 2007 and 8-9 December 2011). It was mentioned that both pieces of legislation, provide the same level of quality and safety. However, it was underlined that the legal requirements should be clear for all stakeholders, and it would be preferable to have the same approach at EU level.

The Commission agreed that this topic should be further analysed. The borderlines could be clarified during any future revision of the EU Blood and/or Tissues and Cells legislations. It was also suggested that the European Medicines Agency (EMA) could also contribute to the discussions for the cases in which blood cells separated by apheresis are used as starting materials for ATMPs.

3.5.2. Responsible Person – meeting laws in other Member States (DK)

The DK representatives queried with the Commission and the group of Tissues and Cells CA whether the responsibility for meeting any supplementary national requirements for distribution falls under the responsibility of the responsible person (RP) at the *receiving* tissue establishment in one Member State or of the RP at the *sending* tissue establishment in another Member State. It was pointed out that Article 17(2)(a) of Directive 2004/23/EC provides that the RP has the duty and responsibility for "ensuring that human

tissues and cells intended for human applications in the establishment for which that person is responsible are procured, tested, processed, stored and distributed in accordance with this Directive and *with the laws in force in the Member State*". It was also recalled that during the Tissues and Cells CA meeting in December 2012, the group concluded that it was the responsibility of the Member States with more stringent testing requirements to check whether tissues/cells sent from other EU Member States fulfil their national requirements.

The IT and NL CA confirmed that in their countries, for tissues/cells received from other MS, the RP needs to confirm that the more stringent requirements were met. The AT and. DE stated that collaboration with the RP at the sending tissue establishment should be put in place. The RP at the sending tissue establishment should inform the receiving country whenever they are aware that sent tissues/cells do not fulfil the legal requirements of the receiving MS. The Commission highlighted that this question needs also to take into account cases of "direct distribution".

The group concluded that the main responsibility lies with the RP in the receiving country, but there is a secondary obligation for the RP in the sending country to share all information relevant for the receiving TE/healthcare professionals/patients which should be specified in the written agreements between them. The Commission also mentioned that this issue could be clarified during a potential revision of Directive 2004/23/EC.

3.5.3. Autologous keratinocytes suspension (FI)

The FI representative sought clarification from the Commission and the group of Tissues and Cells CA whether Directive 2004/23/EC applies to the autologous keratinocyte suspensions. From the technical point of view, autologous epithelial tissue is collected from a patient in a hospital and distributed immediately to a laboratory (outside the hospital). In the laboratory, the keratinocytes are separated mechanically and enzymatically from the collected tissue, and the intermediate product is diluted with a physiological sodium chloride solution. It was clarified that keratinocytes are not manipulated or cultured and the entire processing takes about two hours. After processing, the product will be distributed back to the hospital and sprayed on the same patient's burned area or wound. In relation to the above question, the IT representative described a similar case, in which cells are transported for processing to an outside laboratory in a sealed container, which is closed/opened only in the operating theatre.

It was recalled that the Commission Legal Service provided an interpretation to a similar question during the Tissues and Cells CA meeting in December 2010 (agenda point 3.1.2, *"Interpretation of Directive 2004/23/EC with regard to the processing of pancreatic islets in another establishment during an autologous transplantation in the same surgical procedure"*). According to this interpretation, the exemption foreseen under Article 2.2(a) of Directive 2004/23/EC should not apply if the tissues or cells are taken out of the operating room to a laboratory for processing. It was considered that using a "sealed container" does not provide any additional safety benefit, and the risk of mix-up or mislabelling remains unchanged.

Several MS agreed with this interpretation. The Commission and the group concluded that the above mentioned situations are similar to the one analysed by the Legal Service, therefore the full requirements of Directive 2004/23/EC apply.

4. DEBRIEF FROM THE SEMINAR ON ILLEGAL AND FRAUDULENT ACTIVITIES IN THE ORGANS, TISSUES AND CELLS SECTORS, PARIS, 8-10 APRIL 2013

The Commission informed the group about the Seminar on Illegal and Fraudulent Activities (IFA) in the area of organs, tissues and cells organised by various French SoHO authorities and law enforcement agencies with support from the European Commission. The aims of the seminar were to raise awareness amongst law enforcement officials of IFA in the organs, tissues and cells sectors and also to look at ways, in which different authorities can cooperate to prevent, detect and investigate these types of IFA.

It was emphasised that the seminar achieved its main goals and had been well received by participants. It also received significant media coverage in light of last year's articles published by the ICIJ. The seminar included several workshops providing the participants with case studies and stimulating discussions on both the assessment of IFA and possible solutions to improve their investigation.

A final seminar report including recommendations for future action and cooperation has been published. It was underlined that it is important for MS Tissues and Cells CA to build working relationships with national law enforcement agencies and to share instances of IFA over the RATC platform. The Commission will continue to watch developments in IFA field closely with a view to guaranteeing quality and safety and the free flow of legitimate tissues and cells exchanges.

5. DISTRIBUTION OF TISSUES AND CELLS DIRECTLY TO THE PUBLIC

The issue of direct distribution to the public has been raised by a recent case which had taken place in the UK and received a lot of media coverage. In April 2013, an English newspaper revealed that a mother had forced her 14-year-old adopted daughter to inseminate herself with donor sperm to provide a baby for her after she had been prevented from adopting any more children. The sperm had been purchased from an international sperm bank network based in an EU MS and sent directly to the mother. The article had highlighted how easy it is for an individual to buy sperm online.

In relation to this specific case, the HFEA representative asked the Commission and the group of Tissues and Cells CA:
- Whether the provisions set out in the Tissues and Cells Directives imply that gametes and embryos should only be distributed between 'licensed' tissue establishments;
- How to address the issue of distribution of tissue and cells between Member States in ways that circumvent the laws in place there (e.g. the sperm purchased was procured from an anonymous donor and applied without the involvement of a medical professional, whereas in the UK, only non-anonymous sperm donations are allowed and the use of sperm requires the involvement of an ART clinic).

According to the UK analysis, the EU Tissues and Cells Directives do not cover the end use of tissues and cells, but the "spirit" of this legislation suggests that healthcare professionals should be responsible for the application (use) of tissues and cells (Articles 6 and 2(5) of Directive 2006/17/EC and Article 9(1) of Directive 2004/23/EC). The main argument was that having at least a healthcare professional involved in the end use of tissues would help to ensure appropriate traceability to the recipient.

The DK representative affirmed that the EU Tissues and Cells Directives do not prohibit the distribution to private persons; therefore according to the Danish provisions the distribution and export of tissues/cells are not restricted to tissue establishments or healthcare establishments. It was mentioned that a CA has no possibility to verify the application (use) of

tissues and cells by a member of the public, and stated that tissue establishments in DK are asked to comply with the legal provisions of the receiving countries.

Other MS representatives expressed their points of view and/or presented their national legal framework. The IE representative agreed with the UK, underlining that distribution of reproductive cells is a particular case and, taking into account the welfare of the child, the involvement of a medical professional would be beneficial. IT also agreed that cases of home application should be under the supervision of a healthcare institution/professional. In France, the import of gametes is allowed only with an authorisation based on the national legal requirements; it was mentioned that the use of gametes is restricted to couples, donations should be anonymous and penalties are in place for the illegal selling of gametes. In Sweden only tissue establishments are allowed to distribute tissues and cells to healthcare professionals, but the application of sperm does not require the involvement of a healthcare provider.

It was agreed that irrespective of the responsibility for the application of the gametes, the TEs have to ensure the quality and safety of the distributed cells. It was also mentioned that ethical issues are not covered by the EU Tissues and Cells legislation, but safety and quality issues, including traceability area a major concern in the case of distribution directly to the public. Therefore it was generally concluded that, for the distribution of sperm, the involvement of a healthcare professional is preferable, while the application of sperm at home (without the involvement of a healthcare professional) may be also permitted. This issue should be further addressed during a potential revision of the 2004/23/EC Directive.

6. SURVEILLANCE AND VIGILANCE

6.1. Update on infectious disease risks

6.1.1. Epidemiological update – ECDC

ECDC presented an overview of the communicable disease threats in the first six months of 2013. Data on two outbreaks were presented: the outbreak of the Influenza A (H7N9) virus in China and the outbreak of a variant of the SARS virus - the Middle East Respiratory Syndrome Corona Virus (MERS CoV). ECDC had no data on how these diseases could affect the SoHO sector. A few cases of Hepatitis A were also recorded in DK, NO, SE, FI and IT.

Following a question from DK, ECDC clarified that risk assessments for SOHO-related communicable diseases will be provided starting in 2014. In this regard, ECDC launched a call for tender on "Risk Assessment and Prevention of Infectious Disease Transmission through Substances of Human Origin", the first three diseases to be analysed being West Nile Virus (WNV), malaria and Dengue fever. It is expected that the preparation of a risk assessment for a specific disease would take approximately one year.

Following a question from IT concerning the change of testing requirements for WNV proposed by FDA, ECDC agreed to provide a preliminary opinion in the coming months.

The Commission informed the group about on-going discussions between DG SANCO and ECDC on best solutions to cover the needs of both the Commission and Tissues and Cells CAs regarding communicable diseases related to SoHO. The important role played by ECDC in assessing the risks and providing timely information for SoHO CAs was emphasised.

6.1.2. *Other – Member States will be asked whether they have additional info/updates to report*

PT reported that the Dengue fever outbreak in Madeira was over. No other participant reported any information.

6.2. *Update on the development of the new European code for tissues and cells – EUROCET128 tender*

The Italian National Transplant Centre (CNT), as representative of the EUROCET128 consortium, presented an update on the progress made since December 2012. It was recalled that after development, the two compendia and the code translator application will be hosted by the Commission's servers.

The *development of the compendium of EU tissue establishments and their respective alphanumeric codes* is well on track. It was clarified that no personal data will be included. It was emphasised that the compendium is a good opportunity to fulfil the requirements of Art 10(3) of Directive 2004/23/EC which requires the Member States and the Commission to establish a network linking the national tissue establishments registers. In this regard, even though coding requirements are not to be applied to partner donation of reproductive cells, MS agreed to provide data also for the ART establishments performing only procedures for partners.

Several amendments were debated and agreed (e.g. the date of the last inspection not to be included among the mandatory fields to be filled out for each tissue establishment, allocation of codes should take into account the national codes of tissue establishments as long as there is a single donor number allocation/establishment).

The Commission clarified that MS' CAs will be responsible to update the tissue establishments' data in the registry (e.g. authorisation changes, address changes etc.). Due to this "administrator" role, CAs will be also able to add up/delete tissue establishments in/from the EU registry. The case of federal MS was also discussed. ES, FR and IT confirmed that their national Tissues and Cells CAs will be the contact points responsible to update the tissue establishments' data in the compendium (regional authorities will have no "administrator" role). DE underlined the difficulties to be faced by the national CA (e.g. timely delivery of data, data format, etc.) when data are coming from the regional authorities, and suggested an automatic exchange of data. The Commission indicated that the database is still under development, and technical solutions need to be further discussed. However, due to the responsibilities placed on national CAs by the EU Directives, the preferred option would be have national and not regional contact points for the "administration" of the tissue establishments' data.

Member States were asked to complete the input of tissue establishment data in the coming weeks.

The progress on data collection for the *EU Generic product list of tissues and cells* was also described. Currently it contains approximately 90 generic product names.

CNT informed the group that two user manuals have been drafted, for tissue establishments and CAs. These draft manuals will be made available via CIRCABC and input from both the Commission and the MS was requested (by 15 September 2013).

Regarding WP 3, the *development of the code translator application*, the functions of the system were explained and a mock-up model was briefly presented.

MS were also asked whether they would be interested in participating in piloting the code translator application, foreseen in WP4. BE, CZ, FR, IT, SE and SI volunteered. The pilot was planned to start at the beginning of 2014.

Concerning WP5 - Dissemination, an overview of both past and future dissemination activities was presented.

The Commission closed the discussions by thanking the EUROCET128 consortium for their work and the Member States for giving input and supporting this initiative. CAs were also encouraged to actively inform tissue establishments in their countries about the forthcoming changes. In this context, it was recalled that flyers prepared by EUROCET128 with Q&A for both professionals and CAs have been made available via CIRCABC.

Finally, the Commission called for volunteers for a drafting Working Group, whose main task would be to help the Commission to take into account the specificities of all types of tissues and cells when drafting the legal requirements for the implementation of the single European code. Representatives of the CAs from BE, FR, PL, SK and UK (HTA, HFEA) expressed their interest to contribute. A debrief of the first meeting of this WG (foreseen in September 2013) will be presented during the CA meeting in December 2013, when a timetable for the adoption of this new legal text will be also proposed.

6.3. Rapid alerts for tissues and cells (RATC)

6.3.1. Draft RATC report for 2010-2012

The Commission presented a draft report on the Rapid Alert system for human Tissues and Cells (RATC) for the period 2010-2012. The RATC system, hosted by the Commission CIRCA platform, was officially launched in July 2010. In January 2012, the RATC system was transferred to the new CIRCABC platform.

The report describes the criteria to notify rapid alerts and the classification of alerts, providing also an overview of the rapid alerts initiated by the MS and the European Commission between July 2010 and December 2012 (19 rapid alerts). The Commission also noted that between 2006 and July 2010, 11 rapid alerts were circulated via email.

The Commission informed the group that the draft report already received the input of the RATC WG members and asked the MS to provide their comments in the coming weeks, but not later than 31 July 2013. Publication of this first RATC report was foreseen for August 2013.

6.3.2. New RATC platform – update (alerts, operational issues, connection with other sectors)

The Commission presented an update of the new RATC platform which was launched on 1 February 2013. Since its launch, five rapid alerts have been initiated by three MS.

It was highlighted that two hands-on training courses for RATC users have been organised by the Commission and a third one will be delivered on 7 June 2013. In addition, participants from three MS had given demonstrations and training courses to colleagues at local level.

Concerning the interconnectivity of RATC with other sectors/alert platforms, it was mentioned that similar platforms are under development for the Blood and Organs sectors which, together with RATC, will be distinct components of a single "Rapid alert platform for substances of human origin". The group was informed that up until now the new RATC system had been presented to the national CAs for Medical Devices and to the EWRS national contact points (?) during their regular meetings.

The group was informed that the Commission also addressed the issue of data protection. Following a question received by DK on access to rapid alerts initiated by DK, the Commission clarified that the alerts launched by the MS are the under the responsibility of the Tissues and Cells CAs, therefore access to such information/documents should follow the national rules. If MS wished to give access to comments/contributions provided by other MS to their alerts, the latter should be consulted beforehand.

The Commission announced that an evaluation of the new RATC platform will take place in August. CAs were invited to send their comments to both the SOP and the user manual, if possible by the end of July.

6.3.3. Alerts initiated in 2012 with follow-up in 2013 – update

Follow-up of the Tutogen alert

A representative from the Paul-Ehrlich-Institute (PEI) and a representative from the Bavarian CA (ROB) provided an extensive update on the recall of products issued by the German company Tutogen in 2012 and 2013. It was reiterated that the recall was due to the lack of license for re-importation of tissue products, and not because of quality or safety defects. The preliminary conclusions of the inspections performed to Tutogen Medical GmbH by ROB and PEI were also presented. Following these inspections, PEI did not withdraw Tutogen's marketing authorisation.

During the subsequent discussions several MS underlined the importance of donor documentation (as required in point 1.4 of Annex IV of Directive 2006/17/EC) for traceability purposes and also for the medical and behavioural history of the donor.

It was acknowledged by the DE CA that it would difficult to further investigate the initial allegations of fraudulent procurement of tissues in the Ukraine that were subsequently processed by Tutogen because this issue is subject of criminal investigations by the Ukrainian public prosecutors. Criminal investigations are not in the remit of a third country CA. To investigate these allegations definitively would require, at a minimum, interviewing donor families in the Ukraine and this option is now closed due to the lack of a legal remit within the Ukraine following the revocation of Tutogen's Import licence and the priority of criminal investigations for illegal removal of tissues.

The DE authorities agreed to share the final report of the pharmacovigilance inspection with the MS Tissues and Cells CAs (via RATC). MS were asked to provide any additional information which may be relevant for the investigation of Tutogen by the DE CAs. It was concluded that the case should be summed up by the DE CA during the Tissues and Cells CA meeting to be held in December 2013.

Follow-up of the DK alerts related to the transmission of genetic disease via sperm

The DK representative provided updates on the alerts related to sperm donations initiated in CIRCABC RATC in 2012. It was underlined that all clinics in the receiving countries had been informed of the corrective actions by the Danish tissue establishment.

The UK(HFEA) representative thanked DK for the immediate reaction and follow-up measures, reiterating their concern about the distribution of sperm directly to private individuals, which may not always allow an appropriate traceability. The Commission was asked to take this issue into consideration during a potential revision of the Tissues and Cells Directives.

6.3.4. *Mandate of the European Commission in relation to alerts from third countries (e.g. USA, Canada, etc.)*

The Commission will request MS to provide input in writing. This matter will be then discussed in December 2013.

6.4. Serious adverse reactions and events (SARE)

6.4.1. *2012 SARE draft annual report (2011 data)*

The Commission presented the draft annual report for SARE submitted by MS in 2012 (data recorded between 01/01/2013-31/12/2013). The preliminary analysis showed an improved data collection for the denominators used for the evaluation of Serious Adverse Reactions (SAR)/ Serious Adverse Events (SAE), number of tissues and cells distributed and number of recipients of tissue(s)/cells, and the number of tissues and cells processed respectively. However the lower number of reported SAR/SAE may suggest the persistence of a high degree of under-reporting, especially in some MS. It was noted that ten countries reported that no SAR and no SAE were registered at national level in the past two years. For smaller countries where transplantation and ART services are on a smaller scale these data seem plausible, but in case of larger countries this may indicate an inappropriate implementation of reliable reporting practices at national level from either medical staff and/or tissue establishment staff. Under-reporting of denominators for MS well known for performing a high number of ART procedures was also discussed.

The Commission noted that many MS preferred to report "not-available data" instead of giving partial numbers, and encouraged MS to report also partial data and provide updates at a later stage. MS were asked to update/correct their 2012 submissions (if additional data were available) by the end of July 2013. They were also requested to provide feedback in writing to the draft report for the 2011 SARE data, which should be published in September-October 2013.

Member States congratulated the Commission with the good progress made.

6.4.2. *2013 SARE annual reporting exercise*

The Commission outlined the main novelties for the 2013 SARE annual reporting exercise launched on 31 May 2013. The Commission pointed at Article 7 of Directive 2006/86/EC and reminded the CAs to submit their annual report by 30 June.

7. PROJECTS PRESENTATIONS: SOHO V&S PROJECT (FINAL CONFERENCE, FINAL REPORT AND DELIVERABLES)

The SOHO V&S project, funded under the 2nd Community Programme for Health, ended in February 2013. On behalf of the consortium, the IT and PL representatives outlined the achievements of the project. A training model for the MS' inspectors (including case studies and vigilance communication strategies), guidance documents for the Tissues and Cells CAs (on the communication and investigation of SARE related to the use of human tissues and cells, investigation of illegal and fraudulent activities, vigilance in the ART sector) and also for professionals working in the field of human tissues and cells for human application (SOHO V&S Guidance for clinical users) are now available free of charge and can be translated and used by the MS according to their needs.

The contribution to the WHO-initiative NOTIFY and to the elaboration of the first edition of the Council of Europe' "Guide to the Safety and Quality of Tissues and Cells" was also highlighted.

MS representatives and the Commission congratulated the coordinator (IT) and all partners and collaborators for the project's achievements. The Commission also expressed its gratitude for the help provided during the revision of the SARE reporting tools for the annual reporting to the European Commission.

8. UPDATE FROM THE COUNCIL OF EUROPE. CDPTO MEETING, GUIDE TO SAFETY AND QUALITY ASSURANCE FOR TISSUES AND CELLS – UPDATE FROM EDQM SECRETARIAT

EDQM representative presented the first edition of the Guide to the Safety and Quality of Tissues and Cells, coordinated by IT (tissues) and FR (cells). It was underlined that this guide aims at harmonising this field between EU MS and the Council of Europe MS. The guide will be soon available as hardcopy and electronic version.

It was also mentioned that the next edition of the guide, which will also include a detailed chapter on ART, is planned for 2015. The MS were reminded that an invitation to nominate experts for the drafting group was already sent out (deadline 15 July 2013).

EDQM also presented a preliminary data analysis of the EDQM survey on the compliance with the Council of Europe Recommendation Rec(2004)8 on "Autologous cord blood banks", which states that cord blood banks (CBB) should only be established based on altruistic and voluntary cord blood donation and used for allogeneic transplantation and related research. Twenty five countries replied to the questionnaire, of which 22 were EU MS. According to the data received, 24% of the respondents (5 countries) acknowledged to have only CBB for autologous use. EDQM clarified that the Council of Europe's position was in line with the position of the European Parliament (EP) which encouraged MS to develop cord blood banks irrespective of their status (public or private), without supporting the autologous ones. Following a question from DE, EDQM representative clarified that the cord blood banks project was initiated in the European Committee on Blood Transfusion (CD-P-TS), but transferred at a later stage to European Committee on Organ Transplantation (CD-P-TO), which agreed to take it over as part of its mandate covering human tissues and cells.

9. AOB

9.1. New law for reporting genetic diseases in the ART sector

DK informed the group of a change in their national legislation. The definition of serious adverse reaction was amended so that the birth of a child with a serious genetic disease, born following non-partner donation of gametes, is now considered and should be reported as a suspected SAR. The amendment has been adopted in Denmark and would enter into force on 1 July 2013.

9.2. ART - Screening "known donors" as for partner donation

The DK representative presented a proposal to treat donations from "known donors" as "partner donations". "Known donors" were i.e. donors who are known to the recipients, but with whom they do not have an intimate physical relationship. DK stressed that, according to EU legislation, "known donors" need to be tested as any other non-partner donor, and the costs for such testing is quite high (4.000 to 6.000€).

The UK representative stated that "known donors" should be screened as non-partner donors as there was the same risk as for the donation of a stranger, and that in the UK

only non-anonymous donations are allowed. It was also suggested that the rules for partner donation should be extended to female couples where one partner donates the egg and the other is carrying the child.

The FR representative underlined that French regulations do not recognise "known donors", therefore they are treated as non-partner donors and all donations need to be anonymous.

The Commission clarified that the concept of "known donor" is not foreseen in the EU legislation which only refers to partner and non-partner donation. The Commission stated that this issue needs to be further analysed and it may require the assistance of ECDC for an appropriate assessment of the safety of such an approach.

9.3. ART - Screening of egg donors

The DK representative informed attendees about an upcoming revision of the national requirements for genetic testing. In this regard, the group was asked a) whether MS allowed egg donation in their countries, b) about the existence of egg donation programmes in Europe, and c) what are current national practices for the screening of egg donors.

The UK advised that both egg donation and egg sharing are allowed and a national egg donation programme is in place; egg donors are screened as non-partner donors, and eggs are used fresh (not quarantined). The UK would welcome a genetic screening for egg donors, similar to the one for sperm donors.

Following a question from FR, the DK representative stated that further reflection is needed for the development of a list of genetic diseases for the screening of egg donors.

9.4. ART– recall and look back performed by a sperm bank

DK representative informed the group that for a period of 2 years, from December 2011 until March 2013, only clinics which had purchased sperm straws from a blocked donor had been informed if another donor was blocked. In the customer contract issued by the tissue establishment it is stated, that information concerning reports of malformations and genetic diseases was sent only up to two years after the date of order, unless there was a clear mode of inheritance and high risk of transmission. In practice, only information concerning serious genetic diseases was communicated, while data on multifactorial genetic diseases (where genetic factors have a less clear role) were not given.

The group was informed that national procedures concerning the obligations of the tissue establishments had been changed and from now on all clinics will be informed when a sperm donor is permanently blocked. All purchasers of sperm straws were informed and a full look back of all the customers of the sperm bank had been completed.

9.5. ATIMP's clinical trials – verification of donation, procurement & testing

DK raised an issue regarding the standardised EU application forms for sponsors conducting a clinical trial for Advanced Therapy Investigational Medicinal Products (ATIMP). DK stressed that, according to Art. 3 of Regulation 1394/2007/EC, the requirements for donation, procurement and testing of Directive 2004/23/EC have to be fulfilled if an ATIMP contained human tissues and/or cells. However, the application form for sponsors wishing to conduct a clinical trial for an ATIMP did not specify the measures adopted by a potential sponsor to fulfil the expected practices for donation, procurement and testing. Therefore, DK proposed a new subsection to be added to the current EU application form, to assist with the review process of an ATIMP by the national Medicinal Competent Authority. As the guidelines on good clinical practice for ATIMPs do not clearly specify how to verify the conformity with the requirements of

Directive 2004/23/EC, the ATIMP's applications at the Danish Health and Medicines Authority are predominantly reviewed by the medicinal clinical trial experts, with the opportunity for technical input by tissue/cell experts, on aspects of Directive 2004/23/EC.

The DE representative agreed with DK that a technical guidance is indeed needed. The Commission noted that the Tissues and Cells Directives do not distinguish between tissues and cells and processed tissues and cells, and that this issue could be addressed during the revision of the clinical trials legislation. The Commission agreed to forward this matter to the unit in charge of the clinical trials legislation.

9.6. Revision of the Medical Devices Directive – update

The Commission will update the MS on the revision of the Medical Devices legislation by email.

Dominik Schnichels