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Joint meeting of the Competent Authorities and the Regulatory Committee on Tissues and Cells

20-21 May 2010

Summary Report

The first joint meeting of the Competent Authorities and the Regulatory Committee was convened on 20-21 May 2010.

All Member States except Bulgaria and Cyprus were present at the meeting of the Competent Authorities on 20 May. Bulgaria, Cyprus, Estonia and Luxembourg were not present at the Regulatory Committee meeting on 21 May. Iceland, Liechtenstein, Norway and Croatia, as well as the European Directorate for the Quality of Medicines and Health Care of the Council of Europe (EDQM), the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) also attended the meeting.

1. ADOPTION OF THE AGENDA

The agenda was adopted without change.

MATTERS FOR THE COMPETENT AUTHORITIES

2. UPDATE ON ADVANCED THERAPY MEDICINAL PRODUCT REGULATION

EMA presented the existing regulation on Advanced Therapy Medicinal Products (ATMP) and ongoing implementation activities, including the Commission guidelines on Good Manufacturing Practice for ATMP. Annex 2 of these guidelines, which concerns the Manufacture of Biological Medicinal Substances and Products

for Human Use, is currently subject to revision. The second public consultation of the Annex is open until 15 July 2010. The document can be accessed at: http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/latest_news/gmp_annex2_03-2010.pdf. Member States are encouraged to review it and provide comments. When doing so, please also send a copy to the Commission (contact person: Olga Solomon).

EMA has also developed some draft guidelines on traceability of ATMP that will be forwarded by the Commission to the participants of this Committee. Comments can be sent to the Commission (contact person: Thomas Brégeon).

Another EMA activity of relevance for the field of substances of human origin relates to the classification of ATMP.

3. SURVEILLANCE AND VIGILANCE

3.1. Update on infectious disease risks: latest news

- *Q-fever*

The Dutch Competent Authority provided an overview of the ongoing Q-fever outbreak in the Netherlands. The Dutch Ministry of Health provides continuously updated information at: http://www.qkoortsinnederland.nl/home .

Concerns were expressed by the Competent Authorities of the other Member States, and some questions were raised regarding the rapid spread of the disease and the testing procedures undertaken by the Sanquin Blood Supply Foundation. While it was recognised that Q-fever can have a cross-border impact, Belgium and Germany did not yet report an increase in notified cases.

The ECDC presented its risk assessment on transmission of Q-fever via blood transfusion and clarified that this opinion did not address the risk of transmission via transplantation of tissues and cells[1].

Member States were informed about the conclusions of the meeting of the Competent Authorities for Blood and Blood Components, 12-13 April 2010, where it was agreed that it would be reasonable to apply at least a 5 weeks deferral period to any potential blood donor having visited a farm or stayed overnight in the areas identified by post codes in the Netherlands. However, at the date of the meeting, these codes had not been formally transmitted to the Commission.

With regard to tissues and cells, measures were discussed for two key fields: (1) the management of tissues and cells procured and processed in the Netherlands and distributed to other Member States or exported to third countries (some major Dutch exporting tissue banks were mentioned); and (2) the management of tissues and cells from potential donors returning from the Netherlands, where the procurement, processing and use of the tissues and cells takes place in a different Member State.

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[1] The risk-assessment can be found at: http://www.ecdc.europa.eu/en/Pages/home.aspx.

It was agreed that the Commission will request the assistance of the ECDC to analyse the potential risk associated to different types of tissues and cells. Pending this ECDC analysis, it was considered that the following could be a reasonable approach:

(1) For the first point, the meeting highlighted the duty of the Responsible Person(s) at all tissue establishments (TE) in the Netherlands to implement additional precautionary measures, via for example, donor evaluation, screening and testing on the basis of residence and travel to epidemic areas and taking into account the processing applied at the TE. It was also highlighted that the Responsible Person(s) at these TEs have the duty to perform on-going risk assessments as well as the duty to inform relevant parties of any potential risk related to a distributed tissue/cell and to suggest additional measures that might be appropriate when using these. In particular in case of need for collecting and distributing a highly matched product with a life-saving benefit (e.g. bone-marrow), additional measures are to be considered (e.g. prophylactic use of antibiotics). This information is to be passed to organisations responsible for human application, and to other TEs to which they have provided the concerned tissues/cells. The Dutch Competent Authority has the responsibility to ensure, through their inspection system, that these appropriate risk reduction measures are being taken at the TE level.

(2) For the second point, the Competent Authorities may consider advising their own national tissue establishments of the Q-fever situation and of possible measures to reduce the potential risks. Measures that were discussed include exclusion of potential donors from donation during a period of 5 to 6 weeks after having visited an affected farm or after having spent a night in the affected areas in the Netherlands. In case of need for collecting and distributing a highly matched product with a life-saving benefit (e.g. bone-marrow), additional measures could be considered (e.g. testing, antibiotic treatment of recipients).

- *West Nile Virus*

Italy informed the delegates about the West Nile Virus situation in the country. The disease is becoming endemic in several regions and measures are now in place on donor selection and testing in view of the expected outbreak in 2010.

The ECDC briefly presented the wider European situation in relation to West Nile Virus. Both Italy and the ECDC indicated that the disease would be spreading in more Member States in coming years, not least because of climate change.

3.2. Results of feedback on Rapid Alert System (pilot phase)

The pilot phase of the rapid alert system for tissues and cells (RATC) was initiated during spring 2010. The overall aim was to test the communication network between Competent Authorities and the Commission; to verify the functioning of the CIRCA site and database; and to provide examples of scenarios so that Member States could review, if needed, their national systems for handling the RATC notifications.

The overall feedback from the Members States on the pilot phase was positive. The system will become operational after small changes following comments from the Member States.

The Danish Competent Authority asked the other Member States to provide information on how they interpret article 6 of Directive 2006/86/EC stating that Member States shall ensure that tissue establishments have procedures in place to communicate to the Competent Authority "without delay" all relevant available information regarding serious adverse events. The Commission agreed to circulate a note to the Competent Authorities, asking them to precise how they have defined the concept of "without delay" regarding the reporting of (1) all relevant available information about suspected serious adverse events, and (2) the conclusions of the investigation to analyse the cause and the ensuing outcome.

3.3. Vigilance of human substances: status and next steps

The Commission informed the Member States about the key outcomes from the Working Group meeting on coding held on 19 May 2010.

The goal of the meeting was to (1) reach a joint understanding on the objective and scope of the exercise after several developments in the past two years, (2) take stock of agreements and open points for discussion, (3) agree on the common direction to go, and (4) develop a process and set a timeline for the next steps.

As a starting point the working group agreed on some basic working principles to consider while setting up the European Single Coding system:

- The scope of our exercise relates to substances of human origin, in particular tissues and cells. While later a link is to be foreseen with the field of advanced therapy medicinal products (ATMP), the field of ATMP falls outside the scope of this work.

- The Commission presented the wider context in which the discussion on coding is taking place; coding is a tool to strengthen traceability of tissues and cells across the EU. Traceability is one (1) out of the five tasks required to ensure robust vigilance of tissues and cells at EU level, together with (2) threat/defect detection, (3) alerts, (4) risk assessment and (5) response definition/implementation.

- The future European single coding system aims to interconnect the existing national traceability/coding systems, respecting the national systems as far as possible. However, each system should be prepared to compromise and adapt somewhat. This interconnection requires in particular:

    - A common language that is mutually understood (at least partially);

    - Supporting platforms (IT) that interconnect the actors in this field.

- Coding of tissues and cells has been extensively considered in the past years, in particular in the SANCO coding working group, during the CEN workshop, and in the context of the RAND study. These exercises have been helpful to increase the common understanding on the objectives and means. However, at this stage no final decision on the shape and management of the coding system has been taken.

- The set up and management of the incoming European common coding system should actively involve the Member States' Competent Authorities. At the same time a single approach for the code will require the central support by one EU-coordinator.

- We should aim at a common system, ensuring that all EU Member States can participate.

- The shaping of the European single coding system should make good use of already established initiatives and tools, and integrate these where possible.

The Commission presented to the Competent Authorities the conclusions of the coding working group which focused on three elements:

(1) Donation identification in order to ensure traceability. The code will include a national unique identification number and a unique EU-level number for the tissue establishment of origin. The later includes a reference to the country of origin and leaves room for national codes for TEs. It was recommended to build a EU-level common reference database on TEs based on the EUROCET (European Registry for Competent Authorities for Tissues and Cells) effort.

(2) Product identification in order to identify product characteristics. It was agreed that there is need for a EU-level common reference database on product nomenclature. EUROCODE and ISBT128 were identified as potential candidates. The capacities and modalities of both options will be presented and discussed at the next meeting of the working group. Discussions on expiry date and split numbers will follow at a later stage.

(3) It was concluded that traceability of "last-in-chain TE" is important. However, this traceability is possible through searching in the available data sets, which are mandatorily recorded by hospitals and tissue establishments. Therefore there is no need to create an additional component in the code-label. Such a component would anyhow require frequent manipulations and therefore leave room for errors.

The next meeting of the working group will be planned in summer 2010. The Competent Authorities will be informed on the further discussions in the working group.

3.4. SoHOV&S project on vigilance and surveillance

The project leader informed the Competent Authorities about the SoHOV&S project, which is co-funded by the Second Programme of Community Action in the Field of Health.

The overall objective of the project is to support Member States in the establishment of effective vigilance and surveillance systems for tissues and cells used in transplantation and in assisted reproduction, through:

- Standardisation of principles and practices in the inspection and certification of tissue establishments, including definition of current best

inspection practice, formulation of inspection guidelines and development of training for inspectors;

- Development of a model for the reporting and investigating of adverse events and reactions associated with the quality and safety of tissues and cells in the EU.

3.5. SARE annual report to the Commission – next steps

The Commission announced that the third round of the annual report template on serious adverse events and reactions (2009 data) will shortly be sent out to the Member States. The Member States should report the data to the Commission by 30 June 2010, in accordance with article 7 of Directive 2006/86/EC.

4. VOLUNTARY AND UNPAID DONATION

The Commission announced that the report template on voluntary and unpaid donation of tissues and cells will shortly be sent to the Member States. The deadline for completion is 25 July 2010.

5. AOB

The Commission asked the delegates whether the Icelandic volcano eruption and the closure of the air space had any impact on bone marrow exchange in their Member State. Apart from the UK that reported a few problems related to bone marrow and cornea transplants, Member State had not experienced any disruption.

The Netherlands announced the recent activation of the Worldwide Network for Blood & Marrow Transplantation (WBMT).

Italy gave a brief update on the current activities and data collected by EUROCET[2].

The Commission reminded the Member States, who have not yet done so, to fill in the questionnaire sent out by the EU-funded Poseidon project. The overall aim of the Poseidon project is to improve the quality and safety of unrelated haematopoietic stem cell transplantation (HSCT), to optimise HSC donation policy, and to promote equal access to this therapy throughout the EU[3].

MATTERS FOR THE REGULATORY COMMITTEE

The Chair checked the presence. Bulgaria, Cyprus, Estonia and Luxembourg were not present; however, Cyprus was represented by Greece for the vote under point 6.1.

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[2] Please see: http://www.eurocet.org/.

[3] Further information about the project could be found at: http://www.poseidon-hsct.eu/page.php?url=project.

6. REGULATORY MATTERS

6.1. Inspection guidelines

The draft decision on the guidelines for inspections and control measures and on the training and qualification of inspections in the field of tissues and cells provided for in Directive 2004/23/EC of the European Parliament and of the Council was presented. Denmark considered very restrictive the provision suggesting that inspection by a single inspector should, **as a general rule**, be avoided. Although the guidelines are not legally binding but serve to provide guidance to the Member States, the wording in the draft decision was slightly changed to accommodate the Danish concerns. The draft decision as amended got the favourable opinion of the Regulatory Committee with 327 votes in favour. 24 Member States were present or represented. No Member States voted against nor abstained.

The draft Commission Decision will be entered in the Comitology Register, in accordance with the right of scrutiny of the European Parliament (one month period), before it is formally adopted by the Commission and published in the Official Journal of the European Union.

The draft Decision will be complemented by the Operational Manual on Inspections, which can provide more practical details and be easily up-dated on the basis of Member States' experience. The Operational Manual will be translated in all Union languages and made available on the website of the Health and Consumers Directorate-General. It was not possible at this stage to indicate a timeframe for the translations.

6.2. Update and information on the transposition and implementation of the Tissues and Cells Directives

The Commission informed the Regulatory Committee that it will take the initial steps for transposition check of the Tissues and Cells Directives by sending out a report template during summer 2010. The Commission has identified some main areas which need to be covered in the transposed national laws. These areas include:

1. Designation of Competent Authority or Authorities;
2. Supervision of Human Tissue and Cell Procurement;
3. Selection Criteria for Donors of Tissues and/or Cells (except donors of reproductive cells);
4. Laboratory Tests Required for Donors (except donors of reproductive cells);
5. Selection Criteria and Laboratory Tests Required for Donors of Reproductive Cells;
6. Accreditation, Designation, Authorisation and Licensing of Tissue Establishments and Tissue and Cell Preparation Processes;
7. Requirement for Accreditation, Designation, Authorisation or Licensing of Tissue Establishments;
8. Traceability;
9. Notification of Serious Adverse Events and Reactions;
10. Import/Export of Human Tissues and Cells.

The Commission informed the Member States that it will ask them to fill out the report templates to provide provision(s) in the national legislation transposing the

particular points in the Directives. The Commission expects the completed report templates to be sent back in autumn 2010. Further to this, the Commission will proceed to analyse the report templates and perform a transposition check, looking into whether the provisions in the Directives have been adequately transposed into national laws.

It was also mentioned in the Regulatory Committee meeting that the Commission could later contact the Member States to request additional information and clarification. The Committee was reminded that failure to fully transpose the Directives on tissues and cells may lead to infringement procedures.

6.3. Assisted Reproductive Technology (ART): Feedback from expert group meeting on testing requirements for partner donation

The Commission provided a brief overview of the ongoing work of the expert working group, set up as a response to the raised concerns about the requirements of testing for *each* partner donation of reproductive cells (Directive 2006/17/EC, Annex III) discussed at the Competent Authority Meeting, 19-20 October 2009[4].

The objective of the group is to collect and analyse the available evidence-base. Key aspects include: potential risk of cross-contamination during cryopreservation; potential risk of cross-contamination during other processing and storage steps, and mix-up of gametes. In parallel, DG SANCO has requested the assistance of the ECDC in examining the potential health risks associated with changing the protocol for testing from each donation to periodic testing (e.g. every 12th or 24th months).

6.4. Questions on implementation of the Tissues and Cells Directives

The Commission presented the following questions on implementation which have been raised by the Member States and EEA countries.

6.4.1 Suspension of HTLV testing by the AATB

For a number of years the American Association of Tissue Banks (AATB) has required systematic HTLV testing for donations of tissues and cells occurring on US territory. Recently the AATB board agreed to align with FDA's line not to impose an HTLV test for processed human tissues.

Directive 2006/17/EC requires that HTLV-I antibody testing is performed for donors living in, or originating from, high incidence areas, with sexual partners originating from those areas or where donor's parents originate from those areas.

The Regulatory Committee concluded that the Commission should request the assistance of ECDC to review the elements put forward by the AATB to justify suspending systematic testing for HTLV and to assess the possible risks of the change in HTLV testing for human tissues and cells imported from US into the EU.

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[4] Please see:
http://ec.europa.eu/health/archive/ph_threats/human_substance/documents/ev_20091019_mi_en.pdf

The UK informed the participants that it has decided to maintain its requirements for HTLV testing for tissues and cells imported from the US. The UK will have a technical meeting on the impact of this change in US testing requirements on import of tissues from the United States on 9 July 2010. The UK invited other Member States to pass on to them specific issues or questions they wish to raise at the meeting. The Commission asked to be kept informed on this issue.

Following this meeting and the delivery of the scientific opinion by the ECDC, the Commission will set up a small working group of volunteering Member States (the U.K, Italy and Germany (tbc) to discuss and elaborate on recommendations on how to best face this situation. In the meantime, the EU's requirements for HTLV apply.

6.4.2 Question concerning the processing of pancreatic islets in separate establishment during autologous transplantation within the same surgical procedure

The Human Tissue Authority in the UK raised a question in relation to an autologous and single surgical procedure of pancreatic islet transplantation, where the pancreas is removed, transported to a separate laboratory for processing and returned to the operating theatre where the pancreatic islets are transplanted back into the same patient. The patient remains in theatre the whole time while processing takes place.

The question raised was whether this procedure would be excluded from the scope of Directive 2004/23/EC according to its Article 2, and hence not covered by the requirements of this Directive. In addition, the meaning of the term "banking" in recital 8 was questioned in relation to the above mentioned surgical procedure.

In general, according to the provisions of Article 2(2) of Directive 2004/23/EC and as explained in its recital 8, tissues and cells used as an autologous graft, within the same surgical procedure and without being subjected to any banking process, are excluded from this Directive. However, due to the fact that the second premise, where the processing takes places, is completely separate in terms of management, governance systems and geographical location, the UK Human Tissue Authority expressed concerns over how the quality, safety and traceability of the cells could be assured in this case.

Germany informed the Committee that data available from a study suggest that pancreatic islet transplantations are very limited in number both in Germany and in the Union. The UK explained that the question relates to other similar treatments e.g. a pelvic sarcoma treatment where part of the pelvis is removed, transported to a different hospital where it is irradiated and then returned back to the patient. Poland suggested that the transport of the tissues from the operating room to the place of processing under certain conditions can be considered banking as referred to in recital 18 of Directive 2004/23/EC.

During the discussion the Regulatory Committee recognised that there are some particular elements related to this type of processes, notably their transport and processing in other establishments, with potential traceability and quality/safety considerations which may be different from a typical autologous graft /same surgical procedure.

It was agreed that the Commission will prepare an explanatory note with regard to the terms of "banking" and "same surgical procedure" to be discussed at the next Competent Authority meeting.

6.4.3 Cornea donation in relation to the 24-hour requirement for blood sampling

In a letter of 8 March 2010, the University Medical Centre of Freiburg (Germany) claimed that, due to the requirement for serological viral testing within 24 hours after the donor's death, the number of cornea donors in Lions cornea donation bank, Baden-Württemberg has dropped by 25% over a year. It is explained that often more than 24 hours are needed to fully explain a corneal donation to the deceased person's relatives. As a result, some deceased persons cannot be used as corneal donors because of the 24-hour requirement for blood sampling, even if the cornea can be removed up to 72 hours after death without a risk of metabolic damage. The University Medical Centre of Freiburg also claimed that transmission of HCV or HIV through corneal grafts is very limited.

Most of the Member State delegations informed that to date they had not encountered problems of increase in cornea loss because of the testing requirements in Article 4 and Annex II of Directive 2006/17/EC. In addition many delegations expressed the view that serological viral testing within 24 hours after donor's death is necessary and appropriate.

6.4.4 Follow up from last Competent Authority meeting on concepts of storage and distribution

During the meeting of Competent Authorities in October 2009, France asked for clarification on the need to accreditate/designate/authorise/license and therefore inspect storage for end-use repositories (in hospital or other health care establishments). The Commission explained the provisions relating to the terms of "transport", "storage" and "distribution" within the meaning and scope of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC.

Based on these provisions it can be concluded that:

- Distribution of tissues and cells is an operation to be carried out by the tissue establishment before human application and it is the last point in the chain regulated by the Tissues and Cells Directives.

- Storage of tissues and cells, being a step before distribution, is regulated by the Tissues and Cells Directives only when it is carried out by the tissue establishments before the transport and delivery to the organisations responsible for human application.

- Storage in organisations responsible for human application is not covered by the Tissues and Cells Directives.

- In any case, traceability of tissues and cells shall be ensured from the donor to the recipient (Art. 8 of Directive 2004/23/EC).

The Commission noted that, notwithstanding the above analysis and the exclusion of storage after distribution from the scope of the Tissues and Cells Directives, the objective of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC is according to recital 13 of Directive 2004/23/EC to: "*...establish standards for each one of the steps in the human tissues and cells application process*". Therefore, it is important to ensure safety and quality of tissues and cells notably in terms of storage conditions, traceability and effective recall procedures, also for this step which is not covered by Directives 2004/23/EC, 2006/17/EC and 2006/86/EC.

The safety and quality of tissues and cells during storage after distribution, which is not covered by the Directives, is therefore currently the responsibility of the Member States, who according to Article 4(2) of Directive 2004/23 can maintain or introduce more stringent measures on this matter.

This conclusion was accepted by the Regulatory Committee.

6.4.5 Question about whether heart valves would be considered to fall under the Tissues and Cells Directive

Norway raised the question about whether heart valves would be considered to fall under the Tissues and Cells Directive. The Commission clarified that heart valves fall under the Tissues and Cells Directive. The Regulatory Committee agreed.

6.5. Vigilance traceability and coding of human substances: status and next steps-

There is need for a European system for vigilance, traceability and coding. It was clarified that one central EU-coordination point is needed and that the Commission would therefore need to count on the support of an EU Agency.

The Commission provided the Regulatory Committee with information on the state of play of the steps towards involving ECDC or EMA in the vigilance activities under the Directives on blood and tissues/cells, in order to avoid any misunderstanding regarding the scope and objectives of this involvement. The Commission presented the needs at EU-level and the current understanding of pros and cons of EMA and ECDC for fulfilling a central role. This evaluation will be completed in the coming weeks and the possibilities and interest will be confirmed with both Agencies.

Several Member States agreed on the need for involving an EU agency and on the method pursued by the Commission. France expressed doubts on the competence and current mandate of the EU agencies. This view was supported by Germany. On the other hand several Member States expressed explicit support for the involvement of the ECDC.

The Commission will keep the Competent Authorities informed on further evolutions in the coming months.

Chair of the committee

Patricia Brunko