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

Meeting of the Competent Authorities for Tissues and Cells

20-21 June 2018

Summary Minutes

This meeting of the tissues and cells competent authorities (CA) took place on 20 and 21 June 2018. The previous meeting took place on 15 and 16 November 2017.

PARTICIPATION:

Competent authorities from all Member States (MS) were represented at the meeting, with the exception of Luxembourg and Cyprus. Candidate countries Albania, FYROM and Turkey also attended the meeting.

In addition, the competent authority from Norway, as well as representatives of the Consumer, Health and Food Executive Agency (CHAFEA), the European Centre for Disease Prevention and Control (ECDC) and the Council of Europe (EDQM) were present as observers. The European Medicines Agency (EMA) and the World Health Organisation (WHO) could not attend the meeting. Private experts attended for specific agenda topics, as detailed below.

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

1. WELCOME AND ADOPTION OF THE AGENDA

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

The agenda was adopted without modification.

Participants were invited to declare any conflicts of interest. None was declared.

It was noted that the Summary Minutes of the previous meeting had been approved by email and published on the DG SANTE website.

2. LEGAL MATTERS

2.1. Transposition of Tissue and Cells Directives

The Commission updated the group on the transposition of the EU tissues and cells legislation.

Since the previous meeting, one infringement proceeding relating to Directives 2004/23/EC and 2006/17/EC has been closed following the Commission assessment of amendments to the relevant national legislation. One referral to the Court has been made due to a lack of notification of transposition of Directive 2012/39/EU.

On the 2015 Directives on coding (Directive (EU) 2015/565) and import (Directive (EU) 2015/566), the Commission reported that 26 Member States had notified their transposition. For both Directives, one Member State has yet to notify and one Member State has partially notified transposition.

Infringement proceedings are on-going against both Member States and the Commission encouraged the competent authorities from those countries to liaise with their national colleagues responsible for transposition to ensure notification without further delay, and, if necessary, to communicate the reasons for any further delays or issues to the Commission.

2.2. Request for assessment of Danish non-partner donor testing protocol (ECDC)

Following the discussions in previous meetings on the requirements for testing of non-partner semen donors, ECDC assessed the risks associated with the donor testing protocol for non-partner donations currently being applied in Denmark.[1] The conclusions of the ECDC technical report suggest that the Danish protocol largely ensures an equivalent level of safety. However, under certain circumstances, i.e. when sperm donations are released by NAT for HIV, HBV and HCV, a minor increased risk of missing a window period infection remains (as it does for all tissues and cells released by NAT), which could be mitigated by restricting release for a specified period. In other respects, particularly if the delayed release by serological testing is implemented, the protocol could be considered as more stringent than the Directive requirement.

Following the request in the previous meeting to consult its Legal Service, the Commission reported back on its assessment of the Danish testing protocols for non-partner sperm donation and whether these are in line with the requirements of Directive 2006/17/EC. The Danish testing protocols differ slightly from those laid down in Directive 2006/17/EC, Annex III points 4.2 (amended in Directive 2012/39/EU of 26/11/2012) and 4.3 in terms of frequency of testing.. In particular, where regular donations are on-going, testing is carried out at three monthly intervals and not at the time of each donation and donations are quarantined for the serology window period (180 days).

Based on the conclusions of the ECDC technical report that the Danish serological testing protocol can be considered as safe as, or safer than, the protocol in Directive 2006/17/EC, the Commission concluded that the Danish protocol can be considered as a more stringent national requirement as permitted in Article 4 of Directive 2004/23/EC and article 168 (4)(a) of the Treaty. With regard to the Danish NAT testing protocol, the Commission concluded

[1] While the Directive calls for a donor test with every sperm donation, with a repetition after 180 days if NAT testing is not performed on the donation sample, Danish sperm banks apply a serological test before the first donation and then again every 90 days, with a quarantine period of 180 days followed by subsequent retesting of the donor. If the blood donation sample is subject to additional tests for HIV, HBV and HCV by NAT, retesting after 180 days can be omitted. Also sperm donors are questioned every three months regarding possible changes in relation to risk behaviour.

that this could also be considered as a more stringent national requirement provided that the Danish national legislation is changed in line with the recommendation of ECDC to defer release of the donated sperm until the longest diagnostic window period has lapsed. This would result, in line with the said recommendation, in the Danish NAT testing protocol as begin regarded as safer than the requirements of the Directive. The Danish CA thanked the Commission for this assessment and stated that they would recommend to the Ministry of Health to change the national legislation in this way and report back to the group on progress towards this goal.

Following questions from the group, ECDC confirmed that syphilis testing was not part of its technical assessment of the Danish protocols but is currently being separately assessed in a more general way, with regards to whether repeat testing for tissue and cell donors (after 180 days) is ever necessary. The findings of this assessment will be reported to the group in due course.

The Commission was also asked whether Member States should accept cross-border exchanges of Danish sperm that have been released on the basis of the Danish testing protocol. The Commission reminded the meeting that, as previously discussed in the group, the working interpretation is that, unless a Member State has its own more stringent requirements in place which warrant further assessment / control, or national restrictions on the donation or use of certain tissues and cells, it should accept cross-border exchanges of tissues and cells which have been authorised for distribution by another Member State. The Commission was also asked what Member States should do in the interim, until the Danish legislation is updated. The Commission replied that a Member State may choose to block the cross-border exchange of sperm tested under the current Danish NAT protocol. However, if the ECDC recommendation to defer release until after the longest diagnostic window period is in practice implemented, Member States should carefully consider the necessity of such action.

3. EVALUATION OF THE TISSUE AND CELL LEGISLATION

The Commission is evaluating the blood and the tissues and cells (BTC) legislation in line with the Commission's principles of Better Regulation.

The BTC evaluation was formally initiated in January 2017. An external contractor was engaged in April 2017 to work on a study to support evidence gathering and its work is ongoing. The Commission organised an open public consultation (OPC) and a stakeholder event has taken place[2] together with a series of bilateral and multilateral meetings with key stakeholders[3].

DG SANTE is preparing the final evaluation report (the Staff Working Document, SWD) with the aim to publish it towards the end of 2018 or early 2019. The authorities signalled an interest in closely following the process in 2019, i.e. after the publication of the Commission evaluation report.

[2] The roadmap, along with all other key information relating to the evaluation, is available on a dedicated DG SANTE web-page https://ec.europa.eu/health/blood_tissues_organs/policy/evaluation_en

[3] Minutes of meetings with stakeholders are published here https://ec.europa.eu/health/blood_tissues_organs/events_en#anchor4

3.1. Feedback from consultation activities

The Commission services presented the key messages coming from the OPC[4] and the various bilateral and multilateral meetings with stakeholders held since the last meeting of this group. The work on documenting the evidence on the relevance, effectiveness, efficiency, coherence and EU added value criteria was presented. Stakeholders have raised gaps, inadequacies or inconsistencies under each of the evaluation criteria but particularly under effectiveness and relevance.

The CA thanked the Commission services for the work done so far on the BTC Evaluation. In general, they support the key messages emerging. Some CAs argued that there are certain legal provisions included in the Directives that are too specific as they are prone to becoming easily outdated due to scientific and technological developments. However, other CAs suggested that if the regulatory provisions are too generic it will result in different implementation of the legislation, so a good balance is to be found and legislative reference to robust and regularly updated technical guidance was seen as a good solution. A CA commented that some topics (e.g. Voluntary Unpaid Donation) are sensitive ones and should take account of the legal mandate of the Commission if/when revising the existing BTC legislation.

The Commission noted that the observations of the CA were echoed in a number of submissions to the OPC. The authorities were invited to make a closer analysis of the key messages presented and to send any comments after the meeting.

The Commission services informed the participants about the recent meetings with stakeholders. These meetings were good opportunities to go into detail on the substance on the issues pertinent for the Evaluation of the BTC legislation. The Commission also highlighted that, in order to ensure transparency in the BTC Evaluation process, they publish the meeting minutes from the ad-hoc meeting with stakeholders and that these are being taken into account in the BTC evaluation.

3.2. Update on the Study by ICF

An external contractor, ICF Consulting Ltd., currently conducting an independent study supporting the Commission in the BTC evaluation, presented their results.

The contractor outlined the key messages emerging in their study. In general, the impact of the BTC legislation has been positive and provided added value. Issues that were brought forward frequently included the inflexible two-year inspection requirement, the absence of requirements for clinical follow up data as part of preparation process authorisation and the lack of provisions for donor protection and vigilance that were considered inadequate. The legislation was also considered insufficiently flexible to adapt to the many changes in the sectors. The messages presented mirrored those emerging from the stakeholder consultation activities conducted by the Commission.

The gaps in data identified by ICF were being filled through targeted interviews and organising of focus group meetings, as well as gathering input from the CA.

The Commission highlighted that this study constitutes part of the inputs that the Commission is gathering, which will be taken into consideration in the final Commission Evaluation Report.

[4] The report of the consultation is published on DG SANTE website https://ec.europa.eu/health/blood_tissues_organs/consultations/implementation_legislation_en

A final study report of ICF is envisaged for Q3 2018; it will be annexed to the Commission's final evaluation report.

3.3. Open discussion on evidence gaps

It was suggested that different standards have been introduced in the MS due to the lack of clarity in the legislation and the opportunity should be used to address this issue when possibly revising the legislation.

It was mentioned that the Directives had added value to the regulation of BTC by creating a responsible body in each MS, improving vigilance, traceability and implementing standardised inspection practices. The CA also appreciated that the legislation had been a trigger for strengthened collaboration among the MS in the field of BTC and expertise was being shared through these CA meetings and through EU-funded projects, both of which were seen as bringing significant EU added value.

ICF confirmed that there are indeed findings that the legislation facilitated sharing of best practices between CA, brought together CA and mutual learning was beneficial to improve the efficient implementation of the legislation.

The Commission invited the participants to share the first outputs from the ongoing BTC Evaluation (EU Blood, Tissues and Cells Legislation) with the relevant national, regional and local administrations. Outputs are available on the DG SANTE website.[5]

4. PRESENTATION OF ACTIONS UNDER THE PUBLIC HEALTH PROGRAMME

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

TRANSPOSE representative provided a short update on the project, a timeline and next steps.

The aim of the project is to issue risk-based Guidelines and a standard Donor History Questionnaire for the procedures followed for collection of substances of human origin. TRANSPOSE covers donation of blood, plasma, gametes, HSC and replacement tissues and addresses the selection of donors to ensure safety of the recipient, as well as safety of the donor.

The project leaders plan to organise meetings in September 2018 in Copenhagen to advance the work on Work Packages 4 and 5 (Inventory of Donor Selection and Protection Practices and Development of Donor selection and protection guidelines, respectively).

The Commission noted that donor protection is a very important point, also highlighted in the ongoing BTC evaluation, noting that it would be interested to have inputs to the evaluation. The Commission also mentioned that there is an open call for experts to support TRANSPOSE and suggested that the interested authorities should directly contact the project leaders.

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[5] Summary of the Stakeholder consultation on the BTC Evaluation; https://ec.europa.eu/health/blood_tissues_organs/consultations/implementation_legislation_en https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/2018_consultation_evaluationbtc_report_en.pdf

Summary of the Blood, Tissues and Cells Stakeholder Event of 20/9/2017: https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/ev_20170920_sr_en.pdf

The representative of TRANSPOSE suggested that in the next meeting more information on dissemination of the information of this project would be shared with the CA.

The work of the project can be followed online: https://www.transposeproject.eu/

4.2. Update on the Joint Action ARTHIQS - Good practices on donation, collection, testing, processing, storage and distribution of gametes for assisted reproductive technologies and of haematopoietic stem cells for transplantation

Agence de la Biomedicine (FR) gave a presentation on the ARTHIQS Joint Action. The 3-year Joint Action funded by the European Commission under the 2008-13 Health Programme, dealt with Assisted Reproductive Technologies and Haematopoietic Stem cells for transplantation and recently completed its technical tasks. The ARTHIQS consortium is gathered 16 partners and 9 collaborators from 18 different MS. The overall objective of this JA was to build a common, increased level of expertise amongst the CAs to organise oversight of the ART/IVF and HSC transplants fields.

An overview of the achievements and outputs of the JA was given. The inspection guidance for ART/IVF TE's and for cord blood banks was presented. ARTHIQS presented their ideas to consider creating a network of ART Competent Authorities in the future.

A presentation was also given by the CA that had taken the role of leader for the Evaluation work package in the Joint Action. It was highlighted that, for a period of time, the action had not been productive and progress was hampered by a number of issues, primarily poor communication. A reorganisation had resulted in a significant effort on the part of many partners and, finally, the consortium had succeeded in delivering useful tools of good quality.

EDQM commented that the cord blood banking inspection guides and other documents elaborated by ARTHIQS are appreciated; they will be used and disseminated.

The Commission thanked for all the work, expressed appreciation about the efforts put into this project, particularly in this final period.

All deliverables will be publicly available for the next 5 years[6] and CA were encouraged to make use of them.

4.3. Update on the Joint Action VISTART - Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation

The objectives of the Joint Action are to promote and facilitate harmonization of the inspection and vigilance systems for blood, tissues and cells as well as increasing Inter-Member State collaboration and confidence in each other's inspection, authorisation and vigilance programmes.

The VISTART Joint Action, due to be completed by October 2018, was presented to the meeting. The update on the ongoing JA covered the work to improve inspection systems across EU MS through guidelines, training, auditing and joint inspections of tissue and cell establishments. The main goals, milestones achieved and deliverables still to be developed were outlined.

The presentation particularly focused on sustainability and, in particular, how further training for inspectors can be provided after the end of the action, given the high level of need and Member State appreciation of the training courses provided in the Joint Action. A Common European SoHO inspection auditing programme (CESIP) will offer CAs/Inspectorates an opportunity to participate in a dedicated audit programme of inspection systems in Europe,

[6] http://www.arthiqs.eu/

providing opportunities for improvements in developed systems and identifying the needs for capacity building in developing systems. The planned joint inspections were announced. The next training of auditors for this programme was announced for September 2018 and calls for interest were requested.

The plans for ensuring sustainability of the voluntary CESIP audit programme was discussed. This sustainability discussion could also incorporate the sustainability of some deliverables of ARTHIQS, in particular inspections guidelines for cord blood banks and IVF clinics. In this context, many CA expressed an interest in the possibility to create an expert subgroup on inspection under the CASoHO Expert Group as a means to take forward the inspection work of VISTART in the future (i.e. inspector training, joint inspections, inspection system auditing, inspection guidelines updating). Some CA were interested to verify this within their MS. Possible topics of interest for a such group were for instance to act as a steering group i.e. put in place and implement a work programme, update guidance documentation and ensure the work is carried out and to disseminate results.

The Commission expressed openness about the potential creation of an inspection expert sub-group, analogous to the Vigilance Expert Sub-Group that is working well, and awaits a proposal by the relevant VISTART workgroup leaders. The Commission will bring this topic back to the next meeting of this group, and also to the meeting of the Blood Competent Authorities, as the proposal was that the possible Inspections Expert Sub-Group would be horizontal, working across blood, tissues and cells.

The presentation and discussion on the inspection work packages of VISTART was followed by a presentation on the other work packages. The meeting was updated regarding work on horizon scanning for ensuring adequate responses to new risks. The involvement of ECDC and other relevant professional associations was valuable for the survey conducted and the guidance under development. The first draft of the guidance will be due for sharing with the authorities in autumn 2018.

The work of the action has been extensive and is much appreciated by the Commission and the CA. It can be followed at https://vistart-ja.eu/.

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

EURO GTP II is a three-year year project that started in June 2016. It is led by the Blood and Tissue Bank of Barcelona and brings together 14 associated partners and 13 collaborating partners, amongst them tissue establishments, CA, universities, scientific associations and the Council of Europe's EDQM.

EUROGTP II focuses on establishing good practices with regard to preparation processes and procedures for patient follow-up from the perspective of the professionals working in the fields concerned. This project links to topics that are also covered by other EU-funded initiatives (Joint Action VISTART and the new Joint Action GAPP) and are relevant for CA who authorise preparation processes.

A state of play of EUROGTP II was presented including work on a guide on Good practices for demonstrating safety and quality through recipient follow-up, an interactive assessment tool to determine the extent of studies and follow up programs needed to implement, evaluate and authorise a novel tissue or cell product, process or therapy and a tissue and cell compendium on tissues and cells, products, processes, therapies, authorization status and bio-vigilance data.

The CA expressed an appreciation for the work done by EURO GTP II. The work of the project can be followed at www.goodtissuepractices.eu.

4.5. Facilitating the Authorisation of Preparation Process for blood and tissues and cells (GAPP)

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

GAPP focuses on developing common approaches for preparation process authorisation frameworks, with sharing of information on authorisation decisions across Member States. Particular attention will be paid to innovative processes. Currently, the EU legislative requirements on tissues and cells for the authorisation of preparation process are very generic and implemented very differently in Member States for tissues and cells; they are even less well defined for blood.

The CAs were provided with an overview of the activities that aim to develop common and optimal approaches to assessing and authorising preparation processes, devoting particular attention to new innovative processes under development in these sectors. This included a presentation of the work plan, the project deliverables, milestones, next steps and the feedback from the kick-off meeting in June 2018 in Rome.

GAPP is expected to produce results that will have a positive impact on the way that blood, tissue and cell preparation processes are authorised and how information on these authorisations is shared between MS for greater efficiency and a more harmonised approach, with improved patient access to newly developed blood, tissues and cells.

EDQM mentioned that in the upcoming revision of the Tissue and Cells guide, inputs would be taken from Vistart, GAPP and EURO GTP II in a new chapter dedicated to the development of new tissue and cell processes/products. It added that there is a need to agree and to harmonise terminology and the relevant stakeholders should be involved.

The work will incorporate the outputs of other EU-funded actions including VISTART, EuroGTP II and ECCTR. By providing tools and training to increase the harmonisation of those MS activities that regulate the areas of blood transfusion, transplantation of tissues and cells and ART, the Joint Action will contribute to a common implementation of Union legislation in tissues, cells and blood.

5. DIGITAL DATA in SoHO

The Commission briefly presented the Commission Communication on Digital Health and Care. Then it gave feedback from a SoHO registry meeting organised by the Commission Services in January 2018. Finally, it presented an initiative on Real World Data. The objective was to raise awareness of these initiatives, and their possible future role in the work of the authorities.

First, the Commission noted that Commission Communication on Digital Health and Care (DIGICARE)[7], adopted on 25 April 2018, has an objective to increase the availability of data

[7] *https://ec.europa.eu/digital-single-market/news-redirect/624248*
https://ec.europa.eu/digital-single-market/en/news/staff-working-document-enabling-digital-transformation-health-and-care-digital-single-market

in the EU to improve healthcare and clinical research. DIGICARE is based on three pillars: i) use digital services for citizen empowerment and person-centred care, (ii) connect and share health data for research, faster diagnosis and better health outcomes and (iii) give citizens better access to their health data in the EU.

Secondly, the Commission debriefed participants on a meeting it had organised with 10 registries in the SoHO field on 29-30 January 2018, mainly covering organs and tissues and cells. Several of the registries are organised by professional associations that collect long-term clinical follow-up data from and for professionals in order to improve clinical outcomes. A key challenge these registries face in common was the application of the new EU Regulation on data protection (GDPR). Commission experts on this regulation were available for questions and answers. Other topics of common concern were data quality and standards, governance, sustainability and funding. The meeting included an exchange of information and views with other Commission-related programmes on health data, including the Innovative Medicines Initiative, DG Research and DG CNECT. This highlighted the topic of possible interest from different authorities (e.g. pharmaceutical, SoHO, health technology assessment) to use registry data in a manner secondary to its original purpose. In this context, registry data might support decision-making processes related to authorisations, vigilance and cost/benefit assessments.

Finally, the Commission raised awareness of the initiatives of the Commission on Real World data (RWD) and their possible future role and support for work in the SoHO field. In general, RWD is any type of health related data not collected in randomised controlled trials but derived from a diverse population in real life settings. The sources might be diverse and include extension of clinical trials, medical health records and health insurance databases, but in particular registries with clinical follow-up data, which are historically quite well established in the transplant sector, compared to other sectors of medicine. Together with the SoHO authorities, several groups of other health authorities (pharmaceuticals (EMA/medicines agencies, HTA) are also looking into the possible use of RWD. The Commission is therefore reflecting on how to streamline these different data needs for authorities, and how to support (clinical societies with) clinical registries to provide these data. The SoHO sector will be involved mainly through the GAPP Joint Action (Work package 8).

The participants were invited to share their experience in collecting and using RWD and if, in their view, there were specific areas (e.g. therapeutic) on which collaboration at EU level would best focus first, allowing to demonstrate the benefit of the use of RWD for different purposes. Some questions were to be shared with the participants after this meeting. Participants expressed interest in developments on RWD and possibilities to further support registries in the SoHO sector.

6. COMMISSION'S STRUCTURAL REFORM SUPPORT SERVICE (SRSS)

The Commission presented the SRSS (Structural reform support service). SRSS is a recently launched Commission service with a mandate to support MS with the preparation, design, and implementation of growth-enhancing reforms, provide tailor-made support on the ground and coordinate technical support provided by the Commission. One of the policy areas of SRSS support includes reform of Healthcare systems.

Under the SRSS programme[8], the Competent Authorities/ national health administration might consider applying for technical support (e.g. for joint inspections, exchange visits or training). It was noted that applications must be made in response to a call in October of each year; that the application process can be supported by a dialogue with the relevant SRSS Commission service and that it was important that any application is highlighted by the MS concerned as a priority area. Applications must come via the national contact point for SRSS and might be filtered at a national level. The list of responsible national organisations had been provided to the meeting participants in CircaBC.

Participants expressed interest in possibilities for supporting national transplant and transfusion services and oversight frameworks through the SRSS.

7. FEEDBACK FROM EDQM MEETING ON TISSUE AND CELL ACTIVITY DATA REPORTING

EDQM gave feedback from a meeting on Tissue and Cell activity data reporting organised on 22-23 March 2018 jointly by EDQM and DG Sante, in the context of the direct grant from the EC to EDQM for SoHO work.

The objective of the meeting was to review the various activity data collection activities that are ongoing in the EU (SARE denominators, Eurocet and a number of professional association exercises – all collecting data on donations, number of donation processed, transplanted, imported etc.) and to consider where there are gaps, inconsistencies or duplication. The long term overall aim would be to have a single reliable and consistent reporting of a subset of key data that could be used as denominators for SARE and for transparency to citizens. These would be used by all those collecting data and would be enhanced by professional societies and authorities that need more detail for other purposes such as research and policy development.

The outputs from the meeting were important for the BTC Evaluation as it is generally considered that a certain amount of data reporting should be mandatory in the Directives and that data should be collected once but used often as a general principle. A full report of the meeting will be shared with the CA once agreed by the participants.

8. UPDATE ON IMPLEMENTATION OF CODING AND IMPORT LEGISLATION

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

There are around 3900 tissue establishments in the compendium, with the activities and authorisation status shown. Around 60 national and 30 regional authorities have been registered in the coding platform and are responsible for updating the information contained there.

In 2018, The Commission introduced new EUTC codes for membrane, facia rectus and umbilical cord tissue.

[8] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2017.129.01.0001.01.ENG
https://ec.europa.eu/info/departments/structural-reform-support-service_en

To clarify accumulating implementation questions brought forward by the CA on the implementation of the Single European Code, the Commission plans to organise a dedicated meeting of the Coding Expert Sub-group on 3 October 2018.

Conclusions from the previous meetings of the expert sub-group have been published and are available at DG SANTE website.[9]

9. SURVEILLANCE AND VIGILANCE

9.1. Epidemiological – general update (ECDC)

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

In spring 2018, an Ebola virus outbreak was declared by Congo. There were 66 cases of Ebola virus disease reported in the country, including 28 deaths. An ECDC technical report assessing the risk of Ebola virus disease transmission through substances of human origin was published in October 2014. This was the ninth outbreak of Ebola virus disease over the last four decades in the country. It was noted that, given the experience of the previous outbreak in West Africa where an infected UK health care professional had a relapse after an extended period of recovery, the UK now permanently excludes anyone who has been infected with the virus; FDA guidance has the same policy. The suitability of donors who have been vaccinated for Ebola virus is under discussion.

ECDC also informed the meeting regarding autochthonous cases of dengue in Reunion (FR) where there had been over 4 thousand reported cases by June 2018. The main vector of infection implicated in the outbreak was *Aedes albopictus.* In March 2018, the authorities in the country raised the emergency level and put in place control activities including enhanced surveillance, blood safety measures and measures related to social mobilisation.

The representative also gave a feedback on a West-Nile Virus (WNV) expert meeting held by ECDC on 15-16 March 2018. The meeting was attended by CAs from 11 Member States, the European Blood Alliance and other stakeholders. In the meeting, it was concluded that blood transfusion services and public health authorities in Usutu Virus (USUV) endemic areas should be aware of a potential increase in human USUV infections and of the possibility of USUV cross reactivity with WNV in tests. This phenomenon might give misleading data concerning the spread of WNV. The experts confirmed that EDCD maps with human WNV cases were very helpful for identifying WNV affected areas. It was also concluded that surveying infection in horses is probably not a useful indicator for identifying risk areas for blood donation. It was noted that MS are using different criteria for the initiation of measures in affected areas: most follow the ECDC criteria but at least one uses infection rates in mosquitoes and others apply measures on pre-fixed dates associated with seasonal risk.

DE[10] informed the group that they intend to establish a database defining endemic areas leading to the deferral of blood donors. Epidemiological data from CDC, ECDC, and WHO will beused. The database will be continuously updated and expanded as new significant pathogens emerge. It was noted that other MS also have nationally developed maps or lists of areas associated with these risks. The Commission suggested that the CA share any info on existing/planned publicly accessible platforms/tools indicating geographical areas affected by particular infectious risks.

[9] https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/sec_qa_en.pdf
[10] Paul-Ehrlich-Institut

Other – Member State update

No Member State had specific national surveillance information to report.

9.2. Rapid alerts

9.2.1. General overview

The Commission informed the participants that by June 2018, a number of epidemiological, Q&S, information notices, bilateral enquiries and illegal/fraud cases had been reported via the platform. Although the number of rapid alerts for tissues and cells (RATC) reported each year has decreased in 2013-2017, the reports are important with 23 uploaded for tissues and cells in the first half of 2018. These alerts include an info notice, two inquiries, 19 Q&S and other alerts.

As the number of alerts (23) for the first half of 2018 is similar to the total number of alerts submitted in 2017, it can be anticipated that 2018 will see an increase in alerts compared to previous years.

The Commission informed the participants that a meeting with the Data Protection Officer at DG SANTE had been held to discuss the impact of the new GDPR on the rapid alert and the coding T&C platforms. A few changes in the RATC disclaimers and an update of the DPO notification on the application are needed and will be implemented by end of 2018.

A link between RATC and the EU Coding Platform for Tissues and Cells is planned to be technically established by the DG SANTE. The Commission noted that for the first time the 2017 RAB and RATC activities were summarised in one single report for publication[11].

9.2.2. Danish alerts regarding permanently blocked sperm

DK gave a presentation on rapid alerts by Denmark. The DK authority issues rapid alerts in the RATC system on gamete donors being permanently blocked following the identification of potentially serious genetic disease or hereditary genes for such diseases in a donor. DK reported regarding a recent recommendation from the 'Over-implementation Board',under the Danish Ministry of Employment to the Government Committee on Over-Implementation indicating that the CA should not issue alerts to other EU MS when a child with a genetic condition has been born from a particular sperm donor and sperm from that donor, potentially or certainly carrying the responsible gene, has been distributed to other EU MS.

The CA were unanimously supportive of DK in their efforts to use the RATC platform to share information of this kind rapidly. The representatives considered that transmission of genetic diseases should indeed be seen as 'serious adverse reactions' and that this kind of communication is important for patient safety and that the practice should not be changed. The representatives also noted that the RATC platform is an effective way for such a rapid communication among the MS authorities.

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11 https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/2017_ra_soho_summary_en.pdf

The Commission reminded the participants that in the current 2004 legal framework, genetic transmissions to children from gamete donors are not explicitly mentioned, but that this issue had been raised in the evaluation exercise as a sector development on which EU legislation needs to be aligned for clarity. It was also noted that the Public Health Programme funded project, SoHO V&S, identified a genetic transmission from a gamete donor to the child born as a reportable adverse reaction. Consequently, genetic transmissions are incorporated in the Commissions Common Approach document that gives guidance on how to complete the annual reports on serious adverse events and reactions (SARE) and in the Commission's online template for SARE report submission. In the most recently published Commission Summary of Reported Serious Adverse Reactions and Events for Tissues and Cells (published in 2017[12]), more than 30% of serious adverse reactions for reproductive tissues and cells, reported by 11 MS, were genetic transmissions. It was noted also that the EDQM Guide to the quality and safety of Tissues and Cells for human application makes it clear that genetic transmission in these circumstances should be considered as an adverse reaction.

The representative from one MS confirmed that, in their national legislation, a genetic transmission from a gamete donor to the child born is considered as a reportable adverse reaction and many others noted that, while this is not explicitly stated in their legislation, it is understood implicitly.

9.3. SARE

9.3.1. SARE reporting – preliminary data from 2017 exercise (2016 data)

The Council of Europe (EDQM) debriefed the participants on the preliminary analysis of the 2017 SARE reporting exercise for Tissues and Cells. The numbers and types of SAR and SAE reported were presented, along with denominators and the EDQM team highlighted areas where improvements could be made. A total of 767 serious adverse events (SAE) and 221 serious adverse reactions (SAR) were reported to have occurred in 2016. Importantly, SAR in non-reproductive TC transplantation led to six recipient deaths and, in reproductive TC application in ART, to one recipient death. It was noted, however, that improvements are proposed to enhance the assessment and reporting of imputability for these cases, as many are likely not to be associated with a quality or safety defect in the tissues or cells.

The data collection has gradually improved with 25 countries who have reported. However, EDQM noted that some countries still do not report any SAE or SAR and do not report all denominators. EDQM stressed that, in their submissions, MS must differentiate between "0" and "N/A" (not available) when reporting. In conclusion, SARE reporting is improving but continues to be subject to inconsistencies and heterogeneity.

The SARE report for the 2017 exercise will be shared with CA for comments before publication. The Commission thanked EDQM for the professional and timely way they have carried out this work.

9.3.2. Update from the Vigilance Expert Subgroup

A sub-group to this expert group (CASoHO E01718) working on vigilance across blood, tissues and cells was established in 2017 with the aim of reviewing and improving the Commission's vigilance related activities, particularly the SARE and rapid alerts programmes.

[12] https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/2016_sare_tc_summary_en.pdf

The Commission gave an update on the work carried out by the sub-group. In general, the sub-group considers that informative annual summary reports are being issued by the Commission, including SARE and denominators, but that more can be gained from the data collection exercises with the implementation of various improvements to the reporting templates and their associated instructions for compilation (the Common Approach documents).

The areas where the sub-group might focus on to improve the quality and usefulness of the exercise are the following: SAR definitions and categories, SAR denominators, Reporting of recipient deaths, SAR reporting criteria, Severity Assessment SAR, Imputability Assessment SAR, SAR in donors, SAE definitions and categories, SAE denominators, SAE reporting criteria.

Several proposals ('quick fixes') for implementation in the 2018 reporting exercise (2017 data) were proposed and had already been incorporated in the exercise. The expert sub-group considers that improving reporting of SAR in donors is a priority and, consequently, a list of donor reaction types had been included in the 2018 exercise for blood donation, although those MS that cannot provide donor SAR broken down in this way will still be able to provide just a total number. It is hoped that a similar list might be developed for tissue and cell donors for the 2019 exercise.

A further list of improvements that require more analysis and development will be the focus of the sub-group's work during 2018. A list of remaining issues for improvement will need legislative change.

The Commission expressed appreciation to the expert sub-group for taking forward this important work and concluded that improvements in reporting are an on-going process that will require time.

It was announced that a meeting of this expert sub-group is planned for autumn 2018.

9.3.3 Launch of 2018 exercise (2017 data)

The Commission reminded all participants that the new SARE reporting exercise had been launched in March 2018 with a deadline for submission of July 16th 2018.

The Commission highlighted the need for Member States to submit their country reports on time, stressing that prolongation of the deadline would no longer be possible due to the new contractual arrangement with EDQM.

The MS were invited to carefully consider the SARE Common Approach document and pay special attention to the changes in the reporting template. Some changes have been introduced in the reporting template including more specifications for the SAR/SAE non-reproductive TC, fungal infection in SAR type added, oocytes removed from the SAR/SAE Reproductive, more specifications for the SAR/SAE reproductive Embryos, new SAE encoding table and donor selection added to the list of activity phase.

The Commission highlighted that complying with the new approach is a work in progress that can be adapted gradually.

9.3.4. Update on corneal endophthalmitis clusters (DK)

Denmark gave an update on this topic having collaborated with the CA in the other affected MS. In 2017, the European Eye Bank Association (EEBA) observed several clusters of fungal endophthalmitis associated with the transplantation of corneas and the largest of these had

been reported in the EU SARE reporting exercise; all had involved corneas imported from the United States. In 2018 several CA for TC (UK, DK, DE and IE) coordinated a preliminary investigation. The initial information highlighted eight cases in the UK, four in DK and three in DE. The data indicated that the corneas had been sourced from the US from two different eye banks. An earlier investigation by FDA in the US indicated an increase in fungal contamination had been linked to the warming of the corneas for laser cutting. It was considered that the contamination might have been associated with the laser cutting of the corneas in an eye bank in the EU before supply to the clinics.

Investigations of the clusters in the UK and DK have not yet found a common root cause and it had been confirmed that, in the UK at least, laser cutting had not been carried out on the implicated corneas. Useful data on the extent of fungal endophthalmitis is presented at project NOTIFY and in the literature.

This case highlighted the value of sharing information between MS and demonstrated that good communication with the US has also been very valuable.

The authorities discussed among themselves whether the RATC platform could have been used for this (although there were clusters of transmissions in Member States – all involving imported corneas – no RATC was uploaded). A RATC might have allowed earlier identification and investigation of the problem.

Further to a suggestion from a MS, Germany (PEI) plans to verify a standard protocol on the detection of fungi, addressing potential inhibition by antimycotics/antibiotics, and to share it with other authorities.

10. INTERNATIONAL DEVELOPMENTS

10.1. Council of Europe update

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

In the context of the Commission Evaluation of the BTC legislation, EDQM noted that the EU directives on TC are effective in helping to unify standards across MS. However, technical standards as set out in the directives cannot keep pace with ongoing scientific, medical and technological advances. This requires technical guidance that is regularly updated such as the guides published by EDQM. The representative drew attention to the publicly available inputs to the OPC consultation, which suggest that there should be a cross reference to quality criteria developed by expert bodies, such as the EDQM, included in the legislation.

EDQM reported that the drafting of the newest edition of the guide has started. A lot of attention will be paid to the new version of the Guide, with some significant modifications in particular on a new section providing Good Practice Guidelines (GPG) equivalent to those published in the Blood Guide and referenced in recently revised EU blood legislation. It is considered that the Tissue and Cell GPG will be a very useful tool for inspectors, as they will define generic requirements (similar to GMP in pharmaceutical manufacture) with which establishments should always comply. The Commission noted that it supports the work and the development of the GPG section for tissues and cells, following the successful equivalent development for blood. A series of tissue and cell monographs is also under development and was seen as a very interesting initiative that could link well with the ongoing work on preparation process authorisation, particularly the GAPP Joint Action. A CA added that it will

be important to ensure consistency in guidance developed on preparation process authorisation as it is developed by Vistart, EURO GTPII, GAPP and the EDQM guide.

The CA were reminded about the latest edition of the Tissues and Cells Guide published in July 2017. The guide is available at the EDQM website[13] where it can be downloaded free of charge. The finalisation of the new edition and its publication are envisaged for autumn 2019. On the frequency of the revision of the guide, a CA noted that the guide might be revised less frequently. Other CA did not comment on this point.

EDQM then summarised other activities of relevance to this meeting, including Council of Europe Guide to the implementation of the principle of financial gain published in March 2018[14]. This document gives guidance on how to interpret the principle of the prohibition of financial gain with respect to the human body and its parts from living or deceased donors.

EDQM highlighted ongoing projects in the field of TC including a layperson's brochure on oocyte donation that will be soon published. Other on-going projects include a preparatory study on trafficking of human tissues and cells and donor protection for tissue and cell donors.

10.2. World Health Organisation

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

11. ANY OTHER BUSINESS

The Commission gave a short presentation on the improved DG SANTE SoHO website[15].

12. CONCLUSIONS OF THE MEETING

The Chair thanked the group for their active participation in the meeting and informed them that the next meeting of the tissues and cells competent authorities is planned for Q1 2019. [Note: date tbc].

[13] https://register.edqm.eu/freepub
[14] https://rm.coe.int/guide-ginancial-gain/16807bfc9a
[15] https://ec.europa.eu/health/blood_tissues_organs/blood_en