EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical Products: quality, safety, innovation

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

Meeting of the Competent Authorities on Blood and Blood Components

11-12 November 2015

Summary Minutes

PARTICIPATION:

Competent Authorities from all Member States were present at the meeting of the competent authorities (CAs) on blood and blood components on 11th and 12th November 2015. Norway and Turkey, as well as the European Directorate for the Quality of Medicines and HealthCare of the Council of Europe (EDQM – CoE), the European Medicines Agency (EMA) and the World Health Organization (WHO) also attended the meeting.

Chairman: Mr D. SCHNICHELS (SANTE)

Commission: Mr S. VAN DER SPIEGEL, Mr R. MCGEEHAN, Mr P. CATALANI, Ms I SISKA, Ms H. LE BORGNE, Ms J. SANDBERG, Ms D. FEHILY.

1 CONFLICTS OF INTEREST

No conflicts of interest were declared.

2 ADOPTION OF THE AGENDA

The agenda was adopted without any changes.

3 REGULATORY MATTERS: POINTS FOR INFORMATION

3.1 Infringement proceedings

The Commission informed the meeting that it is likely that there will be a referral to court for one MS that the Commission considers has not yet fully transposed the blood legislation.

3.2 Report on the implementation of the EU Blood Directives (Article 26 of the Directive 2002/98/EC)

3.3 Report on the promotion of voluntary unpaid donations (Article 12.2 of Directive 2002/98/EC)

The Commission informed the meeting that these two reports are still in internal consultation. It is expected that they will be finalized soon. Before they are published, this group will be asked to verify their own Member State data.

3.4 Mapping of More Stringent National Requirements – preliminary feedback

The Commission provided early feedback on the results of a survey aimed at mapping more stringent national requirements or recommendations. This first survey focused on donor testing requirements and will be followed at a later time by a survey of other more stringent requirements. The verified results will be made public on the Commission website. The participants were thanked for their participation in the survey which includes responses from all Member States. Final clarifications with a small number of authorities are ongoing.

The results are presented as an overview sheet for all Member States combined and individual country fact sheets. The most frequently reported additional requirements (legally binding) or national level recommendations are for NAT testing for HIV and hepatitis and for blood grouping.

Participants expressed support for the exercise and saw several possibilities for use. They also indicated the need for an interpretation in an epidemiological context. Participants were informed that the deadline for clarifications of their data was the end of November (November 30th) 2015. The group suggested that the data should be updated with any changes annually. The Commission agreed that the publication of the data should be accompanied by an explanatory introductory text.

3.5 Good practice guidelines for elements of the quality system

The Commission had reflected on how best to refer to the guidelines developed jointly with the Council of Europe (EDQM). The options were to either publish the guidelines in full, in a Commission Decision or as an Annex to a Decision or other legal instrument, and then publish updated versions every time the guidelines are updated, or to amend Article 2.2 of Directive 2005/62/EC, making specific reference to the jointly developed guidelines as published by the Council of Europe. The latter option was considered preferable by the Commission and this approach was strongly supported by the meeting participants. The Commission will continue internal discussions, particularly with its Legal Service, to take this forward. Any proposal to amend Directive 2005/62/EC will need to be approved by the Regulatory Committee on the Quality and Safety of Blood.

3.6 Court cases, parliamentary questions and complaints

The Commission provided a summary of the ECJ ruling on Case C-528/13 (Leger) concerning deferral from donation of Men having Sex with Men (MSM). The preliminary ruling was given on 29.4.2015 and concluded that the French decree is liable to discriminate against homosexuals on grounds of sexual orientation, breaching the EU Charter of Fundamental Rights. Such a breach would need to be justified and proportionate with the objective of achieving a high level of human health protection.

When invoking a permanent deferral on grounds of sexual behaviour, MS need to consider:

- For any given person or group, has a high risk of acquiring severe infectious diseases transmitted by blood been established based on the latest national epidemiological situation?
- Would such a permanent deferral be in line with fundamental rights, i.e. principle of non-discrimination?
- Would any breach of fundamental rights be justified (on public health grounds)?
- Would any breach of fundamental rights be proportionate, i.e. based on the latest scientific / medical evidence, are there any less onerous methods (than a permanent deferral) that could be used to achieve the same goal?

It is now for the French Court to provide a final ruling based on the specific national situation, taking these considerations into account.

The French CA representative confirmed that, in the meantime, an announcement has been made on a planned change to the national rules moving from a permanent to temporary deferral for MSM. The representative stated that FR does not want to discriminate based on sexual orientation. A new article in French law will state that nobody can be excluded from blood donation due to sexual orientation. Following an evaluation of the risk of HIV transmission by blood transfusion, the new law will introduce a deferral period of one year since the last sexual contact. This can be reduced to 4 months for the donation of plasma for quarantine secured plasma. These changes do not affect the donation of plasma for the manufacture of medicinal products.

The Commission also reported having responded to a number of parliamentary questions on the deferral criteria of men having sex with men, along with a question on the regulation of plasma and one on blood donation by minors. Written complaints in relation to plasma procurement and contract manufacturing are also being addressed by the Commission.

4. PRESENTATION OF KEY INTERPRETATION IUSSUES AND DISCUSSION

4.1 Deferral criteria for sexual risk behaviours

At the previous meeting of the group, it was agreed that the Commission would circulate a short questionnaire to update their overview of deferral criteria for sexual risk behaviours in the EU. Twenty-seven Member States and Lithuania and Norway participated in the survey. More than half of the replies indicated the application of a permanent deferral for men having sex with men. A smaller number apply a temporary (12 month) deferral and seven countries conduct individual donor risk assessments. A number of other risk reduction strategies were described, including education of blood collection personnel, of the general public and of the gay community specifically and the use of questionnaires with detailed questions regarding sexual behaviours that incur risk for disease transmission. The Council of Europe announced the establishment of a working group on this topic.

4.2 Lymphocyte immunotherapy (LIT)

The Commission provided feedback on discussions arising from an interpretation question on the regulation of LIT used to treat recurrent miscarriage in pregnant woman. The question

concerned cases where lymphocytes are separated from whole blood collected from the partner of a woman being treated in an IVF clinic and used to treat the woman with the objective of reducing the risk of miscarriage. Although blood is collected, the treatment is carried out in the context of assisted reproduction, a field regulated by the tissues and cells legislation.

Following the agreement to seek advice from its Legal Service, the Commission informed the group that its Legal Service was consulted on three issues: whether withdrawal of whole blood leading to extraction of lymphocytes falls within the scope of blood or tissues and cells legislation, whether Member States may choose to regulate this activity under either their national blood or tissues and cells legislation and finally whether within a Member State, its authorities have the discretion to regulate the activity under both their national blood and tissues and cells legislation.

The Commission reminded the group that only the European Court of Justice can give legally binding interpretations of Union legislation. After careful analysis of the situation put forward and the relevant legislation, the Commission put forward its working interpretation for the group's consideration. It was felt that justifiable arguments could be made for this activity falling under either the blood or tissues and cells legislation. This being the case, based on the specific nature of their national circumstances (assessment of risks to human health / desired level of human health protection / the existence of more stringent protective measures etc…), and given the fact that LIT is typically a local activity not involving cross-border steps, Member States benefit from a certain degree of discretion when deciding whether to classify this activity under either blood or tissues and cells legislation.

On the final point the Commission reminded the group of the importance of maintaining legal certainty within any given national legislative framework but did not exclude the possibility that in this specific case authorities within one Member State could allow the same activity to be governed under both sets of legislation, depending on the establishment which performs it, provided that this is justified by an assessment of the risks to human health and the desired level of protection specific to that Member State focusing in particular on largely equivalent levels of quality and safety assured under both sets of national legislation.

5. PRESENTATION OF EU FUNDED ACTIVITIES

5.1 VISTART: Joint action on blood and tissues and cells

The new Joint Action had its kick-off meeting in October 2015 and will last for 3 years. The action is led by Italy (jointly by the blood and tissue & cell competent authorities) who presented it at this meeting. The scope is broad, addressing a legal framework that includes 7 European directives on blood and blood components, tissues and cells. The key objectives are:

- to promote and facilitate the harmonisation of inspection, authorisation and vigilance systems for blood, tissues and cells, and
- to increase inter-MS collaboration and confidence in each other's inspection and vigilance programmes.

There are 7 technical work packages that will address the following topics:

- Vigilance reporting for blood, tissues and cells

- International collaboration for vigilance communication (collaboration with the WHO NOTIFY project) and preparation process development authorisation
- Inspection guidelines for blood, tissue and cells Competent Authorities
- Training of blood, tissues, cells and ART inspectors with sharing of expertise across Member States
- Establishment of a framework for joint inspections
- A voluntary programme of Inter-MS Inspection Auditing
- Implementation of the Single European Coding system in tissue establishments

The project co-ordinators will regularly update the Competent Authorities on the activities and outcomes of the action.

5.2 Patient Blood Management Service Contract

The Commission presented a short update on this service contract on behalf of the contractor. The contractor will present the outcomes of the work in full at the next meeting of Competent Authorities, at which time the contract will be completed. Guidance on the implementation of PBM is in draft and will be shared with the Competent Authorities. Pilot PBM programmes at 5 hospitals in 5 different countries are ongoing. Challenges related to gathering the required data to enable effective PBM have been largely overcome. The work has been presented to the Commission's Expert Group on Patient Safety in September 2015 where the Member State representatives were positive and supported the initiative. During discussion of the work, it was noted that dissemination needs to be carried out in a balanced way to ensure that the risks associated with blood transfusion are not exaggerated in communications with the general public. Further information can be found at the website: www.europe-pbm.eu.

5.3 EU SoHO activities in neighbouring countries

The Commission informed the group regarding ongoing work in the field of SoHO in countries neighbouring the EU. This work includes assistance in countries aiming for EU accession: Albania, former Yugoslav Republic of Macedonia, Serbia, Montenegro and Turkey, where the focus is on achieving full compliance with the Acquis by the time of accession and on preparation to implement the Acquis and cooperate with the EU. There is also cooperation with 11 other neighbourhood countries on the basis of the European Neighbourhood Policy (ENP) and in particular the Association Agreements signed by the EU and Eastern neighbours (Ukraine, Moldova, Georgia).

In both enlargement and ENP countries, the work includes assessment missions, technical assessment reports, action plans follow-up on EU recommendations, and financial tools to support cooperation (TAIEX, Twinning, Instrument for Pre-Accession Funding, European Neighbourhood Policy Instrument). Activities in the SoHO sector carried out in recent years included events in Serbia, Montenegro, Israel, Turkey, Croatia and Ukraine. The Commission called on the Competent Authorities to encourage experts from the field, or from the Competent Authorities themselves, to participate as trainers in TAIEX workshops and as experts in Assessment missions, to host study visits from experts from EU enlargement and ENP countries and to register on the TAIEX expert database.

6 SURVEILLANCE AND VIGILANCE: UPDATE ON INFECTIOUS DISEASES RISKS

6.1 ECDC update

An update was provided of current infectious threats. The West Nile virus season started later this year and is still active, but at a lower level than last year. There have been 100 cases in EU countries (as of Nov 5th 2015) and 142 cases in neighbouring countries (as of the same date).

Middle East Respiratory Syndrome coronavirus (MERS CoV) continues to be an issue for many countries in the Middle East with 1,637 cases (632 deaths) reported between April 2012 – 5. Nov 2015. The source remains unknown although dromedary camels are the most likely reservoir of infection.

Regarding the Ebola Virus Epidemic, it was noted that one new case was reported in Guinea at the beginning of November. On the 3rd of November, the WHO reported a total of 28,581 cases of Ebola including 11,299 deaths during this epidemic. Following the relapse of recovered nurse, it was noted that persons who recovered should be deferred from donation for 1 year.

Chikungunya monitoring continues at a global level but no autochthonous cases have been reported in the EU in 2015.

ECDC is conducting a rapid assessment on the risk of communicable disease outbreaks among asylum seekers. The main problem to date has been Typhoid fever where some cases are being further investigated.

ECDC also provided preliminary results of a priority setting exercise for an assessment they will conduct on the transmission of bacteria by SoHO. This topic was selected as it is the most common type of infectious transmission reported in the EU. A risk model was presented that will be applied to a list of bacteria for each SoHO category. These lists were constructed

by an Expert Group that reviewed scientific literature and vigilance reports. In the first year (2016) the top 5 bacteria from each list will be assessed. Participants were invited to compare the presented list of priorities with their national experience and provide feedback.

6.2 Hepatitis E – survey feedback

The Commission presented the results of a short e-mail survey carried out in August to which all Member States, and Lichtenstein and Norway had responded. While mandatory testing is uncommon, a number of Member States are gathering information on prevalence and considering whether testing or pathogen inactivation should be introduced, at least for certain recipient groups. In FR, since the beginning of 2015, 20% of the blood supply is tested. It was noted that the great majority of infections are acquired from food.

6.3 Malaria in Greece

Following a 4 year period of intensive measures to control the re-introduction of Plasmodium vivax malaria, there were no locally acquired cases in 2014. However, 6 such cases were reported during August and September 2015 and resulted in the application of a series of measures to avoid transmission by blood transfusion, including the suspension of blood donor sessions and the deferral of potential donors from affected areas, with a consequent loss of around 2,000 blood donations.

7 SERIOUS ADVERSE EVENTS AND REACTIONS (SARE) AND ALERTS

7.1 Rapid Alert Platform - Blood

The Commission presented a summary of the alerts posted in the SoHO alert systems. The organs sector had posted no alerts while there were 5 in the tissue and cells sector and 15 in the blood platform. All 15 were epidemiological alerts, 13 concerning West Nile Virus and 2 concerning malaria.

Meetings of the Subgroup on Haemovigilance and the working group on Rapid Alerts for Tissues and Cells had both reviewed the programmes and made a series of suggestions for improvements that will be made to the platform early in 2016. The proposed changes were approved by the group. In future, ECDC will be given access to the platform, with the possibility to read alerts and possibly to add comments.

It was noted that epidemiological alerts launched on the RAB platform are not also launched on the tissues and cells platform. Competent authorities were encouraged to discuss with their tissues and cells colleagues the option to launch the alerts also on the Rapid Alert platform for Tissues and Cells (RATC). It was also noted that alerts concerning seasonal epidemiological risks (such as West Nile Virus) should be kept open for the duration of the season so that new cases can be added to the same alert.

7.2 Root cause analysis of adverse reactions

Two competent authorities shared their experiences with the meeting concerning root cause analysis of specific serious adverse reactions reported to them and the lessons that had been learned from the cases. Participants expressed interest in this exercise and in the lessons learned.

7.3 SARE reporting exercise 2015

The Commission thanked all Member States and Lichtenstein and Norway for having submitted their annual reports on serious adverse reactions and events (2014 data) via the electronic submission system. Preliminary results were presented and, following verification by the Competent Authorities, these will be the basis for the written report to be issued early in 2016.

The reports indicate improvements in the number of Member States that receive annual SARE reports from all reporting establishments, the number that report serious adverse events and the number that can provide data on number of patients transfused. The denominator data indicate that 23.3 million units were issued for transfusion in 2014 (data from 27 countries) and 21.4 million units transfused: roughly 76% RBCs, 14% plasma, 10% platelets and <1% WB (data from 25 countries). All countries were able to provide at least one of the denominators requested. A downward trend in red blood cell usage was evident in most countries when data from previous years was compared with the 2015 exercise.

There were 1,439 serious adverse reactions reported (Imputability levels 2-3) including 27 deaths. 20 countries also reported 3,723 donor reactions. 4,384 serious adverse events were reported.

Discussion focused on:

a) under-reporting – many 'nil' reports received
b) potential further improvement of denominator data
c) the value of reporting 'imputability level 1' which cannot be included by some countries where it is not mandated
d) the possible need to subdivide SAR categories further (large number of 'other')
e) a proposal to gather more detailed information, including root cause analysis, on SAR involving donor death
f) a proposal to further divide the categories of donor reaction even though reporting is voluntary
g) the wide variability in SAE reporting rates and the need to clarify and standardise further what SAE should be reported.

It was agreed that the report should explain clearly that Imputability Level 1 SAR data are incomplete and that points d) to g) should be explored by the Joint Action VISTART work package 4. In the meantime, further information on the deaths reported for 2014 should be solicited from the relevant Member States.

8 COUNCIL OF EUROPE UPDATE

EDQM (Council of Europe) presented the blood-proficiency testing scheme (B-PTS) and the blood-quality management programme for blood establishments (B-QM), two initiatives supported by a grant from the European Commission. B-PTS had increased its activity in 2015 with 6 proficiency testing studies compared to 4 in 2014, a major challenge for all involved. The studies covered

- NAT for hepatitis B, hepatitis C and HIV
- Anti-HCV
- anti-HIV/p24
- HBsAg

- anti-HBc
- ABO, extended phenotyping and irregular antibodies.

The number of participant laboratories per study ranged from 33 to 76 from 31 countries. The results of the 5 completed studies were satisfactory in 96 – 98% of cases.

As part of the B-QM programme, a training course for quality managers was held in Strasbourg in April 2015 and was attended by 36 participants. Three Mutual Joint Visits and one Training Visit were also conducted during the year. From 2016 the number of visit schemes will increase from 4 to 5 and there will continue to be an annual training course. EDQM is conducting trend analysis of the visit findings.

It was also reported that the Council of Europe is revising Art 21 on the prohibition on making profit from human body parts and is developing a new recommendation on research.

The Blood guide will have a major structural revision whereby the principles and standards sections will be merged. From the next edition of the guide, electronic copies will be free to download from the EDQM website.

A database has been developed by EDQM to support communication between blood services looking for rare frozen red cell units.

9. EMA UPDATE

EMA provided an update on its proposal to implement risk-based inspection planning of blood establishments providing plasma for fractionation. Risk based inspections would allow authorities to evaluate the activities of specific sites and tailor inspections, control measures and inspection intervals to these risks, inspecting sites with less activity and good compliance less frequently and those with higher risk and greater supply impact more frequently.

It was noted that the proposal would underline the need to comply with the 2 year inspection/control measure requirement in Directive 2002/98/EC but that the definition of 'inspection' allowed for measures other than on-site visits to be used (e.g. desk-based reviews) and this would be appropriate two years following an initial onsite inspection of a blood establishment assessed as low risk using the procedure in the guidance document.

The procedure involves classifying blood establishments according to their activities into one of three definitions: BEI, BEII and BEIII.

The intention is that this approach will be applied initially for 3rd country blood establishments where plasma is collected for medical product manufacture. It was suggested that subsequently this approach could also be applied for plasma collection blood establishments in the EU and, later, for all types of blood establishments if Competent Authorities chose to adopt the approach.

A questionnaire will be issued to Competent Authorities in an effort to understand the current practice in relation to frequency of inspection/control measures at blood establishments, taking the categorisation described in the document (BEI, BEII, BEIII) into account.

It was also reported that EMA is revising the Guideline on Epidemiological Data on Blood Transmissible Infections that is issued to Plasma Master File (PMF) holders. The review

follows a meeting of the PMF working group in 2013, a workshop with industry in 2014 and a public consultation in 2015.

10. WHO UPDATE

The WHO updated the group on the major issues being addressed in this field during 2015. The major topic of work during the year has been the response to the Ebola outbreak. A series of guidance documents were developed including

- Guidance on community engagement, education, recruitment and retention of people recovered from Ebola as potential donors for convalescent whole blood or plasma (WHO/HIS/SDS/2015.11)

- Guidance on the use of convalescent whole blood or plasma collected from recovered Ebola virus disease patients (WHO/HIS/SDS/2014.8)

- Interim Guidance on maintaining a safe and adequate blood supply during and after Ebola virus disease outbreaks

Ethics of using convalescent whole blood and convalescent plasma during the Ebola epidemic (WHO/HIS/KER/GHE/15.1).

World Blood Donor Day was celebrated on June 14th 2015 with events around the globe disseminating the theme: "Thank you for saving my life."

WHO also presented their Aide-Mémoire on National Haemovigilance System and a draft document called *'Establishing a National Haemovigilance System: Implementation Guidelines*' that will be finalised during an expert group meeting on 8-9 December 2015.

WHO is supporting recovery and building system resilience for blood and transfusion services in Ebola affected countries. The support is linked with WHO support to the trials of convalescent whole blood and plasma for treating people with Ebola virus disease and its plan to strengthen the neighbouring countries and the whole African Region.

Further work is related to EB Decision EB136 (2) that mandates WHO to convene consultations with Member States and international partners, to support the development of:

- Global consensus on guiding principles for the donation and management of medical products of human origin (MPHO)
- Good governance mechanisms for MPHO and
- Common tools to ensure quality, safety and traceability, equitable access and availability of MPHO.

A document on these topics must be submitted to the 70th WHA (2017) for its consideration.

11. ANY OTHER BUSINESS

11.1 Essential supplies for the blood chain (EL)

Greece shared its experience of compiling a list of essential supplies to guarantee the continuity of blood supply.

11.2 Medical Devices update

The Commission updated the group on the ongoing negotiation on the revision of the Medical Devices Directive. Concern has been expressed by blood establishments (EBA – April 2013) on the importance of being able to use in-house developed in vitro diagnostics (IVD e.g. Q-fever testing in the Netherlands, blood grouping) where there is limited commercial value and therefore no CE-marked kits available. If these IVD are class D, there would no longer be an exemption for in-house manufacturing. The Commission reported that the 'Trilogue' (Commission - European Parliament - Council) is ongoing and that the Parliament has shown more flexibility for IVD, aiming to first agree on the classes of devices to which certain aspects of the exemption apply and then to consider whether the exemptions apply for both public and private entities.

11.3 Taxation of Plasma for fractionation

The Commission informed the meeting that DG TAXUD is currently reviewing public sector VAT rules including tax exemptions. It was noted that it has previously confirmed (DG TAXUD informal Working Paper (771) May 2013) that the tax exemption applicable to whole blood also applies to blood components and therefore to plasma for fractionation. SANTE has raised its concerns as regards the different VAT treatment of tissues (not considered exempted) and blood components and will provide TAXUD with more information on this issue.

11.4 Transatlantic Trade and Investment Partnership (TTIP) and blood, blood components and blood products

The Commission reported in internal discussions regarding the scope of TTIP and whether it might include blood and blood components or plasma derivatives in its scope. It was noted that the detailed scope is to be specified after approval of TTIP.

11.5 Update on Exchange of Surplus Blood (EL)

Greece reported on Surplus Blood Exchange Intra–MS Agreements and contracts under discussion between Greece, Cyprus, Italy, France, Netherlands and UK. The group is considering what would need to be included in an agreement, how reimbursement should be organised and how compliance with traceability, labelling and transport requirements would be guaranteed. They will continue to develop a document to support such exchanges.

11.6 Consultation with Stakeholders

The Commission shared their reflections with the Competent Authorities on the possibility of organising some opportunities for key, EU or international level, stakeholders to interact with the Commission and with the Competent Authority representatives. The suggestion was that, from time to time and when considered appropriate, certain stakeholders would be invited to a meeting that would be entirely separate from the Competent Authorities. For organisational reasons, to facilitate participation of interested Competent Authorities, such meetings could take place on the afternoon, following the closure of the CA meeting. Stakeholders would be selected on the basis of the agenda which would include topics that might benefit from a 2-way exchange of information and views.

The meeting discussed the proposal and stressed that there would need to be a high level of transparency regarding the selection of participants, that there should be no discussion of

national issues, and that it would be very important not allow a conflict of interest to influence discussions.

The Commission will proceed to discuss this possibility with the other Competent Authority groups also (organs and tissues and cells) and will reflect further.

11.7 Basocellular Epithelioma as a Donor Exclusion Criterion

Belgium raised the topic of the exclusion of donors with a history of basocellular epithelioma from donation. It was pointed out that Directive 2004/33/EC, Annex III, 2.1. requires permanent deferral for malignant diseases except '*in situ cancer with complete recovery*'. It was explained that in a strict sense a basocellular epithelioma is not a carcinoma in situ, but an invasive carcinoma with a very low metastatic potential. Given the relatively high and increasing frequency of this condition, the exclusion is having a significant impact on the blood supply. It was proposed that such donors should be accepted for donation and arguments to support the proposal were presented. The discussion on the topic was postponed to the next meeting.

12. FINAL REMARKS

The chairman thanked all participants for their active and constructive participation and declared the meeting closed.