



EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

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

**Ad-Hoc Meeting between Stakeholders and representatives of members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718)
10 October 2018**

Summary Minutes

The purpose of these ad-hoc meetings is to provide an opportunity for an informal exchange of views between key stakeholders, representatives of Member State (MS) Competent Authorities on Substances of Human Origin (CASoHO E01718) and the Commission services on topics of mutual interest. The Commission services published a call to stakeholders for expressions of interest in October 2016. The list of approved stakeholder organisations meeting the criteria defined in the agreed Terms of Reference for these meetings was first published in November 2016 and is updated regularly. The call for expression of interest remains open¹.

PARTICIPATION:

Competent Authorities from all EU-28 MS were invited and most attended. Representatives of the European Centre for Disease Prevention and Control (ECDC) and the Council of Europe (EDQM).

Stakeholders: MedTech Europe, European Blood Alliance (EBA), European Plasma Alliance (EPA), Plasma Protein Therapeutics Association (PPTA).

European Commission/DG SANTE: Mr S. Van der Spiegel (chair), Ms D. Fehily, Mr R. McGeehan, Ms I. Pucinskaite-kubik, Mr P. Catalani

DG GROW: Mr P Piscoi

1 WELCOME

DG SANTE welcomed participants to this ad-hoc meeting, stressing the importance of these exchanges in the context of the ongoing evaluation of the blood, tissue and cell legislation²

¹ https://ec.europa.eu/health/blood_tissues_organ/consultations/call_adhocstakeholdermeeting_en

² https://ec.europa.eu/health/blood_tissues_organ/policy/evaluation_en

and inviting all stakeholders to focus their comments on issues of relevance to multiple or all Member States and avoiding discussions of single MS level topics.

The chair explained that MedTech Europe had recently applied to be on the approved list of stakeholders and had participated in a bilateral meeting with DG SANTE where a number of topics of interest, mainly related to the BTC Evaluation, were discussed. The minutes of that meeting had been published³.

Some stakeholder submissions to the Open Public Consultation for the BTC Evaluation, including that of MedTech Europe, had highlighted the importance to blood services of the continuity of supply of critical medical devices. This issue had been discussed in the blood competent authorities meeting following recent supply interruptions related to defective devices that had been withdrawn from the market. A number of stakeholders had also pointed to the important developments in pathogen inactivation that have taken place since the blood legislation was adopted and this was also discussed in the bilateral meeting with MedTech Europe. The commission considered that a more in-depth exploration of these two subjects with the key stakeholders would be valuable for the Evaluation.

2 INTRODUCTION OF STAKEHOLDERS PRESENT

Five stakeholder organisations had been invited to this meeting based on the agenda topics agreed in advance with the national competent authorities. Four attended and the International Plasma Fractionators Association sent their apologies. Each organisation briefly introduced their aims and activities as follows:

MedTech Europe: MedTech Europe is the European trade association representing the medical technology industries. It is an alliance of European medical technology industry associations representing Diagnostics and Medical Devices manufacturers operating in Europe. It was founded jointly by EDMA, representing the European in vitro diagnostic industry, and Eucomed, representing the European medical devices industry. More information is available at <https://www.medtecheurope.org/>

EBA: The European Blood Alliance represents non-profit Blood Services in Europe. Together these organisations collect the majority of EU blood donations, around 17 million annually, and supply blood and blood components for around 470 million EU citizens. More information at: <http://www.europeanbloodalliance.eu/>

EPA: The European Plasma Alliance represents 12 European private sector companies that collected 2.5 million litres of plasma for the manufacturing of plasma derived medicinal products in 2017. Their companies operate in Germany, Austria, the Czech Republic and Hungary. Their mission is to promote safe plasma collection practices in the EU with focus on donor health and donor safety to ensure patients access to safe products. For more information: epa@pptaglobal.org

PPTA: The Plasma Protein Therapeutics Association is a global trade and standards setting association representing commercial manufacturers of plasma-derived and recombinant biological therapies, collectively known as plasma protein therapies. PPTA also represents

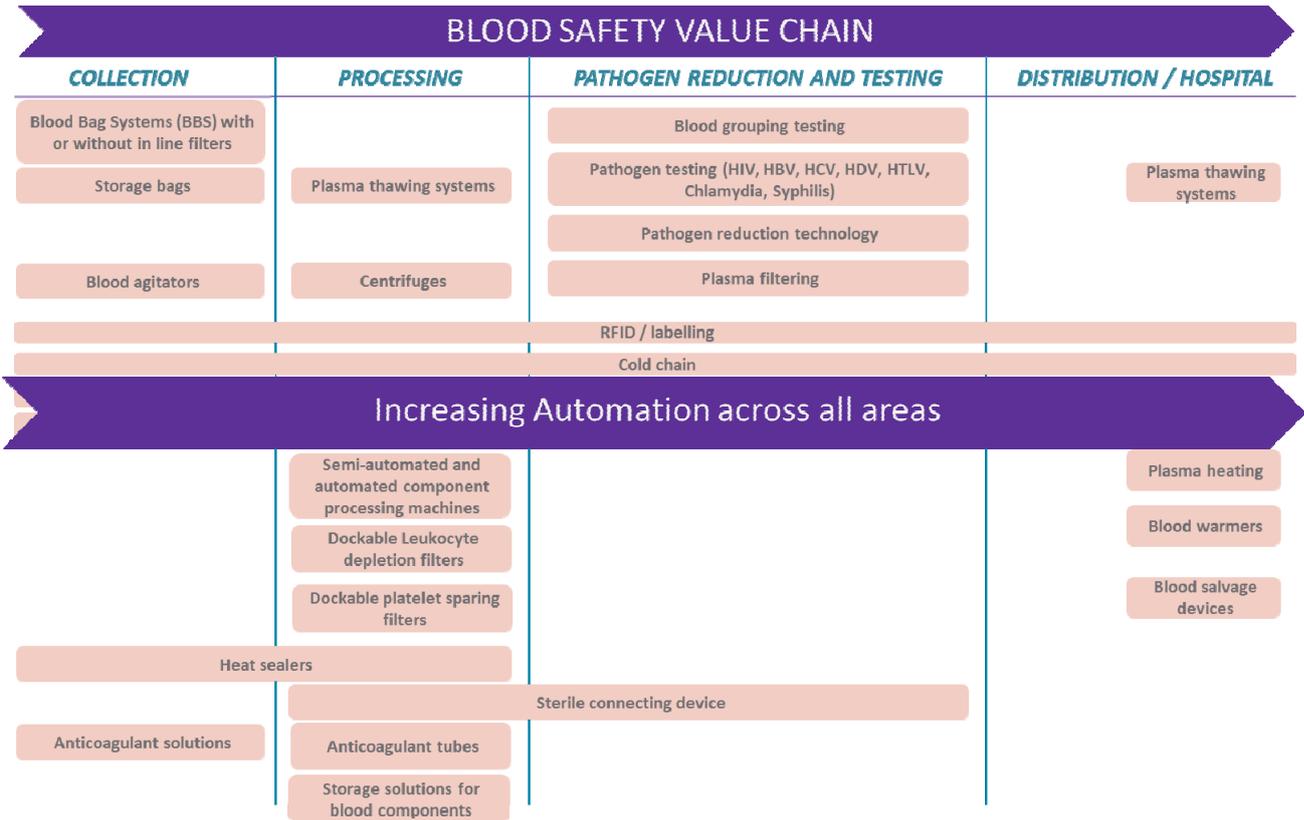
³ https://ec.europa.eu/health/sites/health/files/blood_tissues_organ/docs/ev_20180625_mi_en.pdf

for-profit collectors of Source Plasma. Their members provide around 70% of the world’s needs for Source Plasma (600 plasma collection centres based in North America and more than 100 in the EU) and >80% of the world’s plasma protein therapy products. More information at: <http://www.ppta.org/>

3 CRITICAL MEDICAL DEVICES THAT MIGHT IMPACT CONTINUITY OF THE BLOOD SUPPLY (BLOOD AND COMPONENTS FOR TRANSFUSION AND FOR PDMP MANUFACTURE) – RISKS AND STRATEGIES

Three stakeholders presented on this topic: MedTech Europe, EPA and EBA.

MedTech Europe outlined the criticality of medical devices in all stages of the blood supply chain from collection, through donor testing to distribution, noting that their members supply around 20 million blood collection bag sets to the EU every year. They highlighted that there has been, over time, increasing automation at all stages, a factor that further increases the criticality of the devices that support the different processes. The following graphic summarised the main devices where an interruption in supply could be critical to the blood supply for patients.



MedTech has assessed the criticality of the different device groups in terms of volumes needed and importance to the blood safety and value chain. In this context, they consider that blood and plasma collection systems are the most critical devices with blood testing systems in the second position.

EPA described how medical devices are critical at all stages of the plasma collection and freezing process, prior to despatch of plasma to manufacturers. They are used for donor monitoring, plasma collection by apheresis, quality control testing and freezing. Interruptions

in any of these devices, whether used directly in the chain or in laboratory testing would have a serious impact on supply. EPA raised concerns regarding the limited number of suppliers of some of these devices. In particular, plasmapheresis machines are supplied by only two major suppliers, in addition to one much smaller one and one that was soon planning to launch a device. In some cases, the set components needed for plasma collection can only be purchased from the machine manufacturers, further raising the risk of any supply interruption. The impact of any such interruption would be an inability to collect plasma in the short term and a long interruption could result in bankruptcy of the collection establishments.

EPA illustrated the importance of this issue, using a number of examples in EU countries. A recent device defect and recall in one Member State resulted in the use of 50% of the collection machines having to be suspended. Previous defects in another Member State had similar impacts with a recall of >100,000 fresh frozen plasma units with a significant impact on patient treatment.

To mitigate these risks, **EPA** called on manufacturers to reduce dependency on so few suppliers, to provide prompt and transparent information on any ongoing change in hardware or software that might impact donor safety or product safety or quality and to have robust business continuity plans in place. They proposed that plasma collectors should have a dual supply strategy where possible and should use more than one batch of set-components at any one time. They should also maintain an adequate safety stock and give training to operators to ensure reliable setup of machines, batch documentation and deviation management. They also stressed the important role of authorities in follow-up of all severe events, giving the German procedure and documentation as a good example.

EBA, focusing on the chain from whole blood donation to blood component supply for transfusion, reiterated concerns regarding the small number of suppliers of key technologies, consumables, blood bags, etc. and the importance of having robust contingency arrangements in place both at the level of the device suppliers and that of the blood services. They point to a lack of clear requirements for the testing of contingency arrangements at both those levels. They also considered that the small number of device suppliers, the result of mergers and acquisitions, is a deterrent to investment in innovation.

EBA expressed the view that, at the EU level, although device defects have been communicated via the Rapid Alerts for Blood (RAB) platform hosted by the European Commission, the information in those alerts does not always reach the blood establishments effectively and promptly. They also expressed concerns that the procedures for attaining a CE mark are, in the case of some critical devices, not adequate and need to be supplemented by extensive validation by blood services. Some Member States have introduced additional national authorisations for devices used in the blood supply chain. They consider that the criteria for the issuing of medical device Field Safety Notices by manufacturers are not clear and that in some cases, previous relevant defects are not mentioned in the notices. **EBA** stressed that ICT systems are often as critical to the blood supply as other devices and that there should be uniform standards and interfacing of automated devices to ICT equipment and contingency plans in place for ICT failures or defects.

Issues arising in the **general discussion** included the need for blood services to audit critical device suppliers. This is resource consuming and only some larger national organisations do this. There were suggestions that joint audits should be conducted by 2-3 services on behalf of many or all BEs and that **EBA** could have a co-ordinating role. Joint validations of devices at the blood establishment level were also suggested as a cost-effective approach. However, it

was stressed that for these two measures to be effective Competent Authorities would need to agree that they would accept the outcome of these audits/validation across Member States.

The DG GROW representative stressed that medical device vigilance is a national competence, with manufacturers reporting incidents to competent authorities, while CE marking covers conformity verification at EU level. He outlined that the new medical device regulation would be in application as from May 2020. He also noted that there is a central location for all National Competent Authorities Reports in the EUDAMED and observed that direct contact between national authorities for blood and for medical devices should be the norm. DG GROW informed the meeting of an upcoming consultation in March 2019 on CMR/ED phthalates in medical devices with an associated hearing to which the stakeholders and authorities would be welcome to submit comments. A public hearing will take place on 4th of April. See https://ec.europa.eu/health/scientific_committees/events/ev_20190404_en

The Commission also noted that, in the context of a new grant agreement with EDQM, work on continuity of the blood supply, including the supply of critical devices, would be carried out.

4 THE IMPORTANCE OF MICROBIAL REDUCTION STEPS IN BLOOD COMPONENT PREPARATION (FOR TRANSFUSION) – CURRENT AND FUTURE PERSPECTIVES

Two of the stakeholder organisations, MedTech Europe and EBA presented on this topic.

MedTech Europe began by providing an overview of the main pathogen reduction systems on the market and under development in the EU: three for platelets, three for plasma and one for whole blood, currently on the market and two for red blood cells and one for whole blood, under development. They noted that, since Directive 2002/98/EC was adopted, pathogen reduction has been implemented to varying degrees across the EU, resulting in blood supplies of different quality and safety in different Member States. Belgium adopted a Royal Decree in 2009 mandating that all platelet concentrates be subjected to pathogen reduction. A similar approach was adopted in France (and Switzerland) while a more partial implementation is seen in a number of other Member States where the application is not mandated.

MedTech presented published data showing a reduction of both infections and deaths from transmitted infection in those three countries to zero, compared with 50(10), 16(3) and 9(0) transmitted infections (deaths) without pathogen reduction in those countries over 10 years. They stressed that testing is a less effective measure, given the increasing numbers of infectious pathogens and the costs of the multiple agent-specific tests. They consider that the costs of introducing pathogen reduction can be compensated, or possibly neutralised, by the elimination of a need for irradiation, some testing, reduced wastage and reduced complications as well as possibly reduced donor deferral.

EBA began by illustrating, with data from the European Commission annual report of Serious Adverse Reactions and Events for Blood and Blood Components (2016 report, 2015 data), that, relative to the numbers of units transfused, transmitted infections are rare events, making up only 2.52% of the total serious adverse reactions recorded, when both viral and bacterial transmissions are combined. For that year, for 21,443,125 units transfused, there were 17 bacterial infections and 17 viral infections in recipients, with 1 death. The 2016 AFSAPPS (now ANSM) report in France calculated the risk for a bacterial transfusion transmitted infection as 0.04 bacterial infections per 100,000 red blood cell transfusions and 0.33 per 100,000 platelet transfusions. The SHOT report in the UK compared transfusion related risks

to risks in other life activities. The risk to contract an HIV, HBV or HCV infection after transfusion was said to be equivalent or lower than the risk of death from lightning strike. They also pointed to published data showing that hospital acquired infections in all patients are in the region of 6%, putting into perspective the additional risk reduction from pathogen reduction of blood components to the benefit for patients.

EBA continued by pointing out that current pathogen reduction technologies are not effective against all viruses (no efficacy against non-enveloped viruses such as Parvovirus or hepatitis E) and do not inactivate bacterial spores. They also suggested that donors in the acute stage of infection would have high viral load that would not be effectively inactivated and that, similarly, the technologies available would not effectively inactivate massive bacterial contamination. EBA also raised concerns emerging from a published Cochrane systematic review that showed that pathogen reduced platelets result in shorter time intervals between transfusions and that they increase the risk of developing platelet refractoriness. The consequence is a need for more platelet transfusions and lower platelet increments after 24 hours compared with non-pathogen reduced components. There is moderate quality of evidence that there is probably no difference in increased risk of developing severe bleeding (WHO grade 3) and clinical significant bleeding (WHO grade 2). They are also concerned about increased operational complexity, the need to adapt previous processing steps and the potential loss of product. They reported that a number of countries had conducted cost: benefit analysis of introducing pathogen reduction and concluded that the benefits are not justified by the costs.

In general, EBA recommends to allow alternative strategies for reducing infectious transmission risk, e.g. the use of bacterial testing of platelets that can have the added benefit of increasing platelet shelf life. They consider that, in the future, genomic screening for pathogens may be an attractive alternative to explore.

Meeting Close

The chair closed the meeting, thanking the participants for the high quality of their inputs and underlining that they would form an important element of evidence for the ongoing evaluation of the legislation.