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COMPETENT AUTHORITIES ON SUBSTANCES OF HUMAN ORIGIN EXPERT GROUP
(CASOHO E01718)

COVID-19 MEETING OF THE COMPETENT AUTHORITIES FOR BLOOD AND BLOOD COMPONENTS

11 FEBRUARY 2021
09:00 – 12:30 CENTRAL EUROPEAN TIME
13:30 – 17:00 CENTRAL EUROPEAN TIME

BY TELECONFERENCE

SUMMARY MINUTES

The meeting for competent authorities for blood and blood components. The previous CA meeting was held on 15th of October.

PARTICIPATION

There were 23 Blood Competent Authorities attending the meeting, as well as Norway, Iceland, North Macedonia and Turkey. The meeting was also attended by representatives from the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), and the European Directorate for the Quality of Medicines & HealthCare (EDQM).

The representatives of the European Commission/DG SANTE Unit B4 chaired the meeting.

1. WELCOME, INTRODUCTORY REMARKS AND ADOPTION OF THE AGENDA 09:00-09:15

The Head of Unit B4 in DG Sante welcomed the authorities to the meeting. The meeting's agenda with its focus on the process of and proposals for the revision of the BTC legislation was introduced, and the use of an anonymous online polling tool was explained. It was highlighted that responses would be considered as indications of initial reactions only, not as representative quantitative data. Finally, it was explained that minutes of the meetings would be circulated for comments in due time.

2. COVID-19 AND SURVEILLANCE (9:15h-11:00h)

2.1 Epidemiological state of play COVID and other CD (ECDC 9:15h)

The European Centre for Disease Control (ECDC) presented a short epidemiological update on communicable diseases, including COVID-19, that were relevant to the SoHO sector. It was reported that, in spite of rising test rates, positive cases of COVID-19 were decreasing in the EU. High case rates were reported from the US, South America (esp. Brazil), and Europe, resulting in a 2.2% overall worldwide fatality rate. B.1.1.7, B.1.351, and P.1 were highlighted as "variants of concern" and ECDC recommendations on avoiding non-essential travel were recalled. Regarding the impact of COVID-19 on the SoHO sector, the ECDC recommendation for a four-week deferral after vaccination with a vector-based vaccine was presented; no such deferral was deemed necessary after vaccination with a vaccine that does not contain live agents.

Beyond COVID-19, the situation on MERS-COV and Dengue was covered, concluding that levels were expected to normalize soon. Finally, a resurgence of Ebola Virus Disease in the Democratic Republic of the Congo was reported, and further information on the situation was promised.

2.2 Current Evidence COVID-19 Convalescent Plasma (CCP) (ECDC 9:30h)

ECDC provided a short update from literature on published findings on risk/benefit of CCP as COVID therapy. The presentation recalled the main drivers behind research on CCP, namely the disease impact, the absence of effective therapies or vaccinations, and the positive historical examples of influenza and SARS. It was summarized that the initial phase of developing donation and production protocols for CCP was mostly concluded, but that some open questions remained. Conclusions from the initial research phases were drawn, focussing mostly on strong signals for acceptable safety risks and weak signals towards reduced mortality if a CCP with a high titre of neutralizing antibodies is applied to non-intubated patients in the early stage of disease.

Building on this base of the initial phase, newer developments were summarized. This focused firstly on alternative CCP forms (such as pooled samples, cryosupernatant, or antibody hyperconcentrate), secondly on improved testing standards, and finally on guidelines for the donation of CCP after vaccination. In this case, the ECDC recommended that the position of the FDA, according to which individuals who were vaccinated without ever having been infected with SARS-CoV-2 are not eligible to donate CCP while recovered patients remained eligible after their vaccine only for 6 months within the resolution of symptoms, could be adopted in the EU.

The presentation went on to introduce the possible mechanisms of action, with a focus on the importance of neutralizing antibodies. Recent evidence from systematic reviews and meta-analyses was used to conclude that CCP does not seem to be effective in treating severe and critically ill patients, while an association was found between high-titre neutralizing antibodies and decreased mortality in general. Drawing from this evidence, the presentation recommended standardization of methods for determining the titre of neutralizing antibodies, defining discriminating values and minimum therapeutically effective doses, and discouraging the use of low-titre CCP.

Finally, the presentation highlighted a standardized protocol for donation and preparation of CCP, the creation of a monograph, approval of CCP as standard treatment for moderately ill patients, affordability in low and middle-income countries, use as

prophylaxis in specific populations, and the production of anti-SARS-CoV-2 hyperimmune gamaglobulins from CCP as goals for the upcoming research phases.

2.3 RTD projects Plasma (9.50h)

DG RTD presented the Horizon2020 funding to combat COVID-19, which included support for research on CCP under the coordination of EBA in the SUPPORT-E project. Of the overall pledge for 1 billion Euro, about 800 million Euros were reported to have been mobilized so far; of this money, 4 mio. Euros have gone to EBA. It was summarized that this project would focus on three elements over the next 2 years: assessing CCP, using the CCP database, and harmonized recommendations. Past achievements of the project were summarized, focussing on support of high-quality clinical studies, the creation of the EU CCP database, a survey on antibody testing/virus neutralization testing, and a cost-benefit consultation with Oxford University. Finally, the presentation pointed to a recently published Opinion Paper. A future outlook was given on plans for a clinical trial on clinically vulnerable individuals (COVIC-19), support for improved laboratory testing capacities, as well as standardization of assays, clear recommendations, and monitored access use programmes.

Links were shown to other ongoing projects under H2020, such as firstly ATAC, investigating the development of antibodies against SARS-CoV-2, which has concluded a benefit of hyperimmune plasma in COVID-19 patients; secondly REMAP-CAP, which investigated CCP amongst other treatment possibilities and concluded the absence of benefit; and thirdly EVAg, which provides a virus archive that could promote biomedical research.

To summarize the actions taken, a video on convalescent plasma and EU research support was shown.

2.4 EU CCP database (10.10h)

Sinead Masterson (on behalf of the SoHO Team) presented the recent progress on the EUCCP database and its role in supporting ongoing efforts by collecting and providing data on CCP donations and patient outcomes after transfusion. The structure of the database around three components (registration, data entry, and analysis) was outlined and some public dashboards were presented as examples of provided information. At the time of presentation, 86 Blood Establishments from 21 countries were registered, of which 37 Blood Establishments had entered data in relation to 15 331 donations and 215 transfused patients. It was further summarized that most of these donations are collected by apheresis, largely from male donors, and that most transfusions occur in monitored use programs, largely into male patients with co-morbidities. Moreover, the restricted access section was presented to show how specific data could be uploaded/downloaded by authorities and establishments. As future priorities, the presentation listed various aspects of functionality and user-friendliness that would be improved in the upcoming time.

When asked about the apparent lack of data so far, it was pointed out that hospitals are still facing significant challenges in transferring data. Concerns were also raised regarding the privacy of donation numbers under GDPR, and reference was given to published documents on the matter.

2.5 ESI support for national blood services (10:30h)

Giuseppina Facco presented the current state of play of the ESI grants for increasing capacity for CCP. The presentation specifically recalled the objectives of the project, focussing on improvements for the health of COVID-19 patients through improved availability of CCP and the optimisation of its treatment use while ensuring adequate availability of equipment and trained staff. Monthly online meetings between the 24 project coordinators and the EU Health Policy Platform were presented as two tools that would support the networking throughout the project. As specific benefits of this project, procurement of equipment and associated materials, progress in CCP donation and collection, and increased visibility of EU funding were highlighted.

2.6 Supply of Plasma Derived Medicinal Products (EMA 10:45h)

The **European Medicines Agency (EMA)** presented current findings on the supply of plasma and plasma-derived medicinal products (PDMP). The presentation summarized the effects of COVID-19 on the supply of plasma in the EU, highlighting that shortages had been notified in December 2020 and January 2021 and that all Plasma Master File Holders were monitoring the situation closely, having activated mitigation plans to ensure supply. Further work of EMA together with EDQM and the European Commission was expected to provide more information. In addition, measures taken to facilitate the use of PDMP were included in a CHMP position statement that firstly allowed countries to set deferral periods for MSM in accordance with national epidemiological and scientific considerations, and secondly increased flexibility for exchange with third country blood establishments (esp. in the UK). Finally, the presentation highlighted some clinical studies on COVID-19.

From the audience, the need for increased flexibility in the process for creating a new Plasma Master File was highlighted. This comment was duly noted. A second question highlighted concerns regarding the application of revised positions applying in third countries, specifically regarding the lacking clarity on plasma as a staring material for PDMP that is exchanged with the UK. The question was deferred.

3. REVISION FOR THE EU LEGAL FRAMEWORK (11:00h)

DG SANTE presented the current state of the revision of the EU legal framework. The presentation was structured according to the findings of the 2019 evaluation and included options/measures laid out in the IIA, the feedback received on this, and the relevant questions posed in the Open and Targeted Public Consultations. Before the presentation, it was stressed that views of the national Ministries of Health were important in addition to those of the National Competent Authorities. Participants were also invited to express all concerns in response to any of the presentations, and encouraged to carry all potentially sensitive or disruptive issues into internal discussions in the Member States to ensure that opportunities opened by the revision were optimally used. Finally, participants were reminded that the SoHO-Team was available for bilateral meetings with authorities and ministry colleagues in case direct discussions on any topics were needed.

In an anonymous online poll, most participants indicated already being familiar with the questions of the consultation. Around a third indicated being only partially or not at all familiar. When asked about the most interesting topics of discussion for the following meeting, a wide range of responses was received, focussing for example on CCP, the future roles of ECDC and EDQM, and oversight.

3.1 Process – state of play and planning (11:15h)

DG SANTE presented the process, state of play and planning of the Impact Assessment (IA) and Revision. The presentation reiterated the main objectives of the revision: firstly, ensuring safety and quality for patients, donors, and children born from MAR through up-to-date safety and quality requirements, secondly, optimizing access to and avoiding shortages of BTC therapies based on improved oversight, monitoring, and emergency preparedness, and finally ensuring that the framework is future-proof and facilitates the development of innovative BTC therapies through trusted authorization procedures and clear borderlines with other frameworks. On that basis, the further process of the revision based on the Better Regulation Guidelines was outlined, aiming for an adoption of the legal proposal in Q4/2021. Specific emphasis was put on the involvement of stakeholders in that process, highlighting the key steps for feedback (the Inception Impact Assessment (IIA), the online consultations, and the workshops as part of the study supporting the Impact Assessment). Additionally, the two studies supporting the IA process were presented, summarizing that one would focus on comparatively assessing the costs and impacts of the different policy options while the other would focus on assessing the feasibility of future data systems that could support the new legal framework in the future. This second so-called "feasibility study" was further explained to include work on oversight data for authorities as well as clinical data for professionals, thus responding to feedback received on the IIA. Finally, a list of topics for workshops was presented and the overall timeline of the revision initiative was summarized.

In response to questions on the registration for workshops, DG SANTE clarified that EU Survey would be used to allow all NCAs to register interest for the topics they would like to attend.

3.2 Updated safety/quality guidelines for recipients, donors and offspring (11:45h)

3.2.1 Options in and feedback from the Inception Impact Assessment

DG SANTE presented the three different policy options developed to improve the guidelines on safety and quality that should protect recipients, donors, and offspring in the future frameworks as follows:

1) Strengthened quality and safety requirements defined by blood and tissue establishments with strengthened national inspection, EU audits of national control systems (self-regulation).
2) EU-level safety and quality requirements defined by European Expert Bodies (ECDC, EDQM, …) and strengthened national inspection, EU audits of national control systems (co-regulation).
3) EU-level safety and quality requirements laid down in the BTC legislation with improved national inspection systems.

It was furthermore reiterated that all policy options would include measures to clarify the situation of currently unregulated SoHO, and that combinations between them could be possible depending on the need of each technical topic.

The feedback from the IIA was shortly summarized, focussing on the general support for the revision procedures and its underlying objectives. Specific emphasis was put on the need for inclusion of new substances (such as human milk or faecal microbiota) and the general preference for Policy Option 2.

3.2.2 Consultation questions

To conclude the presentation by DG SANTE, the relevant questions of the public consultation questionnaires were presented. NCAs were once again encouraged to focus on the issues of particular relevance to them.

3.2.3 Inputs from expert bodies

EDQM shortly explained the structure and adaptation process of the Guidance on Safety and Quality of Blood (Blood Guide). The presentation started by reviewing Recommendation R(95)15 of the Committee of Ministers of the Member States as the legal basis for the Blood Guide and reiterated that the guide's aim was the provision of safety, efficacy, and quality requirements for blood components through European harmonised standards. It was reiterated that periodic updates of the guide were possible (every two years) without changing its legal basis. This revision process was outlined in more detail in the following to provide a better understanding of the timeframes and steps involved. The structure of the guide was exemplified to explain its four different levels and its links between Principles, the EU Directive Standards, and the Blood Guide Standards.

ECDC shortly presented its ongoing role in the BTC sector as the provision of "services supporting transfusion, transplantation, and medically assisted reproduction" and the potential extension thereof in the future. The presentation summarized the proposals made to generally extend the mandate of ECDC in response to COVID-19, focusing for example on the provision of technical and scientific expertise to the Commission and the Member States, enhancing the preparedness and response planning activities in the EU, assessing the risk of communicable disease transmission to safeguard patients in need of therapies based on SoHO, and recommending preventive interventions. For that sake, the need for a network of national blood and transplant services and their authorities was outlined. While details related to its organisational structure are still under discussion, a focus on access to sero-epidemiological data for the monitoring of disease outbreaks as well as its support for the development of guidelines for quality and safety of BTC were highlighted as key aspects of its role. The process towards this network was briefly outlined.

3.2.4 Discussion and next steps (12:15h)

Comments from the participants were invited.

Firstly, concerns were raised regarding the pressure that blood establishments were facing from industry to implement expensive pathogen reduction systems. Question regarding their efficiency and cost-effectiveness were deferred to a later point. As a separate point, concern was expressed that pressure from industry lobbies may result in the removal of plasma supply from the present legislation, thus threatening donor protection and the rights of plasma donors. DG SANTE responded that no suggestions for the complete removal of plasma from the legislation had come up in talks with plasma industry representatives.

When asked in an anonymous online poll what the appropriate role could be for NCAs in the process of adopting technical guidance, most respondents agreed on a privileged opportunity to review and comment before public enquiry and a nomination of experts to the drafting committees. A strong majority indicated that this referenced expert guidance should be disseminated in one online location or one publication.

3.3 Oversight (13:30h, latest 14:00h)

3.3.1 Measures in and feedback from the Inception Impact Assessment

DG SANTE presented the measures proposed to tackle problems related to oversight. These include as common measures firstly strengthened principles in EU legislation, secondly risk-based inspections, and thirdly mutual peer audits, training, and guidance. In addition, some specific measures could be added depending on the final choice of Policy Option (EU audits, or joint inspections among Member States). Based on the feedback received on the IIA, the presentation concluded that there is general support for strengthened oversight measures.

3.3.2 Consultation questions

Again, the presentation included a brief overview of the questions related to oversight in the public consultation questionnaires.

3.3.3 Issues arising in the Inspection Expert Sub-group

DG SANTE went on to present ongoing work from the IES. Firstly, a pilot "remote audit" of the Austrian inspectorate for BTC was summarized, concluding that it proved to be a positive and valuable exercise. Participants were reminded of the possibility to volunteer for another such pilot audit in the course of 2021; the possibility of organizing a joint inspection onsite was also discussed. Secondly, feedback from the recent IES discussion on oversight measures was provided, focussing especially on the support expressed for EU principles on requirements and trainings for inspectors, the potential role of EU audits to promote trust among Member States, and the possibility for joint inspections.

3.3.4 Issues arising in the Vigilance Expert Sub-group (TRIP)

The Vigilance Expert Subgroup (VES) presented on various issues related to vigilance and on the potential impact of the legal revision. The presentation outlined the differences in definition of a "Serious Adverse Event" in the Blood Directive, the Tissue and Cell Directive, and the FDA definitions before summarizing past improvements of vigilance in the BTC sector achieved through collaboration between VES and the NCAs. Specific emphasis was put on the inclusion of transfusion reactions in the Blood sector even when there were no specific quality or safety concerns, and the inclusion of offspring born from MAR in the Tissue and Cell sector. Consideration was also given to audits of national vigilance systems and the role of the VES in developing tools for this.

The presentation further summarized the importance of well-functioning vigilance firstly for donor protection and secondly for self-sufficiency in supply. It emphasized the importance of reporting SARE occurring in donors to ensure informed consent and willingness of donors, as well as an assessment of any potential long-term unwanted effects in repeat donors. Moreover, it connected the collection of high-level vigilance data to the transparency needed to support cross-border exchange and thus contribute to EU self-sufficiency. Looking into the future, the presentation summarized ongoing work on an EU-wide harmonized dataset for blood.

3.3.5 Discussion and next steps

The floor was opened for any questions or concerns.

Support was expressed for the harmonization of definitions (e.g. SARE). Concerns were raised regarding the feasibility of joint inspections in Member States not sharing common languages; DG SANTE responded that considerations on this question were ongoing. In further discussion, it was clarified that an interpretation service is provided for EU audits

with auditors from DG SANTE, but that the issue was not yet fully resolved for joint inspections. Further concerns were expressed regarding the workload associated with audits in Member States, especially in those where hemovigilance systems are ISO certified and thus already regularly audited. DG SANTE referred to the Targeted Public Consultation questionnaire as the right place for these concerns and raised the possibility of EU support as well as a push for more staff in National Competent Authorities after discussions with DG SANTE's Directorate F and the national Ministries of Health. In response to a question regarding confidentiality at joint inspections, reference was made to the existing Code of Practice under the IES and its provisions for confidentiality statements. As a final comment, it was suggested that reports should be published to allow for mutual learnings.

In an anonymous online poll, a slight majority of participants indicated that they would find the development of a common list of senior inspectors appropriate, while a significant group remained unsure. In a second question, a majority indicated concern regarding the availability of resources and skills available in their NCA to comply with strengthened oversight measures.

3.4 Innovation (Latest by 15:00h)

3.4.1 Measures in and feedback from the Inception Impact Assessment

DG SANTE presented firstly risk assessments and a proportionate collection of clinical data on innovative BTC and secondly a mechanisms for clarification of the scope of the future framework as the two key proposals regarding innovation. These measures are shared between all options. As a basis, the concept of novelty was explained in the context of the trade-off between historical evidence of benefit and safety and the increasing complexity and risk levels brought about by innovation. It was clarified that existing treatments within the BTC sector fall largely under the realm of historical evidence, while ATMPs and PDMPs fall at the other end of the spectrum of higher risk and complexity, thus leaving an area of novelty in between.

On the issue of clarification of borderline classifications, a BTC advisory mechanism was proposed. This could combine expertise from relevant fields and interact with the equivalent EU-level mechanisms in other legal sectors.

Feedback received on the IIA was briefly summarized, focussing on comments related to the difficulties in defining the borderlines to other frameworks and the different views expressed regarding the form of a classification mechanism.

3.4.2 Consultation questions

On that basis, an overview of the relevant consultation questions was provided.

3.4.3 Issues arising from the GAPP joint Action

The GAPP Joint Action presented views on how to assess and authorize novel BTC preparations.

The presentation summarized the project's underlying aim of supporting CAs in the authorization of novelties while taking both harmonization and innovation into account. Specific emphasis was put on the value of EU level tools and best-practice exchange. Linking directly to the legal revision, the presentation further outlined the project's inputs

into the revision process, focussing on its recommendation for dynamic rule-setting, for example based on the EDQM guides, and for the establishment of a board to support the evaluation of novel BTC products.

3.4.4 Discussion and next steps

The floor was opened for questions or comments.

A reminder was issued that the GAPP Joint Action shall finalize and submit its request for an amendment to the grant agreement within the upcoming weeks. A question regarding the assessment of risk levels based on which clinical data requirements would be set was deferred, responding that the GAPP Joint Action would add this to their tasks.

In an anonymous online poll, participants expressed wide agreement with an upfront risk assessment for novel blood therapies, with proportionality as a principle for setting evidence requirements, and with the creation of a dedicated EU-level mechanism to provide advice on the application of the BTC framework. Moreover, most respondents indicated having good cross-sectoral interactions with the authorities governing Medical Devices or Medicinal Products "rarely" or "from time to time".

3.5 Supply sufficiency (Latest by 16:00h)

3.5.1 Measures in and feedback on the Inception Impact Assessment

DG SANTE presented strengthened supply monitoring and emergency supply measures as the two proposals for addressing issues related to supply sufficiency. On the basis of the mantra "collect once and use often", the need for effective activity data reporting was underlined and various benefits thereof were presented. A basic data set allowing for transparency for citizens and biovigilance was suggested, and the example of a mandatory data reporting set for corneas was shown. Ongoing work on the development thereof under the leadership of EDQM was presented.

Summarizing the feedback received on the IIA, general support for monitoring and data supply was reported. The high importance of dependencies in the field of plasma was underlined, as well as the concern that monitoring data may not be sufficient to tackle underlying drivers of supply insufficiencies.

3.5.2 Consultation questions

DG SANTE presented the relevant questions in the consultation surveys.

3.5.3 Datasets for blood

Jo Wiersum summarized the process of developing a harmonized guideline for activity data reporting based on questionnaires issued to relevant stakeholders, the results of which would then be summarized and turned into a draft for NCAs to comment on.

3.5.4 Discussion and next steps

Participants were invited to take the floor with any questions or comments.

Concerns were raised that EU level regulation of appropriate use would not be flexible enough to quickly adapt to progress in the medical field.

In response to an anonymous online question on success factors for activity monitoring exercises, a range of responses were received, centring for example on the need for harmonization and communication as well as clarity of all definitions. In addition, a majority of participants agreed both that future BTC legislation should address allocation and appropriate use for prioritization of patient needs, and that it should foresee EU-level exchange tools between Member States, although a significant group of participants remained unsure in the second case.

Two final online questions were asked to summarize the session. Firstly, respondents were asked to indicate whether they saw any topics not sufficiently addressed in the revision process. Mentions included inspector trainings as well as clinical follow-up. In response to a second question, participants indicated that they would take all topics back for discussion in their Member State, with a specific focus on audits, borderlines, and data collection.

4. ANY OTHER BUSINESS

None.

5. FINAL REMARKS

DG SANTE closed the meeting by thanking all participants and speakers for their valuable contributions. It was also highlighted once again that any engagement with the revision process is highly appreciated.