EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems, medical products and innovation
Medical products: quality, safety, innovation

Brussels
SANTE.DDG1.B.4/MA/ARES (2022)

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

COVID-19 meeting of the Competent Authorities for Tissues and Cells

12 February 2021

09:00 – 12:30 (CET)

13:30 – 17:00 (CET)

BY TELECONFERENCE

Minutes

Meeting for competent authorities for tissues and cells. The previous CA meeting was held on 19th of May 2020.

PARTICIPATION

There were 22 Tissues and Cells Competent Authorities attending the meeting, as well as Norway, Iceland and Turkey. The meeting was also attended by representatives from the European Centre for Disease Prevention and Control (ECDC) 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

DG SANTE welcomed the authorities to the meeting of Competent Authorities for Tissues and Cells. The status of the BTC revision was defined as focus of the meeting, and the use of online polling to gauge initial reactions to the presented material was introduced. It was clarified that the results of these polls would not be used as 'scientific opinions', but rather as indications to flag any significant concerns to the ongoing work. A change of agenda was announced, shifting the presentations on COVID-19 and Surveillance as well as that on the proposals for technical rules for quality and safety to the afternoon to accommodate for the absence of the representative of the European Centre for Disease Prevention and Control (ECDC). No conflicts of interest were declared.

2. COVID-19 AND SURVEILLANCE

2.1 Epidemiological state of play COVID and other CD (ECDC)

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.

3. REVISION FOR THE EU LEGAL FRAMEWORK

3.1 Process – state of play and planning

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, around half of the participants indicated already being familiar with the online consultations, while the other half was either partially or not familiar with them yet. Participants also confirmed that the topics proposed were the ones that should be discussed, signalling special interest in the role of expert bodies and inspections, as well as an overview of the proposed legislation under the different options.

3.2 Oversight

3.2.1 Measures in and feedback from the Inception Impact Assessment

DG SANTE presented the measures proposed to strengthen oversight under the future legal framework. These were divided into measures common between all policy options (including stronger principles in the legal text, developing a scheme for risk-based inspections, and supporting NCAs through mutual peer audits, training, and guidance). In addition, EU audits and joint inspections among Member States were proposed. These measures would differ depending on the final choice of policy option.

The presentation concluded by reporting general support for these measures from the IIA.

3.2.2 Consultation questions

A brief overview of the questions relating to oversight in the public and targeted consultation surveys was given.

3.2.3 Issues arising in the Inspection Expert Sub-group

DG SANTE went on to report from the meeting having occurred at the Inspection Expert Sub-group from February 2, 2021. Firstly, experience from a pilot 'remote audit' in Austria was presented. The exercise was considered positive and valuable, and interest for an additional pilot project in the year 2021 was invited. In addition, the IES underlined that they would be also willing to organise a joint inspection on-site if the pandemic situation allowed. Secondly, support for the proposed measures, specifically for principles on the requirements and trainings for inspectors, as well as EU audits and joint inspections, was reported. Specifically, EU audits were seen as a way to increase trust and confidence among Member States and thus decrease barriers for exchange of BTC, although a dissenting view from one Member State was reported as well. Joint inspections were considered particularly helpful in case of fraudulent activities impacting different Member States, when starting materials moved between Member States, or as a way to improve mutual support in case of lack of specific expertise.

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

The **Vigilance Expert Subgroup (VES)** reported on their work conducted over the last year, including an outlook into the future and the group's comments on the revision process. The presentation started by recommending that the definition of 'serious adverse event' be revised to align it between with other accepted definitions such as that used in Directive 2001/20/EC or by the FDA. It went on to report improvements in vigilance achieved through collaboration between the VES and NCAs, as for example the inclusion of transfusion reactions not linked to specific quality or safety concerns in the blood field as well as the inclusion of offspring from MAR procedures. In addition, audits for the national vigilance systems were suggested – these could be based on VES inputs for the tools for inspections and be used to encourage reporting. Opportunities for improvement of vigilance activities were presented firstly for the protection of recipients (these included clarification at the borderlines, specifically for novel products, improvements in communications within and beyond the SoHO sector, an inclusion of autologous procedures, and a need to improve the scope of SAE reporting by including issues in delivery and transport and considering to include errors/failures in clinical use) and secondly for the protection of donors, which the VES considered essential for informed consent and willingness to donate. This should include an active monitoring system for adverse reactions in donors as well as the long-term unwanted effects of repeat donations, and apply also for related donors and autologous applications. The presentation concluded by presenting the links between vigilance and self-

sufficiency in the EU, outlining how transparency, a harmonized activity data set, and an effective rapid alert system would bring mutual benefits.

3.2.5 Discussion and next steps

Four questions were asked through an anonymous online poll. The first one asked whether Tissues and Cells would be better regulated with separate sets of implementing regulation. A majority agreed while a significant minority disagreed, only few participants indicated that they were not sure. In the next questions, all participants agreed that they would welcome EU audits of their national oversight systems as well as an EU register of national inspectors with specialized/senior expertise that can be called upon to join/help national inspections. Finally, DG SANTE asked whether the participants were concerned regarding the resources and skills available in each CA if strengthened oversight measures were adopted. While few participants indicated that they were not sure, a vast majority indicated concern. DG SANTE underlined that considerations on support and a balance between binding rules and flexibility were ongoing. A question regarding the levels of regulation anticipated under Option 2 was posed, but could not be answered at this time as this depends on the outcomes of the Impact Assessment.

3.3 Updated safety/quality guidelines for recipients, donors and offspring

3.3.1 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.

3.3.2 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.

3.3.3 Inputs from expert bodies (EDQM and ECDC)

EDQM presented their work on the "Guide to the Quality and Safety of Tissues and Cells for Human Application", currently in its 4th edition with work ongoing for the 5th edition. The structure of the 4th edition was outlined (with a general part, a tissue-specific part, a part on developing applications, a part on GPG, a part on monographs and appendixes), and a more detailed breakdown of topics to be included in each of the parts of the 5th edition was provided.

The concept of monographs was specifically elaborated on to explain that these were procedures conducted along well-established criteria for safety and quality, thus replacing the need for a heavy preparation process authorisation or clinical studies. Furthermore, the presentation commented on the fit of the Directives from the EU with the technical guides from EDQM, outlining that the latter provided technical guidelines, based on regular and detailed updates, that supported the implementation. To place the guidance into the context of the wider sector, the role of professional associations in its drafting and the synergies with EU-funded projects were outlined.

The presentation went on to elaborate how an adoption of Policy Option 2 may impact their future work. While the coordination and the secretariat would fall to EDQM, the funding would come from both EDQM and the EU. The working group tasked with the elaboration of the guides would consist of 40 official experts nominated by the CoE Member States, selected finally by the Secretariat on the basis of expertise, drafting needs, participation in the previous work on the guides, and a balanced and broad geographical representation. A possibility to engage external experts for areas in which the Working Group felt to be lacking in expertise was also provided, as well as an opportunity for stakeholder consultation for 6 weeks. A more detailed elaboration of the process was given.

The presentation closed with additional information on two other projects. Firstly, participants were informed that a survey would be distributed to European TEs in the near future in the context of a project aiming to evaluate post-mortem testing practices and elaborate tailored recommendations for their improvement. Secondly, work on a critical pathway for deceased tissue donation was presented.

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, focussing 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.

3.3.4 Discussion and next steps

The contents of the presentation provided the basis for another round of anonymous online questions. First, participants were asked to choose from a range of options ('Nomination of experts to drafting committees', 'Privileged opportunity to review and comment before public enquiry', 'Nomination of voting members in parent committee', 'Veto if one or a certain number of authorities disagree with a point of guidance', 'Commission power to withdraw any legal reference to guidance on request of CA expert group') those that they considered most appropriate for the inclusion of NCAs in the adoption process of BTC guidance. The largest groups approved of 'Privileged opportunity to review and comment before public enquiry' and 'Nomination of experts to drafting committees'. The second question asked whether the referenced expert guidance should be made available through one online location or publication. The majority of participants agreed, while a significant group indicated that they did not hold a strong view on this.

The floor was then opened for further discussion. Concern was raised by a participant as to how the EDQM guide would fit into the legislation as a legally binding EU guide although it is not an EU document, and how its fit into national legislation would be supported. DG SANTE explained that the experiences of existing examples of this integration were being considered. EDQM further underlined that the drafting of the guidance had always been guided by EU legislation. The EDQM representative further mentioned that concerns came rather from non-EU Member States of the CoE, who were at times not sure whether their systems could comply with the strict EU guidelines.

3.4 Innovation

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 facilities of other 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 (CNT)

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

In response to the questions presented, almost all participants indicated support for an upfront risk-assessment as a starting point to authorize novel preparations and therapies and the need for clinical outcome data assessment proportionate to the identified risk/benefit balance. The creation of a dedicated EU-level BTC mechanism to advise on whether and what BTC requirements apply on a certain substance/product was also widely supported, although a group of participants indicated they were not sure. Finally, participants were asked to indicate whether they currently had good cross-sectoral interactions with the authorities for Medicinal Products or Medical Devices in their Member States. Most participants reported having interactions 'from time to time' or 'rarely'.

As the floor was opened for questions, a participant enquired on the role of the advisory committee, asking whether it would imply that the requirements set for the quality and safety of each type of tissue or cell would leave a margin of interpretation in which additional advice would be required. DG SANTE replied that further details were not yet clarified.

It was stated that BTC authorities should have more say in classification decisions, which is not sufficiently the case at present. DG SANTE replied there will anyhow be a need for a possible EU-level advisory body on the application of the BTC legislation to interact closely with equivalent bodies in other legal frameworks in case questions relate to the borderline. Such consultation and coordination should allow for inputs in classification decisions that relate to the borderlines of BTC and other legal frameworks.

A final question addressed the implementation of the Medical Device Regulation, asking whether there were any difficulties foreseen regarding the potential re-classification of tissue-derived products. DG SANTE replied to say that work bringing together a group of experts from both the Medical Device field and the BTC field was ongoing.

3.5 Supply sufficiency

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.

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 Tissues and Cells

On the basis of the mantra "collect once and use often", **EDQM** presented the need for effective activity data reporting and its various benefits. 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.

3.5.4 Discussion and next steps

Some questions were posed to the participants. When asked to enter keywords to describe key success factors for any activity monitoring exercise (for example regarding supply, exchange, import, or export), different responses were presented. The most widely recurring concern was legal clarity. Participants had different views on whether the revised BTC legislation should also address allocation and appropriate use of BTC, ensuring prioritising the need of most critical patients. Finally, a majority indicated that the revised BTC legislation should foresee EU-level exchange tools to optimize use of BTC amongst Member States, while some participants remained unsure.

Closing Questions

To draw the session to a close, the participants were asked to enter keywords for any topics or issues that they did not consider sufficiently addressed by the policy options, consultations, or workshops. Concerns were raised regarding sustainability, manipulation within the surgery room, genetic testing for gamete donors, and product authorisations for well-known products.

The final question asked participants to indicate which topics they intended to discuss with colleagues from their authorities or ministries. Answers focussed mostly on participation in the further process of the revision (consultation questionnaires and workshops) as well as the resources needed to prepare for the new framework. One comment stated that communication with the Ministry of Health was anticipated to be difficult, as experience showed that it was rather assumed that the NCA would handle any issues related to the BTC legislation independently.

4. ANY OTHER BUSINESS & CLOSING REMARKS

As final remarks, the participants were invited to respond to a survey developed by the French Authorities and DG SANTE regarding the regulation of bed-side devices. In addition, participants from Poland presented an update on the CRYOSAVE file. Finally, DG SANTE thanked participants and presenters for their active participation and reiterated that their engagement and support would be counted on in an intense and important period ahead.