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

Meeting of the Competent Authorities for Tissues and Cells

16 June 2022

13:30 – 17:30 (CET)

BY TELECONFERENCE

MINUTES

Participants: representatives from all 27 EU Member States except for Hungary and Poland, as well as representatives from EEA Members Iceland and Norway and candidate countries Montenegro and Turkey participated in the meeting. In addition, representatives from the European Directorate for the Quality of Medicines (EDQM) and the European Centre for Disease Prevention and Control (ECDC), as well as a representative from the EU's Health and Digital Executive Agency (HADEA) were present as observers. Some speakers joined for dedicated items of the agenda, such as representatives from DG SANTE and from the Swedish NCA for pharmaceuticals.

1. WELCOME, INTRODUCTORY REMARKS AND ADOPTION OF THE AGENDA

A representative from DG SANTE opened the meeting and welcomed all participants. The agenda was adopted as shared in advance with the participants on CircaBC, after confirming that no national competent authority (NCA) had additional points to add. Participants were reminded that minutes would be prepared by DG SANTE and published on their website and invited to use the chat box or the 'raise your hand' function to ask any questions.

2. REGULATORY MATTERS: POINTS FOR INFORMATION

2.1. State of play of the BTC legislation revision (INFO)

DG SANTE presented the state of play of the BTC legislative revision. After reiterating that it is not yet possible to present the concrete substance of the proposal, participants

were informed that the content of the proposal is in last internal discussions, and the ongoing administrative process would likely result in an adoption in summer 2022 (possibly July). The presentation also gave an outlook on the political discussions which would be organised in the Council after adoption, particularly the opportunities for feedback and involvement of stakeholders. Participants were invited to start bringing their views forward in their ministries and to liaise with colleagues to prepare for the new proposal, especially in coordination with the implementation of the revised rules for Medical Devices and the ongoing revision of the pharmaceutical framework.

2.2. Presentation on the pharma revision process and plans

A presentation by DG SANTE started with a brief introduction of the Pharmaceutical Strategy for Europe, which was adopted in November 2020 as the long-term agenda in the field of pharmaceutical policy, aiming to create a future-proof regulatory framework that supports industry in promoting research and the development of accessible technologies and therapies. As the four pillars of the strategy, the presentation highlighted:

1. Learning form COVID-19, towards a crisis-resistant system
2. Ensuring accessibility and affordability of medicines
3. Supporting sustainable innovation, emerging science, and digitalisation
4. Reducing medicines shortages and securing strategic autonomy.

The presentation went on to elaborate on actions under four flagships of the pharmaceutical strategy:

1. The strategy aims to **ensure access and affordability of medicines for patients and health systems sustainability** by *fulfilling unmet needs* (such as support on novel antibiotics and medicines for children and rare diseases, optimisation of the use of antimicrobials) and generating further evidence on other potential unmet needs. It further aims to improve *accessibility* by revising the system of incentives and obligations in legislation that determine innovation, access and affordability and supporting access to generic and biosimilar medicines. Finally, it aims to improve *affordability* by addressing in legislation the market affects and improving exchange and mutual learning on policy responses in the pharmaceutical market.

2. To **enable sustainable innovation,** the strategy focusses on creating a *fertile environment* by optimising the supplementary protection certificates system, supporting the creation of interoperable data access infrastructure (for example under the European Health Data Space), and supporting public-private and public-public partnerships. In support of *innovation and the digital transformation*, it supports the adaption of legislation to scientific developments and transformation as well as enhanced stakeholder dialogues. Other measures include taking forward HPC and AI and establishing access to genomes. Finally, both the approval procedures and the lifecycle management of medicines shall be streamlined, simplified, and optimised by *flexible regulatory systems*.

3. Working towards **ensuring availability and addressing shortages,** the strategy has launched a structured dialogue to identify vulnerabilities in the global supply

chain and taken steps to improve the transparency on this matter in industry with the aim of *securing supply*. This aspect is also central to the revision of the legislation, along with ensuring *environmental sustainability* and preparedness and revising environmental risk assessment requirements. Finally, the strategy interlinks with the proposal for a EU Health Emergency Response Authority (HERA) as a key *crisis response mechanism*.

4. Finally, the strategy works together with EMA and the network of national regulators to **succeed on the global level** by promoting regulatory convergence to ensure access to safe, effective, high-quality, and affordable medicinal products globally.

To close the presentation, the speakers presented the indicative timeline of the revision process.

After the presentation, participants of the T&C national competent authorities were presented with a range of questions in an online poll:

- Respondents indicated with a wide majority that they **expected impacts of the revision of the pharma framework on the scope of the BTC framework to be possible**. Respondents used free text boxes to indicate both possible advantages (especially regarding more clarifications of the borderline between the two frameworks, including for starting materials, but also regarding harmonised implementation, facilitated authorisations or securing of products in the non-profit sector) and possible disadvantages (increase in costs and reductions in access, more commercialisation of substances from the BTC sector, more uncertainty/lack of clarity, heterogeneous evaluation of products and suboptimal applicability of the pharmaceutical framework to the activities in blood and tissue establishments (BE/TE)).

- When asked for their views on **the current list of exemptions in Article 3, if the reference to 'prepared industrially or manufactured by a method involving an industrial process' were removed from Article 2**, respondents used the free-text box to indicate a concern on legal clarity and the need to carefully assess the potential effects of any changes on the borderline with BTC.

- Around half of the respondents indicated seeing a need for a **new additional exception for blood components.** Around the same number of respondents indicated they were not sure, while two respondents indicated they did not see this need. When asked what should be covered by such an exemption, responses included serum eye drops, platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and blood products that are not industrially prepared. Respondents also called for a European classification mechanism on borderline substances, and more clarification on the future interaction of the two frameworks.

- Over half of the respondents indicated seeing a need for a **new additional exemption for tissues and cells.** Some respondents indicated that they were not sure, while one disagreed. When asked what should be covered by such an exemption, respondents mentioned partner donations, adipose cells, SoHO or tissues and cells in general, bedside preparations (as these were currently also excluded from the Tissue and Cell Directive and thus not covered, and risks to also fall into the ATMP legislation if the reference to industrial processing were

removed), breast milk, personalised treatments for small patient groups, or any tissues or cells covered by the EDQM monographs.

- Around half of the respondents indicated seeing a need for a **new additional exemption for SoHO**, while the remaining participants indicated that they were not sure. Asked for examples, respondents referred to SoHO used with non-commercial purposes or where consent for use with profit was not given, autologous transplants as part of the same surgical procedure, faecal microbiota transplants (FMT), or all SoHO covered by the current or future frameworks.

- When asked for their views on the presented considerations on the **hospital exemption for advanced therapies** and their impacts, some respondents indicated that it should be kept (or extended), while others indicated a need for a better link with existing GMP or increased flexibility, and a third group raised general concerns of the exemption's impact on patient access.

- Participants were finally asked what other **measures would be needed to ensure a common legal view on whether a therapy is subject to the pharma legislation or not, if the 'industrial preparation' criterion were removed** from Article 2. In free-text responses, respondents gave suggestions such as the need for consideration of the GAPP guides, the number of patients able to be treated, a classification board or other formal coordination mechanism or procedure, a living list of classification for reference, a risk-based assessment to be applied for all products, and a clarification or reinforcement of the other criteria (substantial modification and non-homologous use).

- When presented with concrete suggestions for a **consultation mechanism with authorities and advisory bodies in BTC frameworks**, all the respondents agreed that this should provide legal clarity on the applicable legal framework, and almost all of the respondents agreed that this should develop common guidance for the therapies where requirements of both frameworks could be combined (i.e., where SoHO are starting materials for pharmaceuticals).

- When asked for **other measures needed,** respondents suggested considerations are needed for: cost and accessibility, risk assessments, (binding) classifications, harmonisation, measures tackling plasma shortages, improved cross-referencing between the two frameworks, and that the Committee on Advanced Therapies (CAT) and the Medical Device Committee could be combined with the new consultation mechanism.

2.3. Other Member State legislative updates

Member States were invited to flag any national legal developments of possible interest. No Member State reported any development.

3. PROJECTS

Representatives from DG SANTE provided introductions to different projects and actions to be implemented soon under the EU4Health scheme.

3.1. New SoHO Joint Action – follow-up, pilot and take-up the GAPP approach by national authorities

The presentation opened with a quick summary of the outcomes of the past GAPP Joint Action (completed in 2021), highlighting the resulting concept for a common tailored approach to authorise new BTC preparations based on risk assessments, proportionate clinical evidence, and conditional authorisations. It was underlined that this is expected to facilitate access to safe and effective innovative BTC therapies, and thus supports the EU4Health objectives to support innovation and the availability of crisis-related projects.

As a follow-up, the objectives and expected outcomes of GAPPII were introduced. This new project will aim to test and refine the GAPP methodology for use by professionals and authorities, particularly by considering new developments in the BTC sector (such as blood and plasma for transfusion in the blood sector, cells for transplantation and gametes for reproductive medicine in the tissue and cell sector, or newly regulated SoHO such as FMT or breast milk). The presentation also highlighted that the project aims to include pilot cases to document lessons learnt and formulate recommendations, focussing for example on challenges and success factors in different Member States, cross-country applications and assessments, or the interactions with other EU legal frameworks (such as those for medical devices or medicinal products).

The presentation closed with a summary of key practical points, explaining the scope of the research and the criteria for beneficiaries, affiliated entities, and associated partners. Participants were informed of the deadline for submission of a proposal and strongly encouraged to consider their participation in the Joint Action.

3.2. Information on upcoming procurements under EU4Health (including service contract on management of SoHO within the hospital)

DG SANTE went on to present two other upcoming procurements under the EU4Health as well as the current state of the IT project SoHO-X.

- Training oversight staff - procurement

Participants were reminded that a call for tenders for organising "Training and networking of Substances of Human Origin (SoHO) Competent Authorities' staff for oversight" has been published on Monday 10th of May and is open till 17 June 2022.

Hospital management of SoHO (blood banks) - procurement

Participants were given initial insights into the development of a project which aims to map the current approaches to ensuring safety, quality, and traceability of SoHO in hospitals across the EU and identify the roles of different departments in the hospital (such as the hospital blood banks, quality management departments, haematology departments, pharmacies, or others). This project is expected to result in recommendations built on wide stakeholder involvement and support for the optimal management of SoHO safety and quality in hospitals.

- IT planning (SoHO-X)

The presentation started with a quick summary of the aim of the SOHO-X platform in embedding different IT modules to support data flows and use by professionals, national authorities, and EU, thus supporting the functioning of the sector in ensuring safety and

quality as well as oversight, innovation, and supply sufficiency. The speaker went on to provide an update of the current state of the project, explaining that an overarching set-up is being created and that the development of first modules is scheduled to start at the end of 2022. It was further elaborated that these first modules would include a registry of all entities, a dissemination platform for all (EU and national) technical guidelines and the GAPP support module for applicants (professionals) and assessors (authorities). It was particularly highlighted that input from NCAs and other stakeholders would be key in the design process of the platform.

3.3. EU4HEALTH new project "EGALITE"

A speaker from a new project called 'European Group for Accreditation and Liaison of Blood-Tissues and Cells Establishment' (EGALiTE) presented the project's goals, partners and expected outcomes to the participants. The presentation first outlined the context of the project, which is financed under the EU4Health scheme in response to the concerns and needs identified by the sector during the COVID-19 pandemic. It was elaborated that the project would aim to:

1. Develop a European Accreditation Program to achieve mutual recognition amongst SoHO organisations
2. Optimize resources and improve collaboration, hoping ultimately to define strategies to promote self-sufficiency in the EU
3. Enhance the ability of SoHO organisations to respond during crisis to ensure the supply of essential SoHO and define technical assistance projects.

These aims are to be achieved by October 2024 and consider blood, tissues, and haematopoietic stem cells (HSC).

The presentation went on to highlight the use of available resources, such as the EDQM guides on blood as well as the EuBIS and CATIE projects. Furthermore, it introduced the 15 beneficiaries (including BE/TE, NCAs and scientific societies from 10 Member States) as well as the 10 organisations which would be involved through external experts. The role of the Banc de Sang i Teixits as coordinator was especially highlighted.

The timeline of the project, including its 8 work packages, was presented.

4. EUROPEAN AGENCIES AND INTERNATIONAL ORGANISATIONS

Speakers from EDQM, ECDC and the Heads of Medicines Agency/Borderline Classification Group were invited to the floor to give their own updates.

4.1. EDQM: update on recent activities and introduction to the new ERiCA tool and *post-mortem* testing activity

The presentation started by outlining the governance structure of the SoHO activities in the Council of Europe, highlighting the six fields of activity in the field of transplantation (legal guidance, fight against organ trafficking, following scientific developments, international monitoring, international cooperation, visibility awareness raising, and cooperation with the EU). The technical guidelines were then presented in more detail, highlighting their aim of employing the best available scientific evidence to ensure high levels of safety and quality through harmonised and consensus-based implementation as well as their development in 2–3-year cycles.

The presentation further focussed on the microbiological risk assessment tool ERiCA, which fill gaps left by existing risk assessment tools for the aseptic procurement and processing of T&C. The presentation outlined how this tool can help tissue establishments to calculate a risk score for their activities in procurement and processing, and then define the minimal requirements and identify areas for improvement.

After that, some further insights were given to the updates planned for the 5th edition of the tissue and cell guide. This included the inclusion of additional substances (breast milk, faecal microbiota, and tissues and cells used as starting materials for ATMPs) and the expansion to 43 monographs.

The presentation finally provided additional information on some other ongoing projects, namely:

- **Training on Quality Management for tissue establishments**: an online training course aiming to supply tissue establishments with tools for successful implementation of a quality management system

- **Harmonising activity data collection**: a project focussed on developing recommendations for a minimum data set (supported by a glossary) to assess availability and needs of tissues and cells throughout Europe, with the goal of improving distribution and self-sufficiency

- **Understanding post-mortem blood testing practices for tissue donations**: recommendations on improving the current state-of-the-art, which is characterised by heterogenous approaches that leave room for sample loss as well as donor loss due to sampling delays. This project has concluded recommendations for the European Commission, the National Competent Authorities, tissue establishments, and screening laboratories which allow to increase the number of tissue donors while maintaining necessary safety parameters in screening.

- A range of additional projects around the work of EDQM in tissue and cell donations.

4.2. ECDC update on communicable diseases and introduction to the Network for the Microbial Safety of Substances of Human Origin (SoHONet**)**

The presentation from ECDC started with an update on Monkeypox, outlining the geographical distribution of the current total of 1 884 cases in the world as well as the known pathways of transmission (through respiratory droplets in prolonged face-to-face contact, close contact with infectious material from skin lesions of an infected person, fomites and contact with infected animals) and the clinical manifestations (fever, myalgia, fatigue and headache, lymphadenopathy, maculopapular rash). It was specified that the transmission of monkeypox through SoHO was not documented but likely possible based on virus presence in the blood and reported cases of virus transmission from mother to child during pregnancy. As preventive measures, the presentation recommended careful interviews with potential donors on contacts with confirmed or suspected cases (as well as with infected animals), the collection of hetero-anamnestic data for deceased donors, and the deferral of asymptomatic contact persons for at least 21 days with a careful examination for any possible signs of infection after this deferral. The presentation also referred to the ECDC's risk assessment for Monkeypox, found here.

The second part of the presentation outlined health considerations associated with the arrival of people displaced from Ukraine to the EU, noting that overcrowding could favour outbreaks of infectious diseases, in particular respiratory infections. The presentation also highlighted difficulties for displaced people accessing healthcare and sub-optimal vaccine coverage in Ukraine, as well as possible increases in demands for SoHO.

The presentation also touched upon other topics, such as the reporting of measles in the EU/EEA, a new Ebola virus disease outbreak in the Democratic Republic of Congo, and Chikungunya virus disease and dengue fever. It was elaborated that the newest update for the risk assessment on SARS-CoV-2 was yet under revision but would cover the expansion of the donor interview to include SARS-CoV-2 symptoms, the need for universal microbiological screenings of donors, and the procedures for donors with a previous diagnosis of COVID-19. Regarding severe acute hepatitis of unknown aetiology in children, it was highlighted that an infectious aetiology was not confirmed, while detailed epidemiological and laboratory investigations were still ongoing.

The second part of the presentation focussed on the establishment of the ECDC SoHO expert network (SoHONet), which aims to ensure microbial safety of SoHO and protection of patients in need of SOHO by encouraging cooperation between Member States, supporting work on cross-border health threats, obtaining technical and scientific expertise from ECDC, and enhancing preparedness and response planning activities in the EU. The plans for SoHONet were elaborated on.

Finally, the presentation encouraged participants to respond to a call for interest regarding expert contributions to an ad-hoc panel developing guidance on Chagas disease (in particular SoHO donor selection and preventive measures in EU/EEA countries), especially those with knowledge on transplantation (tissues and cells), diagnostic test methods for *Trypanosoma cruzi*, and processing methods regarding elimination of parasites.

4.3. Heads of Medicines Agencies/Borderline Classification Group (HMA/BLCG)

A representative of the Swedish National Competent Authority for pharmaceuticals presented the work of the Borderline Classification Group (BLCG), set up in 2021 within the context of the EU Innovation Network (EU-IN) established by the European Medicines Agency and the Heads of Medicines Agency. The wider role of the EU-IN was elaborated before focussing specifically on the problem statement for borderline products, meaning products on which competent authorities in member states are not able to determine a clear-cut decision on whether it is a medicinal product or not. The presentation highlighted the goals of the BCLG, namely the provision of informal discussions between competent authorities and other relevant groups from different scientific fields, and the development of recommendations on an EU-wide classification system/collaboration for developers of innovative complex products.

The presentation closed with achievements from 2021 (development of a template for presentation of cases by members, discussions on 13 borderline cases and case law with its impact on classifications, interactions with members of other relevant entities and the drafting of a list of groups and bodies that discuss and perform classifications) and from 2022 (the formation of a ‘Rapid Discussion Group’ as well as the continuation of work on interactions and discussions and an exploration of education and training opportunities).

It was further highlighted that BLCG is open for some SoHO/TC NCAs as observers/participants. The presentation closed with a call to encourage NCAs to express

interest to participate, and then report back to future BTC NCA meetings. NCAs were also encouraged to be in touch with national members of BLCG.

5. AOB

5.1. HPC collection kit supply issues

A representative from DG SANTE relayed information from the World Marrow Donor Association (WMDA) and the European Society for Blood and Marrow Transplantation (EBMT) regarding an imminent shortage of bone marrow collection kits. It was explained that this shortage, expected to affect the market as of August 2022 because of the withdrawal of two main suppliers (Fresenius and Bio-Access) from the EU market, would affect about 1000 transplant per year (mainly paediatric).

Elaborating on actions taken, DG SANTE highlighted planned meetings between SANTE-B4, SANTE-B6, the companies and German authorities/Paul Ehrlich Institut (as most of this bone marrow is collected in Germany). The presentation further outlined some potential approaches, such as creative/new administrative procedures including a protocol to self-assemble the kits in transplant centres, or authorisation of imported, non-CE marked kits.

Member States were asked for further information or points to raise in this regard.

5.2. SARE web reporting

A representative from DG SANTE provided a summary of the latest available SARE web reporting.

5.3. **Final Remarks**

The meeting was closed, and all participants were thanked for their attendance.

PLEASE NOTE THAT ALL SUPPORTING DOCUMENTS WILL BE SENT TO YOU VIA THE CIRCABC SITE BEFORE THE MEETING.