EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

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

Brussels, SANTÉ/DF

Workshop with Stakeholders and Blood, Tissue and Cell Competent Authorities Substances of Human Origin Expert Group (CASoHO E01718)

6 May 2021, 09:30-13:00

By teleconference

WORKSHOP TOPIC: Setting Technical Rules for BTC

Participants: All EU blood and T&C competent authorities as well as the authorities of Iceland, Liechtenstein, Montenegro, Norway, Serbia and Turkey are in attendance. In addition, representatives of the European Directorate for the Quality of Medicines (EDQM, Council of Europe) and from the European Center for Disease Prevention and Control (ECDC), as well as from the following stakeholder organisations attended: European Blood Alliance, European Plasma Alliance, Plasma Protein Therapeutics Association (PPTA), International Plasma Fractionators Association (IPFA), European Association of Tissue and Cell Banks, European Eye Bank Association, European Society for Blood and Marrow Transplantation, European Society for Human Reproduction and Embryology, the Consortium of SoHO Associations, the Cord Blood Association, and the International Society for Cell Therapies (ISCT) and the ATMP interest group of ECA.

Problem addressed in this workshop: The current BTC legislation includes many technical rules that have not kept pace with innovation. The BTC Impact Assessment is exploring 3 policy options to address this shortcoming.

Workshop objectives: Based on preliminary feedback from the Inception Impact Assessment, this workshop aimed to focus on policy option 2, with the objective of considering the key success factors for referencing technical rules defined by expert bodies in EU legislation. Issues to be explored included the governance and management of the updating of technical rules, the use of evidence, ensuring transparency and adequate consultation. As appropriate, policy options 1 and 3, as approaches to defining technical rules, were also to be discussed.

1. WELCOME AND INTRODUCTION OF STAKEHOLDERS PRESENT

DG Santé opened the Workshop by welcoming all authorities and stakeholders. The context of the Workshop was explained, highlighting that it formed part of the Impact Assessment process for the revision of the legislation on blood, tissues, and cells (BTC). Specifically, the key aim of addressing problems regarding the setting of technical rules, which, in the evaluation of the legislation were found to lag behind scientific and epidemiological developments, was reiterated. Attendees were reminded that this workshop was organized as a hearing, in the same format as those on the previous days, giving stakeholders active in the field an opportunity to

present their positions on this issue to the national competent authorities. It was reiterated that all views expressed would add to the evidence base for the Impact Assessment.

Authorities were reminded of the opportunity to ask any questions to the presenters, and the concept of anonymous online polling during the workshop as a way of gathering reliminary reactions to stakeholder proposals was introduced. Looking forward, a reminder was issued that competent authority meetings in June were already scheduled and planned as open discussions on the issues arising from the hearings organised by DG Santé, including this one, as well as the workshops organized in the context of the external study supporting the Impact Assessment.

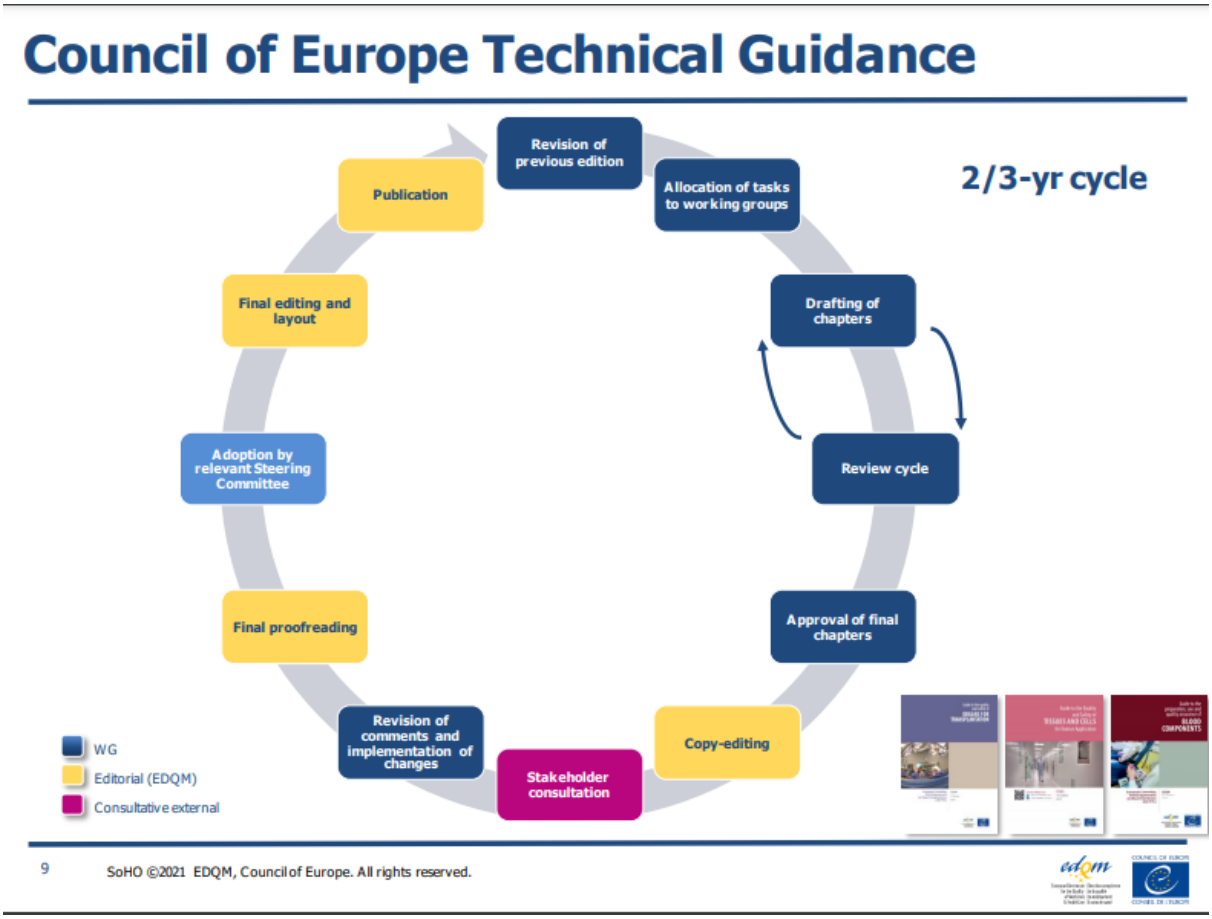
2. INTRODUCTION TO THE WORKSHOP TOPIC – DG SANTÉ

To further introduce participants to the topics of the Workshop, DG Santé gave a presentation of the issues arising from technical rules that are not kept up-to-date, specifically inadequate protection of patients on the one hand and donors and offspring on the other, were reiterated. The presentation outlined the three policy options available, namely the defining of technical rules either by (1) professionals on the basis of local risk assessment and evidence gathering, (2) expert bodies such as ECDC and EDQM with references to those rules in EU legislation, or (3) the inclusion of detailed provisions in EU legislation with more frequent updating. The possibility of combinations of these options was highlighted, for example by adding principles to the EU law regardless of the option chosen for specific rules, as well as the need for considerations of the appropriate extent of 'bindingness' and the time needed for updates. Participants were also reminded of the feedback expressed in response to the Inception Impact Assessment, from which Option 2 had emerged as a general preference.

Preliminary conclusions of the Public and Targeted Consultations were also presented by DG Santé. The presentation highlighted the high rates of response to both, as well as the spread of participants across and between sectors and stakeholder groups. A range of specific questions were presented, in which respondents to the questionnaire had expressed their preferences for one of the three policy options in relation to this topic. It emerged that professionals were seen as the most appropriate group for setting of technical rules in BTC allocation and distribution channels, while expert bodies were preferred by a majority of respondents for rules on air quality requirements, deferral/exclusion criteria and communicable disease testing, donor age limits, donor medical/behavioural history screening, follow-up of patients or offspring, genetic testing of gamete donors, quality controls, quality management, risk assessment for novel procedures, and storage conditions. Finally, respondents tended to favour rules set in EU law for issues regarding contingency/emergency planning, consent, donor protection, donor reimbursement/ compensation, reporting (activity data reporting to the NCAs, SARE reporting to BE/TE and onwards) and traceability systems. The presentation further highlighted the wide agreement found in the Public Consultations regarding the role of ECDC in communicable disease testing (both the types of diseases to be tested for and the methods to be used for testing) as well as donor deferral/exclusion criteria. It was also reported that a majority emerged in favour of making EDQM's Good Practice Guidelines on Blood and those on Tissues and Cells mandatory, with a second-largest group favouring legal references to the entire Tissue and Cell Guide. Finally, preferences given in response to different options for the role of professional and scientific associations in the context of rule setting were reported from the TPC. These concluded that representation on expert committees established for this purpose was regarded as most important.

3. EDQM - BUILDING ON EXISTING EXPERIENCES WITH REFERENCING EXTERNAL STANDARDS/GUIDANCE IN EU LEGISLATION

The presentation by EDQM started by outlining their existing work on technical guidance for the safety of BTC, and how this work complements the role of the EU. It was specified that the Council of Europe supports the harmonized implementations of legal texts and their requirements and benchmarks through comprehensive guidelines which are continuously updated to include state-of-the art evidence. After introducing the structure of the Guides for Tissues and Cells as well as for Blood, the process of the development thereof was summarized as shown in the graphic below.



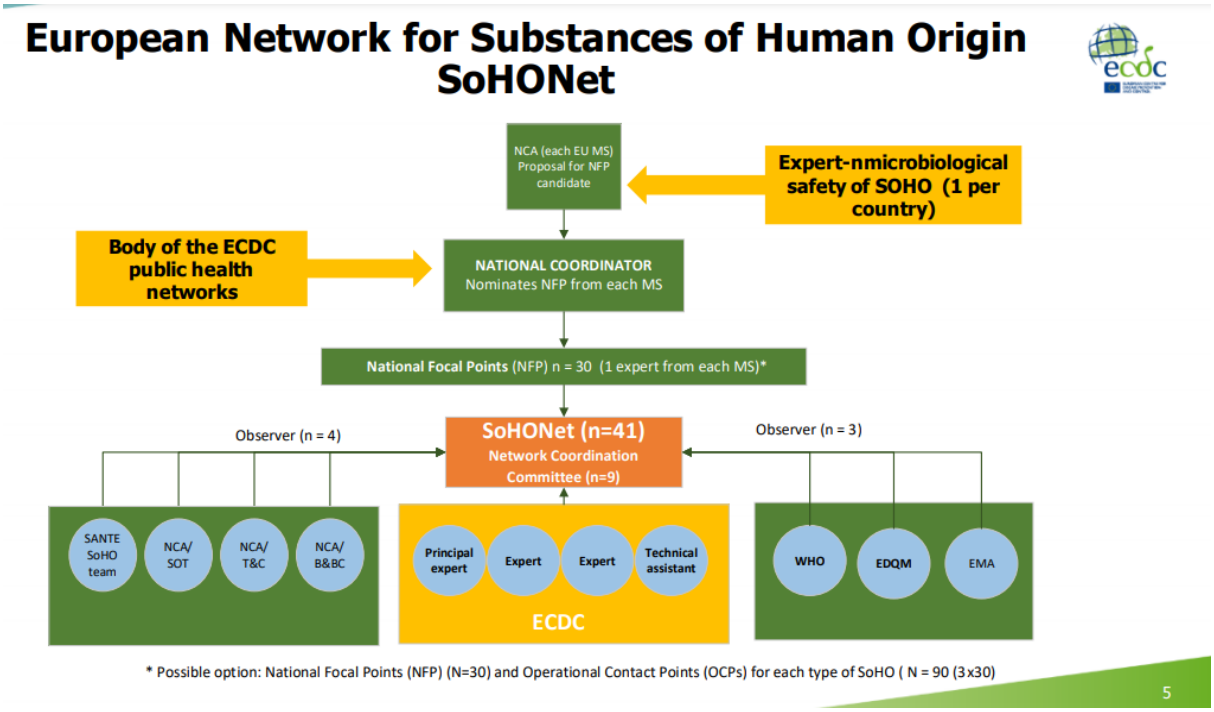
The presentation then addressed the potential practical implementation of Option 2, using an approach similar to that applied for the European Pharmacopoeia (Ph.Eur.), as an informative precedent. It was described how the binding monographs developed by the Ph. Eur. Expert working groups serve as a legal and scientific basis for the quality control throughout the life cycle of a medicinal product, being applied by regulatory authorities, quality controllers, and manufacturers of (active substances of) medicinal products. Further explanations were provided regarding the process for developing such monographs. Following an initial request, which the Ph. Eur Commission then endorses the proposal. Submitted data is reviewed by a specifically assigned Ph. Eur. group of experts. On that basis, a monograph/chapter is drafted and published for comments, which are evaluated after a consultation period of 3 months. After adoption by the Ph.Eur. Commission and publication of the monographs, registered products must comply with their requirements. Responsibility for this lies with the national competent authorities or the European Medicines Agency (EMA) at the time of submitting the Marketing Authorisation dossier.

Modelled after this example, it was suggested that a similar revision process should be used for the implementation of Policy Option 2 in the BTC field. Coordination for this should lie with the EDQM as it is currently the case, while the drafting groups would be composed of members (experts) nominated by the delegates of the relevant Steering Committees (CD-P-TO or CD-P-TS), which then adopt the guides Member States should take responsibility for overseeing the compliance of blood and tissue establishments.

In response to a question regarding the selection criteria for drafting groups of the EDQM guides, EDQM highlighted that nominations are invited from all 47 member states of the Council of Europe including all EU Member States. In establishing drafting groups, geographical representation, required expertise (dependent on the technical topics that needed to be drafted) and conflicts of interest were taken into account.

4. ECDC – Extended ECDC mandate and future plans for SoHO communicable disease guidance

Following a summary of the role of ECDC in the field of BTC to date, the presentation described plans for a European Network for Substances of Human Origin (SoHONet) according to the structure presented below and in line with the Commission Proposal for an extended mandate for ECDC.



The presentation elaborated on ECDC guidelines on infectious safety for professionals, outlining firstly the role of ECDC, the European Commission, and the EU Member States as initiators in the process, and secondly the development of guidelines on an ad-hoc basis, within the ECDC annual work plan, or as part of a Rapid Risk Assessment. To close the presentation, the existing role of ECDC in setting rules for the prevention of communicable disease transmission through substances of human origin was summarized.

In response to audience questions, some further elaborations were provided regarding the potential inclusion of scientific professional societies as well as existing SoHO platforms into the design of the future procedures. It was also confirmed that the final decision-making power

regarding the acceptance of nominated experts should remain with ECDC. Finally, in response to concerns raised by audience members regarding the nomination of one single expert from each MS to represent both fields (blood on the one hand and tissues and cells on the other), ECDC replied that coordination in these cases should be conducted at the Member State level.

5. A SERIES OF SHORT PRESENTATIONS BY BTC ASSOCIATIONS ON *HOW TECHNICAL RULES FOR BTC CAN BE KEPT UP TO DATE AT THE EU LEVEL*.

a. EUROPEAN BLOOD ALLIANCE

EBA expressed a preference for Policy Option 2, based on the opinion that the technical provisions of the current EU Blood Directive are too detailed and difficult to update. The presentation specifically recommended firstly that the EU should qualify blood, tissues and cells as strategic resources and ensure collection through voluntary non-remunerated donation (VNRD), secondly that EU legislation should set and define the general and ethical principles, and thirdly that the updating, scope, and specifics of these principles should be developed in technical rules developed by expert bodies.

EBA further suggested key features for inclusion in new EU legislation:

1) Rules for donor protection (specifically donor/family consent, protection and follow-up, and compensation and reimbursement)

2) System requirements for safety and traceability

3) Reporting requirements for (serious) adverse reactions and events to the BE/TE and to the authorities

4) Requirements for quality management

5) Requirements for contingency/emergency planning, including rules for risk assessment and requirements for activity data monitoring and reporting.

The presentation finally expressed support for the inclusion of references to the Blood guide and the Tissue and Cell guide from EDQM in future EU legislation.

Answers to an anonymous online poll indicated that a majority of participants agreed or partially agreed that updates, scope, and specifics should be developed through technical rules developed by expert bodies, while a significant group also flagged a need for more information/discussion. When asked which rules should be defined in EU legislation, the most selected topics were donor protection rules, vigilance rules, traceability rules and requirements for activity data reporting to NCAs. A slightly smaller majority expressed support for quality management principles and contingency planning requirements to be defined in EU legislation, and slightly less than half of all participants also supported the inclusion of rules for risk assessment for innovation.

b. PLASMA PROTEIN THERAPEUTICS ASSOCIATION

PPTA reiterated that technical rules are not up to date with innovation, science, and manufacturing practice. On that basis, they expressed the need for the creation of a ‘plasma

expert body' that would set rules applicable to plasma for manufacturing, taking into account the involvement of external experts with relevant expertise, considering that plasma for manufacturing is different from labile blood components used for transfusion purposes in terms of processes. PPTA also stated the need for utilisation and improvement of existing governance frameworks (e.g., EMA guidelines, EMA Plasma Master File (PMF) system, Annex II 2002/98/EC reporting). PPTA welcomed the proposed stronger mandate of ECDC in routine surveillance of communicable diseases but remarked on the need to consider current requirements for EU PMF Holders in order to avoid duplication of efforts. PPTA also reiterated the need for EU-level transparency and rule setting mechanisms (e.g. stakeholder consultation processes) for any guidance issued by expert bodies such as the EDQM and ECDC.

In an anonymous online poll, participants flagged a significant need to discuss further the distinction between plasma for manufacturing and plasma for transfusion when setting technical rules for infectious disease testing or when developing EDQM guidance. A similar need for discussion was found with regards to the set-up of a 'plasma expert body'. Wide support was indicated for EU principles for transparency and inclusion to be applied to the drafting and adoption of EDQM guidance, with a smaller group still highlighting a need for further discussion.

c. Consortium of Representative SoHO Associations

CoReSoHO outlined non-renumerated donation, the principle of not for profit/non-financial gain, sufficiency, and sustainability of access as fundamental principles to be maintained in the BTC revised legislation. On that basis, support was expressed for Policy Option 2, with a specific focus on allowing innovation, addressing commercialization, speeding up the updating of standards, merging legislations, and tackling contingencies and threats. The presentation further underlined the key role of professional expert representation at the EU level, and the added value of flexibility in the choice between policy options. This choice, they underlined, should be made based on a trade-off between flexibility and enforcement assurance.

Of the respondents to an anonymous online poll of participants, around half expressed full agreement that the choice between policy options should be adapted to different types of rules, while a significant group flagged a need for further discussion. A less clear picture emerged when assessing whether the trade-off between flexibility and assurance of enforcement should be used to govern the choice between policy options, in this case, many saw a need for more discussion on the details.

d. European Association of Tissue and Cell Banks

EATCB expressed support for Policy Option 2, based on the expertise of ECDC and EDQM. They further suggested that these bodies should be advised by experts from the field, modelled after the working groups that contribute to the Tissue and Cell Guide of EDQM. Moreover, the presentation outlined that this guide should be used as a template for the format in which quality and safety requirements are communicated, distinguishing between parts that are mandatory, advisory, or for information. Finally, they insisted that urgent updates must be possible in between full guide revisions.

In an anonymous online poll of participants, a large majority expressed full agreement with the use of the EDQM guides as a basis for future rules and with the need for real-time updates for

urgent cases. Especially regarding the updating frequency, a need for further discussion was indicated.

e. EUROPEAN EYE BANK ASSOCIATION

EEBA reiterated the underlying challenge for the revision, namely keeping the technical rules up-to-date and in line with the evolution of scientific knowledge and guiding principles. The presentation summarized the underlying trade-off between flexibility and consistency of enforcement in the decision between the 3 policy options, and proposed a system according to which the definition of rules should be linked to a set of specific criteria. Overall, a preference was expressed for Policy Option 2, while recognizing that Policy Option 3 is more appropriate in some instances. As a separate point, EEBA raised the need for coherence between the oversight of innovation in different legal frameworks (medicinal products, medical devices, and SoHO) and suggested addressing this problem either through the set-up of a new commission for SoHO or an expansion of CAT into a Joint Commission for all frameworks. The Association also proposed clarifying (and potentiating) the role of a medical representative in the tissue establishment, capable of evaluating the donor risk profile and essential for tissue certification before release.

An anonymous online poll of participants was conducted. It indicated that while there is consensus that technical rules for should address quality and safety, over half of participants also voted for introducing technical rules for efficacy, and around a third voted for having technical rules on achieving sufficiency.

f. EUROPEAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

EBMT highlighted Policy Option 2 as favourable for the regulation of hematopoietic stem cells. The presentation underlined that the integration of experts into the rule-setting process in the European expert bodies should be improved, and highlighted the need for sound, evidence-based decision-making. Moreover, the importance of flexibility was stressed to ensure that rules would not become too prescriptive and to prevent appropriate risk:benefit analysis for specific patients. Finally, clarity for the development of requirements from recommendations was called for.

In an anonymous online poll of participants, wide agreement was expressed on the need for inclusion of professional associations in the rule-setting process of European expert bodies if Option 2 is selected, although a significant need for discussion seemed to remain. With regards to increased flexibility in donor selection in the HPC field, an more significant need for discussion was expressed.

g. EUROPEAN SOCIETY FOR HUMAN REPRODUCTION AND EMBRYOLOGY

ESHRE presented the key challenges to the medically assisted reproduction (MAR) sub-sector presented by each of the three policy options, focussing firstly on potential impacts on innovation, secondly feasibility, and finally the need for inclusion of specialized MAR experts in the development of technical rules. As an ideal balance of all aspects, the presentation expressed preference for a combined approach based on basic rules in EU legislation, detailed specifications from European expert bodies, and improved national inspections.

Respondents to an anonymous online poll of participants signalled a need for discussion in this regard, with around half either fully or partially agreeing to the proposed approach.

h. THE CORD BLOOD ASSOCIATION

CBA briefly introduced their role in the European SoHO sector, and outlined their key goals based on specific and harmonized regulations for cord blood and perinatal tissue banking and an important link to birthing tissue-derived ATMPs. Support was expressed for Policy Option 3 in view of its expected harmonizing effect.

Around half of the participants flagged a need for further information on this issue in an anonymous online poll of participants.

g. Further Comments from Relevant Stakeholders

Representatives of professionals using **BTC** to manufacture medicinal products were invited to add any further comments or recommendations not covered by the previous presentations.

The International Society for Cell and Gene Therapies **(ISCT)** raised issues relating to the quality and the consistency of the material intended for ATMP manufacturing, aspects that are impacted by the technical rules in place. They specifically mentioned emerging concerns in industry regarding the possibility that new mandatory guidelines could lead to double standards, thus duplicating existing guidance for the manufacturing of the ATMPs. They further highlighted the need for predictability and trust in the EU legal framework, for guidance on novel processes and technical guidance as highly relevant for industrial stakeholders. The representative concluded that the overall legislative changes could bring singnificant changes to the ATMP field.

The ATMP interest group of **ECA** reported a shift in manufacturing of ATMPs towards industry. They underlined the importance of regulation for starting materials and encouraged an increased focus on traceability and coding systems. Finally, they reminded participants of the high complexity of the manufacturing chain for ATMPs, and of the existing regulation in many fields.

6. WORKSHOP CLOSE

To close the presentation, DG Santé thanked all presenters and participants for their constructive contributions. Participants were reminded that the presentations were already provided to all competent authorities, and that minutes of the meeting would be shared for comments in due course. Finally, it was concluded that the information and views expressed in this meeting would be given into due consideration as an important input to the BTC Impact Assessment.