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B4 – Medical products: quality, safety and innovation

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SANTÉ

Meeting between American Association of Tissue Banks (AATB) and the European Commission (DG SANTE B4)

9 March 2018

Summary Minutes

Participants: **AATB:** Frank Wilton, Roman Hitchev
ALLOSOURCE (AATB Affiliate Member): Trevor Wright
LIFENET HEALTH (AATB Affiliate Member): Brittany Beasley
DG SANTE (Unit B4): Anna Eva Ampelas, Stefaan Van der Spiegel, Deirdre Fehily

Background:

DG SANTE had requested the meeting with AATB as part of a mission to the United States by a European Commission (EC) delegation to discuss the Evaluation of the EU legislation on Blood, Tissues and Cells¹ with a number of key international stakeholders. It was agreed in advance that the topics discussed at this meeting would focus on requirements for tissue import from the US to the EU, EU tissue coding requirements, alignment EU and US safety and quality standards, progress on the ongoing Evaluation of the EU blood, tissues and cells legislation.

Key discussion points:

1. The AATB participants introduced their organisation to the EC representatives. The AATB is a professional, non-profit, scientific and educational organization. It is one of the only national tissue banking organizations in the United States, and its membership totals more than 125 accredited tissue banks and 2,000 individual members. These banks recover musculoskeletal, cardiovascular and skin tissue from more than 30,000 donors and distribute in excess of two million allografts for more than 1.75 million tissue transplants performed annually in the U.S. The great majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks. The association also has some members working in eye banking and the banking of gametes but these are largely represented by other associations. The association trains and certifies tissue bank personnel, organises scientific conferences and liaises with regulatory authorities on behalf of its members.
2. The EC delegation summarised progress with the evaluation of the blood, tissues and cells legislation in the EU. An Open Public Consultation was held during 2017, a contractor is conducting an independent evidence gathering exercise that will result in a published study and

¹ https://ec.europa.eu/health/blood_tissues_organs/policy/evaluation_en

many bilateral and multilateral meetings with stakeholders are taking place. The final Evaluation Report is due for publication towards the end of 2018. Any decisions on a potential revision of the legislation can only be made after this evaluation has been completed. The evaluation is exploring whether the legislation achieved its original objectives and whether it is still fit for purpose. The assessment is based on 5 criteria: effectiveness (did it achieve its aims?), relevance (are the provisions still appropriate given any changes in the sectors affected?), efficiency (were the costs justified by the benefits for patients?), coherence (is it consistent with other EU legislation and with relevant legislation outside the EU?) and EU added-value (could the outcomes have been achieved equally well with national legislation or global standards?).

3. AATB stated that it represents banks supplying more than half of the human cells, tissues and cell or tissue based products (HCT/Ps) used in clinical applications in EU Member States. It was clarified that this estimate does not include cells, ocular tissue or gametes but mostly musculoskeletal tissues together with some cardiovascular and skin products. AATB accepted that this was a rough estimate and that it does not seem to be consistent with data published by Eurocet and the Council of Europe. AATB clarified that the estimate referred also to tissues supplied from banks in the EU that are subsidiaries of US companies and are AATB accredited. All agreed, however, that the complete picture regarding the scale of imports of tissues from the US to the EU is currently difficult to estimate with accuracy but is clearly very significant. AATB suggested that if international tariff codes could be harmonised for tissue products then the situation would be much easier to verify.
4. In this context, AATB explained that their key concern is the alignment of standards to facilitate the supply from the US to the EU. There are no export restrictions when health products are legally marketed in the US (e.g. 361 HCT/Ps). There are several conditions that also have to be met in order to export these types of products and in some cases notification to, or approval from, the FDA is required. A series of related export requirements for drugs, biologicals and devices were summarised, including in circumstances where unapproved products in the US may be exported for investigational use.
5. US companies can request Export Certificates, referred to as Certificates to Foreign Government (CFGs), from the FDA for 361 HCT/Ps when required by the importing country. These are generally provided within one week. If a tissue supplier has been the subject of an inspection resulting in an Official Action Indicated (OAI), they will not be issued with a CFG until it has been confirmed by the District FDA that the inspection observations have been adequately addressed.
6. Noting that, contrary to the EU legislation, certain musculoskeletal tissues are regulated as medical devices in the US (primarily demineralised bone combined with handling agents, e.g. gels or putties) and a CFG can also be provided by the FDA for any FDA-cleared or approved product that is legally marketed in the US.

7. The AATB raised a number of questions in relation to the export of tissues to the EU, in the light of the adoption of a new Directive on Tissue and Cell Import in 2015 (Directive 2015/566)² as follows:

- a. Are all the different national competent authorities actively going to ask all Importing Tissue Establishments (ITE) to provide all of the information listed in the Directive (considered by AATB to be extensive)?
- b. Will there be a national approval per product/tissue type?
- c. Will ITEs need to reapply for an import license and supply the requested information?

DG SANTE responded, in general terms, that the EU Competent Authorities would need to authorise ITEs in compliance with the Directive and on the basis of the information listed in its annexes. Approvals are per product/tissue type according the product compendium on the EU Coding Platform; these categories are very broad, e.g. '*Musculoskeletal, Bone, Putty/Paste*' or '*Musculoskeletal, Bone, Shaped Graft*'. More detailed questions on the implementation of the legislation could be responded to following the meeting, on the basis of written requests.

8. AATB called on DG SANTE to provide clarity and uniformity of implementation and enforcement of Annex III of the Directive (Minimum requirements concerning the documentation to be made available to the competent authority or authorities by tissue establishments intending to import tissues and cells from third countries) in all EU Member States. They also called for work to be carried out with EU Member States and the US agencies and organisations to achieve greater uniformity of requirements and expectations and facilitate tissue flow to and within the EU.

9. AATB informed DG SANTE that many of their members export to the EU via the United Kingdom and that all are preparing for transferring their export activity to ITEs in other Member States, in view of the withdrawal of the UK from the EU. Allosource noted that it has an ITE in every EU-MS it supplies. LifeNet exports to Spain via the UK. Otherwise, it works through its Austrian affiliate, but still faces many barriers between EU Member States.

10. AATB noted that no EU tissue donations are used for the preparation of tissues for supply in the United States.

11. On the topic of tissue coding, AATB noted that Directive 2015/565/EC³ permits the use of just three coding systems: the new EUTC, ISBT 128 or Eurocode while, in the US, there are three code Issuing Agencies accredited by the FDA: GS1, HIBCC and ISBT 128. AATB raised concerns regarding potential errors and additional costs associated with recoding of tissues sent by the US to the EU when systems permitted in the US, but not in the EU, are used. DG SANTE clarified that the permitted coding systems apply only to the product identification sequence. The Single European Code also includes a donation identification sequence that must include the TE code of the EU importing tissue establishment supplying the tissue or cells, even if these were imported from outside the EU. In this context, any tissue must, in any case be relabelled on import. AATB recommended greater EU-US harmonisation of tissue coding system requirements. The AATB stressed that the requirement for the SEC to contain the TE code of the ITE is challenging if this

² <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32015L0566&from=EN>

³ <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32015L0565&from=EN>

labelling is expected to be performed by the US tissue establishment in cases where a single US supplier exports to multiple ITEs across the EU.

12. AATB noted that the EU Tissue and Cell Directive (2004/23/EC) allows Member States to put in place more stringent requirements, in particular where a Member State wishes to restrict imports of tissues and cells in accordance with Article 4(2) of Directive 2004/23/EC. This has resulted in a very complex situation in the EU where companies wishing to export to different Member States face a widely varying situation regarding national rules. DG SANTE explained that this provision arises from the legal basis of the tissues and cells legislation, a public health article of the Treaty on Functioning of the European Union, as opposed to any article regarding trade of commodities. They referred to a mapping exercise of more stringent testing requirements, published online.
13. AATB called on DG SANTE to support the development of comprehensive donor eligibility guidelines based on clear deferral criteria that would be applicable both in the US and in the EU. They considered that making the EDQM (Council of Europe) standards mandatory might support that objective.
14. AATB raised concerns regarding the new EU Medical Device Regulation (2017/745/EC)⁴ where they see a lack of clarity regarding the inclusion, or otherwise, of tissue products. During the meeting, and in subsequent correspondence, DG SANTE reiterated the joint statement issued by DG SANTE and DG GROW (responsible for medical devices); a statement the AATB had appreciated as an important clarification. DG SANTE confirmed that demineralised bone matrix (DBM), like any other tissue matrix, combined with carriers or handling agents (e.g. glycerol, gelatine, collagen, and others), bone-suture-bone allografts, and different combinations of non-viable human cells and tissues with other materials that constitute a medical device, should be regulated as traditional tissue under EU Directive 2004/23/EC, if the action of the human cells/tissue component is the principal action, and not ancillary. Collagen fillers, i.e. collagen extracted from tissues and cells, are covered by the new MD Regulation (provided that they otherwise fall within the definition of a 'device' and a 'derivative'). AATB stressed that this is unclear in the current tissues and cells legislation and could lead to confusion.
15. AATB also noted that it is not clear in the current EU legislation whether the Single European Code needs to be affixed to the internal packaging of double-wrapped tissue products.
16. Finally, AATB raised the subject of the application of VAT to tissue products in the EU. They had also raised this issue in their presentation at the Stakeholder Event held in Brussels in September of 2017⁵. They reiterated that the VAT Directive excludes human organs, blood and milk from its scope but not tissues and cells with the consequence that some Member States apply it and others do not. They called for a clear exemption of tissues and cells in line with the exemption of other substances of human origin.
17. The EC participants thanked the AATB for their hospitality and for the informative discussions.

⁴ <http://eur-lex.europa.eu/legal-content/ENG/TXT/PDF/?uri=CELEX:32017R0745&from=EN>

⁵ https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/ev_20170920_sr_en.pdf