

10 February 2017

**Submission of comments on the
“Roadmap on the evaluation of the EU blood and tissues
and cells legislation”**

Comments from:

Dr Aurélie Mahalatchimy, Prof Alex Faulkner and Prof Andrew Webster on behalf of the REGenableMED consortium

Please find below comments on the “Roadmap on the evaluation of the EU blood and tissues and cells legislation” by the REGenableMED consortium.

REGenableMED - REGenableMED is a United Kingdom Economic and Social Research Council (ESRC)-funded project (N°ES/L002779/1: <http://www.york.ac.uk/satsu/regenablemed/>). It brings together research team builds on work by social science experts based in Birmingham, Edinburgh, Sussex and York in the UK. It is coordinated by Pr Andrew Webster, Science and Technology Studies Unit at the University of York, UK. The project aims to examine the dynamics of innovation within the field of regenerative medicine. Using a mixed-methods social science approach, the project will undertake a detailed analysis of the interplay between business models, measures of clinical utility, patterns of regulatory oversight and clinical workflows within healthcare settings. The results of the research will inform strategies aimed at facilitating the responsible development of effective and useful regenerative medicine products and services.

All work packages of the project consider what we call the ‘institutional readiness’, i. e. the capacity and willingness of key pre-existing organisations and inter-organisational structures to adopt, respond to and utilise novel technologies, such as advanced therapy medicinal products as part of regenerative medicine. One work package led by Prof Alex Faulkner, Centre for Global Health Policy, School of Global Studies, University of Sussex, the UK is dealing with the role of a range of intermediary agencies, patient groups and health insurance companies, in determining what can be called 'healthcare readiness' for the field, that is, how the field aligns with and can be embedded in existing practice and how far changes need to be made. As part of this work a regular survey of regulatory tools (including relevant linked public consultations) that influence the pathways through which the field develops is performed. The draft response has been prepared by Dr Aurélie Mahalatchimy (academic lawyer), Prof Alex Faulkner and Prof Andrew Webster (sociologists). A discussion between persons interested was then organised and the attached answer circulated to all project participants before submission.

The REGenableMED consortium is grateful to the European Commission to have been given the opportunity to contribute to this consultation.

COMMENTS

General comments

The directives on blood and tissues and cells have been a good achievement to protect public health in the field of substances of human origin. However, they should be adapted to the new landscape, notably regarding the potential increase of infectious diseases risks (anti-microbial resistance) and of cross-border exchanges of blood and tissues and cells, the current support for the industrial commercialisation of Advanced Therapy Medicinal Products and the new collaboration it involves, the necessary recognition of patients rights and the strengthened EU competency in the field of public health since the adoption of the Lisbon Treaty.

Specific comments

1. To what extent is the legislation and its original objectives still valid and meeting current regulatory needs? In particular to what extent is the legislation:

a. Sufficiently adapted to, adaptable to, and up-to-date with scientific, technical and epidemiological developments / innovation?

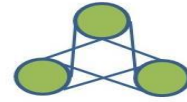
Donor testing requirements should be adapted regarding new infectious diseases, or the potential increase of infectious diseases risks (anti-microbial resistance).

b. Adapted to other changes in the sector such as commercialisation and internationalisation?

An increase of industrial demand for starting materials (blood, cells, tissues) to develop regenerative medicines (for instance cellular therapies or advanced therapy medicinal products) could be expected. The Directives should ensure the donor requirements would not be diminished to address a higher industrial demand.

Moreover, compared to 2004, public- private collaborations between academia and industry have increased to develop advanced therapy medicinal products because of complementary competences and resources. The Directives should ensure one actor would not be disadvantaged compared to another. More specifically, only few advanced therapy medicinal products have had commercial viability so far. It may be considered that many cell therapies will not be commercially interesting for the industry while still needed for targeted patients. The Directives should ensure tissue establishments in clinical institutions such as hospitals, are supported to provide cell therapies for patients.

c. Are there any gaps in terms of substances of human origin or activities that are not regulated by the Directives?



It should be ensured that a substance of human origin is regulated under the same regulatory framework in every EU Member States. To this end, it should be made clear whether the withdrawal of whole blood (that corresponds to the legal definition of blood) leading to extraction of lymphocytes (that corresponds to the legal definition of cells) falls within the blood or the tissues and cells directives. Similarly, it should be paid attention to the legal identification and characterisation of other growth factors as many are used in culturing systems, for instance via specific provision.

Moreover, it should be considered whether specific provision for the “GMP-like” safety measures should be built for closed system (Celution type) of device and their inspection as long as they could require the implementation of both the medical devices directives (or future regulations) and the tissues and cells and blood directives.

Finally, it is important that the Directives play some role in providing regulatory thresholds for all private clinics currently using tissue and cell therapies, often in ways which are open to clinical doubt and high levels of patient risk. This may require some ongoing liaison with national bodies in Europe typically responsible for consumer safety, since such clinics are typically outside of formal clinical governance and oversight procedures.

2. To what extent has the legislation increased the quality and safety of blood and tissues and cells and achieved a high level of human health protection?

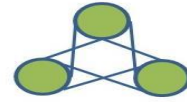
The legislation has increased the quality and safety of blood and tissues and cells in establishing minimum requirements in every Member States, especially regarding obligations for tissue establishments and their authorisations by national competent authorities.

3. Has the legislation led to any unintended effects (positive or negative)?

4. What, if any, have been the barriers preventing effective implementation of the legislation?

5. Are the rules on oversight sufficient to address the increased internationalisation?

Regarding the high flows of substances of human origin for therapeutic purposes in the EU but also more globally, it should be kept in mind that these flows are not equivalent as regards as the direction of the flows and the types of human materials exchanged. Given the infectious diseases risks (virus, anti- microbial resistance), it may be necessary to centrally collect data on the cross- border flows (within and outside the EU) of substances of human origin for safety. Although no authorisation should be necessary to circulate within the EU or export outside the EU substances of human origin, the flows between countries should be notified to the national competent authorities of the relevant Member States. These data should be centralised at the EU level by a specific Committee such as the Competent Authorities on Substances of Human Origin Expert Group with extended remit and make publicly available. Indeed, even though ethical considerations rely on Member States, it should be taken into account substances of human origin come from human persons, who have given their consent for the



use of their substances. Such consent generally covers or should cover cross-border use of substances of human origin.

6. What, if any, are the challenges to maintaining compliance with the legislation?

7. To what extent, if any, has the legislation impacted on patient access to blood, tissues and cells.

8. How cost-effective has the application of the quality and safety requirements in the legislation been for operators (have the benefits outweighed the costs)?

9. Are there particular administrative or other burdens for specific groups of operators, including downstream users of blood, tissues and cells as starting materials for medicinal products?

It should be considered that 3D bioprinting may require reconfigurations of liabilities and responsibilities if hospitals become manufacturers using this technology

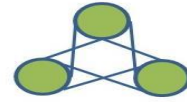
10. To what extent has the legislation resulted in cost implications for hospitals/patients using/receiving blood, tissues and cells?

11. To which extent does the oversight required by regulatory bodies pose a burden to public authorities (has the burden been proportionate to achieving the original oversight objectives of the legislation)?

12. To what extent is the legislation on blood and tissues and cells consistent and coherent within its own provisions? To what extent is the legislation coherent and consistent with other relevant Union legislation? Are the requirements of the Directives suitable when blood, tissues and cells are used as starting materials for the manufacture of medicinal products/medical devices? To what extent is the legislation coherent with other relevant international / third country approaches to the regulation of the quality and safety of blood and tissues and cells?

More and more real world data are necessary to develop regenerative medicine based products, it implies the setting- up of registries. The latter are more or less established for specific disease areas or for specific substances of human origin without global relevance. The directives on blood and tissues and cells should provide the legal basis to report data on a multinational level either for the establishment of European registries or to coordinate the various existing registries. A European Committee such as the Competent Authorities on Substances of Human Origin Expert Group with extended remit could identify the existing registries. A publicly available webpage on the DG Health Website should provide links towards these registries. Consequently, potential gaps could be identified within the EU and actions should be taken in these areas.

Moreover, "There is no comprehensive EU regulation of patient safety of therapeutic questions surrounding human materials and no central regulation/ harmonisation of standards of patient care across the EU. This remains



undoubtedly a concern, not least as indicated by the debates concerning patient mobility and the EU Patients' Rights Directive."¹ Consequently, it is worth considering patients in a potential revision of the blood and tissues and cells directives.

Finally, ethical issues have been raised during the adoption processes of both the directives on tissues and cells and the regulation on Advanced Therapy Medicinal Products. While ethics rely on Member States competencies, it would be relevant to "align" the regulation of clinical trials applicable to Advanced Therapy Medicinal Products with the regulation of blood and tissues and cells regarding the involvement of ethics committees and the necessary consent given the human characteristic of the substances of human origin.

13. To what extent has the legislative framework at EU level added value to the regulation of blood and tissues and cells across the EU-28 in a manner that could not have been achieved by measures taken at national or global level?

14. To what extent do stricter national measures pose an obstacle to exchange of supplies between Member States?

¹ J. V. McHALE and A. MAHALATCHIMY, "EU law and policy on human materials" in T. K. HERVEY and C. A. YOUNG, "Research Handbook in EU Health Law and Policy", Edward Elgar, 2017 (In Press).