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15 April 2021

Sandra Gallina
Directorate-General for Health and Food Safety
European Commission
1049 Bruxelles/Brussel
Belgium

Dear Director-General Gallina:

On behalf of the International Society for Stem Cell Research (ISSCR), I write to share our comments on public and stakeholder consultations for the revision of the European Union's (EU) legislation on blood, tissues, and cells (BTC). The ISSCR is the leading professional organization of stem cell researchers and represents more than 4,000 members in Europe and around the world. Our members are scientists, clinicians, ethicists, and educators dedicated to the responsible advancement of stem cell research and its translation to the clinic. Our comments focus on concerns regarding the premature commercialization of cellular therapies and the implications of the BTC legislation for the oversight of Advanced Therapy Medicinal Products (ATMPs).

Curbing the Premature Commercialization of Cellular Therapies *(Public Consultation Question 1)*

We appreciate that the European Commission's evaluation of the BTC legislation identified unsubstantiated claims for clinical effectiveness as a limitation of the current regulations. We are also concerned with businesses selling unproven cellular therapies. These businesses often escape the safety and efficacy testing requirements for ATMPs by inappropriately claiming that their products are exempt from the regulations for ATMP. They often cite anecdotal findings or results obtained with unrelated products as evidence that their products are safe and effective while selling scientifically implausible products that are unlikely to provide any benefit. It has also become clear that purveyors of unproven therapies often ignore good manufacturing processes. There have been a number of examples of patients who have been harmed by unproven therapies that were contaminated with pathogens.

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The EU's rules for ATMPs broadly classify cell and tissue products that have been "substantially manipulated" or are "not intended to be used for the same essential function or functions" (non-homologous use) as ATMPs (EC No 1394/2007, Chapter 1, Article 2, (c)). This distinction is crucial because the processing and use of these products pose more significant risks to patients. All cell therapy products that have been substantially manipulated are complex and speculative interventions that come with processing and contamination risks not addressed by the BTC rules and must be assessed by the European Medicines Agency (EMA) or national regulators. Furthermore, cellular products for non-homologous treatments have been shown to have other risks, including tumor growth and blindness. We encourage the European Commission to revise the BTC rules to ensure their connection to the ATMPs regulations is well understood and universally enforced.

The Use of Blood, Cell, and Tissue Products as Therapeutics (Targeted Stakeholder Consultation Question 33)

The unproven use of BTC-based products (non-ATMPs) as therapeutics (e.g., platelet-rich plasma) threatens public confidence in the safety and efficacy of other medical products available in Europe. These therapies should also be rigorously evaluated in controlled clinical trials before being sold to patients.

Advancing the Development of Safe and Effective Regenerative Therapies

Stem cell-based therapies and other regenerative medicines have great potential to yield new treatments for unmet medical conditions and improve the quality of life for patients with chronic and debilitating diseases. However, many of these products have yet to be proven safe and effective and face many commercialization challenges. The developers of these therapies will need access to global markets to have patient populations large enough to recover their development costs. Access to global markets is essential for rare diseases, where the patient population in one country is too small to recover the cost of developing new therapies.

Harmonization of International Regulations for ATMPs (Public Consultation Question 8 and Targeted Stakeholder Consultation Questions 44 and 45)

The divergent donor testing and screening requirements for communicable diseases create significant barriers to developing stem cell-based therapies and other regenerative medicines for global markets. While the goals for each country are similar—preventing the transmission of communicable diseases—the differences in the details of the regulations increase the cost of developing therapies and can result in significant delays. For example, if a European product developer neglects to consider the US Food and Drug Administration's donor eligibility requirements, their product may never be eligible for use in the US. To further illustrate this point, consider the screening and testing requirements for West Nile Virus. The European Directorate for the Quality of Medicines (EDQM) only recommends screening the travel history of BTC donors, while the FDA requires year-round testing using nucleic acid assays for West Nile Virus for imported products. We encourage the Commission to prioritize the harmonization of donor screening and

testing requirements for cells and tissues used in the development of ATMPs to facilitate the development of stem cell-based therapies.

Screening and Testing for Communicable Diseases (Public Consultation Question 21)

While the current framework for screening and testing donors for communicable diseases has minimized the risk of transmission from blood transfusions and organ transplants, it is not optimized for the development of ATMPs. As mentioned previously, the lack of harmonized donor screening questions in Europe and other countries makes it very challenging for products to be eligible for use around the world. Furthermore, the development of higher-specificity tests for most infectious diseases, such as polymerase chain reaction-based assays, and the use of these assays to directly test ATMPs, negates many of the donor screening questions that vary across borders. While these tests are not always practical or affordable for screening individual blood donors, they are a more realistic way to minimize the transmission risk from cells and tissues donated to develop ATMPs. We encourage the Commission to create an exemption for cells and tissues used in ATMPs from the donor screening questions and related record retention requirements when the use of high-specificity tests can mitigate transmission risks.

Technical Requirements of the BTC Legislation (Public Consultation Question 1 & Targeted Stakeholder Question 20)

The development of higher-specificity tests for infectious diseases over the last 15 years has made the requirements of the BTC legislation (2006/17/EC) obsolete when compared with the testing recommendations from the EDQM. For example, the BTC legislation (Section 1.1 of Annex II) requires antibody testing for HIV-1, HIV-2, Hepatitis B, and Hepatitis C, while the EQMD's Guide to the Quality and Safety of Tissues and Cells for Human Application recommends RNA or nucleic acid testing for the same diseases. Since the EQMD guidelines are updated routinely to respond to new risks (e.g., Zika and West Nile Virus) and scientific advances (e.g., higher specificity tests), we recommend requiring testing for certain diseases (e.g., HIV and Hepatitis) and refer to the recommendations of EU and international expert bodies, including the EQMD and the European Centre for Disease Prevention and Control (ECDC) for the technical standards. EU expert bodies should be encouraged to consult with other regulators and, whenever possible, harmonize the standards with international norms.

Public and Stakeholder Consultations for Guidance from Expert Bodies (Targeted Stakeholder Consultation Question 21)

Whenever possible, stakeholders and the public should have an opportunity to comment on proposed changes to the guidance documents through a simplified process to encourage feedback on new proposals. For instance, the public and stakeholder consultations for the BTC legislation contained 84 questions—many of which overlapped, were not relevant to all stakeholders, and required a significant time commitment from respondents.

Thank you for considering our comments regarding the stakeholder consultations for the revision of the EU legislation on BTCs. If the ISSCR can clarify any of these views or be of assistance, please contact Eric Anthony, ISSCR's Director of Policy at eanthony@isscr.org.

Sincerely,

Christine Mummery
President, ISSCR