INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

13 March 2020

Sam Atkinson, PhD
Director of Inspection, Enforcement and Standards
Medicines and Healthcare Products Regulatory Agency
10 South Colonnade
London
E14 4PU
United Kingdom

Dear Dr. Atkinson,

On behalf of the International Society for Stem Cell Research (ISSCR), I write to urge you to increase enforcement activities to prevent the marketing and commercialization of stem cell-related products that do not conform to United Kingdom (UK) and European Union (EU) Advanced Therapy Medicinal Product (ATMP) regulations. The ISSCR is the leading professional organization of stem cell researchers and represents more than 4,000 members in the UK 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. We were alarmed to learn about the surge of clinics and providers marketing unproven therapies to patients in the UK, and we urge you to make enforcement a priority to protect public health.

While stem cell treatments may someday have the potential to treat a wide range of serious conditions, clinical trials are necessary to rigorously evaluate the safety and effectiveness of each potential therapy. The premature marketing and commercialization of unproven and unapproved stem cell-related interventions, whose safety and effectiveness have not been established in clinical trials, is a global issue that puts patients at physical and financial risk and undermines the development of legitimate new therapies.

Unproven treatments marketed by clinics and providers have resulted in patients being blinded in the UK and US, paralyzed, and infected with dangerous pathogens. Regulators in Europe and around the world need to increase enforcement activities to

5215 Old Orchard Road, Suite 270
Skokie, Illinois, USA 60077
T +1 224 592 5700
F +1 224 365 0004
info@isscr.org
isscr.org

prevent these unscrupulous clinics and providers from capitalizing on the hype by selling stem cell therapies. Regulators around the world must act in unison to protect public health and prevent the premature commercialization of unproven treatments.

The EU's regulations define what types of interventions require regulation as ATMPs by broadly classifying 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)). The European Medicines Agency's (EMA) Committee for Advanced Therapies (CAT) further clarified the definition of ATMPs in 2015 with the adoption of the reflection paper on the classification of advanced therapy medicinal products that included clear guidance on substantial manipulation and non-homologous use.

Substantially manipulated cell- and tissue-based products are regulated as ATMPs due to the risks associated with the manipulation, including contamination, mishandling, the use of undisclosed additives, and potential cellular and genomic changes, and others. The CAT's reflection paper provided important examples regarding cell culturing and enzymatic digestion that clarifies that some of the common practices at clinics providing unproven therapies are considered substantial manipulation. Similarly, the non-homologous use of stem cell-based interventions is complex, speculative, and has been shown to have risk. The CAT's reflection paper also provided several examples to clarify that many of the products sold by clinics marketing unproven therapies are examples of non-homologous use. The examples include the "use of adipose cells transplanted to other than fat tissues" and the use of "bone marrow cells or peripheral blood cells" for functions other than hematopoietic or immune construction. These are crucial examples of non-homologous use commonly advertised by clinics marketing unproven stem cell-based interventions.

Furthermore, the CAT has released multiple product classifications that illustrates that many of the products sold by clinics marketing unproven stem cell-based interventions should be regulated as ATMPs. For example:

- 1 April 2016, the EMA/CAT concluded that autologous adipose tissue-derived mesenchymal stem cells and Wharton's jelly suspended in freezing solution for the treatment of Amyotrophic lateral sclerosis (ALS) is a substantially manipulated product within the definition of somatic cell therapy products.
- 27 April 2017, the EMA/CAT concluded that the use of autologous bone marrow-derived mesenchymal stem cells for the treatment of comas is a substantially manipulated product within the definition of somatic cell therapy products.
- 19 July 2017, the EMA/CAT concluded that autologous adipose-derived mesenchymal stem cells, freshly isolated for the treatment of autoimmune drug-resistant epilepsy is a substantially manipulated product within the definition of somatic cell therapy products.

- 24 August 2017, the EMA/CAT concluded that the use of stromal vascular fraction for the treatment of osteoarthritis is a non-homologous use within the definition of a somatic cell therapy medicinal products.
- 3 May 2018, the EMA/CAT concluded that mesenchymal stem cells from cord blood and bone marrow for the treatment of multiple sclerosis are substantially manipulated products within the definition of tissue-engineered products.

While we understand that individual products must be evaluated by the EMA before they can be officially classified as ATMPs, the standards suggest that many of the unproven products marketed by clinics as stem cell-based interventions should be regulated as ATMPs based on existing guidance from the CAT. The only notable exception is platelet-rich-plasma (PRP), which is concentrated platelets and not considered an ATMP. Regardless, we believe the safety and effectiveness of PRP as a medical intervention should be rigorously evaluated in clinical trials before it is marketed and sold to patients.

We hope you will prioritize the safety of patients and increase enforcement activities to protect public health and curb the premature commercialization of stem cell products.

Thank you for considering our request. 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,

Deepak Srivastava, MD
President, ISSCR
President, Gladstone Institutes