

ISSCR



INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

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30 May 2018

Assistant Director Linda Woo
Drug Office
Department of Health
Room 1856, 18/F
Wu Chung House
213 Queen's Road East
Wanchai, Hong Kong

Dear Ms. Woo,

On behalf of the International Society for Stem Cell Research (ISSCR), the leading professional organization of stem cell scientists, I write to share our views regarding the Department of Health's Consultation Document for the Regulation of Advanced Therapy Products. The ISSCR represents more than 4,000 stem cell researchers around the world, including many in Hong Kong. We are pleased to see that Hong Kong's Department of Health is joining other global regulators in endeavoring to develop strong rules to improve the regulation of new stem cell therapies and help assure patients that these products are safe and effective. We appreciate the opportunity to submit comments regarding the Consultation Document and urge you to consider revisions that will further protect patients from unproven products and procedures falsely marketed as stem cell therapies.

While we appreciate that the Health Department has proposed adopting the European Union (EU) paradigm for Advanced Therapy Products (ATPs), we urge to include clear examples and definitions with your regulations. In 2015, the European Medicines Agency's Committee for Advanced Therapies released new guidance to clarify the classification of Advanced Therapy Medical Products in the EU. Over the last few months, U.S. Food and Drug Administration (FDA) and Australia's Therapeutic Goods Administration (TGA) released new guidance to clarify their regulation of cell and tissue products. By including similar clarifying guidance as part of the Department of Health's regulatory framework, Hong Kong can ensure that stem cell therapies are regulated as ATPs.

With the new regulatory framework for ATPs, Hong Kong has an opportunity join the countries that have modernized their regulation of cell and tissue products to rein in the unscrupulous clinics marketing unproven therapies as stem cell treatments. These clinics often exploit common loopholes in cell and tissue regulations. Your new rules must be carefully drafted to allow routine and well-established medical procedures such as skin grafts and breast reconstructions to continue, while ensuring that

complex and more speculative medical interventions are more stringently regulated as ATPs. The ISSCR urges the Department of Health to consider the following recommendations to strengthen the Department's guidance and harmonize it with other global regulators.

Definition of Tissue Engineered Product

We ask the Department of Health to adopt a definition for "Tissue engineered product" that is similar to the EU definition in [Regulation No 1394/2007](#), which further defines "engineered" as cells or tissues that have been substantially manipulated or cells or tissues for non-homologous uses (Article 2, Section 1.(c)). The level of risk due to cell or tissue manipulation and the non-homologous use of cells and tissues is similar for both somatic cell therapy products and tissue engineered products; therefore, we urge you to use similar criteria for classifying these products as ATPs.

Definition of Substantial Manipulation

The adoption of the EU's list of exempted manipulations is insufficient to define the meaning of substantial manipulation; therefore, we urge you to include additional guidance and examples to clarify your definition. At a minimum, we urge you to adopt a definition similar to the EMA's [Reflection paper on the classification of advanced medicinal products](#), which defines the culturing, expansion, differentiation, and activation of cells or tissues as substantial manipulation. Extended culture periods are associated with greater risk of contamination, mishandling, and microbial infection. Additionally, cell culture can lead to the selection of subpopulations, sometimes with genetic mutations that contribute to oncogenic transformation. We also urge you to include an example that clarifies that the processing of adipose tissue by centrifugation and/or enzymatic digestion to isolate the "stromal vascular fraction" is considered substantial manipulation. This would harmonize your guidance with the FDA's [guidance regarding minimal manipulation](#) (example 14-1) and TGA's [regulation of autologous human cell and tissue products](#) (Adipose tissue example b).

Homologous Use

In addition to including specific guidance regarding the level of manipulation, we urge you to include the concept of homologous use as a criterion for determining the regulatory path for products and therapies. By regulating all cellular-based products intended for non-homologous uses as ATPs, Hong Kong's rules will become more consistent with those of other global regulators. The use of cell-based products as non-homologous treatments are complex, speculative and have been shown to have risk, including [tumor growth](#) and [blindness](#); as a result, these products should be regulated as drugs or biologics with peer-reviewed clinical trials to establish their safety and efficacy. We also encourage you to include unambiguous examples of homologous and non-homologous use to illustrate how the non-homologous use of cells poses greater risks to patients and must be regulated as an ATP. Examples regarding adipose tissue are particularly important, as adipose tissue is often used as a source for mesenchymal

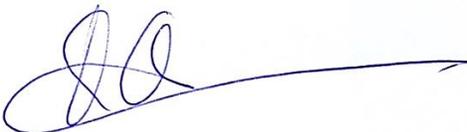
stromal cells, sometimes improperly referred to as mesenchymal stem cells, and these cells are commonly advertised by private businesses marketing unproven “stem cell” interventions. The EMA’s reflection paper included an example to clarify that “adipose cells transplanted to other than fat tissue” is a non-homologous use. The FDA’s guidelines for [Minimal Manipulation and Homologous Use](#) (Example 19-6) also included four specific adipose tissue examples that explain the FDA’s rationale for considering the transplantation of adipose tissue for breast reconstruction and other cosmetic uses a homologous use, while the use of adipose cells and tissue to treat neurological disorders or musculoskeletal conditions, for example, is considered a non-homologous use. Similarly, the TGA’s guidelines included adipose tissue examples to delineate homologous and non-homologous use.

Regulation of Low-risk Cells and Tissues

We encourage you to carefully craft the exemption for low-risk cell and tissue products to allow common medical procedures like breast reconstructions and skin grafts to continue while regulating more complex and speculative products as ATPs. Many countries have adopted hospital or same surgical procedure exemptions to allow low-risk procedures to continue under the practice of medicine. We encourage you to adopt the [FDA’s approach](#), which narrowly exempts low-risk autologous cell and tissue products that have been rinsed, cleansed, sized and shaped. We also encourage you to explicitly exclude cells and tissues for non-homologous uses from this exemption as these therapies are speculative and should be regulated as ATPs. We also recommend including specific examples that clarify the level of processing allowed through the low-risk cell and tissue product pathway. The FDA’s [guidance regarding its same surgical procedure exemption](#) included an important example to clarify that processing adipose tissue to isolate cells (Example 7-2, stromal vascular fraction) would disqualify the process from the exemption. By including a similar example, your rules will better protect patients from being exploited by clinics marketing unproven interventions as stem cell treatments.

Thank you for considering our recommendations as you develop your rules for regulating Advanced Therapy Products. If the ISSCR can be of further assistance to you as you move forward on this issue, please contact Eric Anthony, ISSCR’s Director of Policy at eanthony@isscr.org.

Sincerely,

A handwritten signature in blue ink, appearing to read 'Hans Clevers', with a long horizontal line extending to the right.

Hans Clevers, MD, PhD
President, ISSCR
Professor of Molecular Genetics at Hubrecht Institute
Research Director at the Princess Maxima Center for Pediatric Oncology