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Dr. S. Eswara Reddy
Drugs Controller General of India
Central Drugs Standard Control Organization
Directorate General of Health Services
Ministry of Health and Family Welfare
Government of India
FDA Bhavan, ITO, Kotla Road, Mandi House,
New Delhi, Delhi 110002, India

Dear Dr. Reddy,

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 Central Drugs Standard Control Organization's (CDSCO) draft rules for the regulation of stem cell and cell-based products under the Drugs and Cosmetics Rules, 1945. The ISSCR represents more than 4,000 stem cell researchers around the world, including many in India. We are pleased to see that CDSCO is joining other global regulators in endeavoring to develop strong rules to improve the regulation of new stem cell therapies and help assure patients these products are safe and effective. We appreciate your draft guidelines, and urge CDSCO to consider the following revisions, which will further protect patients from unproven products and procedures falsely marketed as stem cell therapies.

Specifically, the ISSCR encourages CDSCO to include explicit definitions and concrete examples in the stem cell and cell-based product rules that ensure stem cell-based interventions are regulated as drugs. We believe that such interventions should only be marketed to patients after being tested in adequately-designed, registered clinical trials, with institutional oversight, peer-review, and systematic reporting of results. CDSCO should build on the National Guidelines for Stem Cell Research released by the Indian Council of Medical Research (ICMR), which seeks to protect patients from the premature commercialization of these products.

CDSCO has a unique opportunity to align India's regulations with those of other 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. New rules must be carefully drafted to allow common 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 drugs or biological products. The ISSCR urges CDSCO to consider the following recommendations to harmonize India's rules with other global regulators.

Definition of Substantial or More than Minimal Manipulation

We ask that CDSCO adopt a definition of "substantial or more than minimal manipulation" that is consistent with the ICMR guidelines and the definition used by other regulators around the world. The European Medicines Agency (EMA) and the Australian Therapeutic Goods Administration (TGA) broadly define the processing of cells or tissue that results in the alteration of "biological characteristics, physiological functions, or structural properties" as substantial or more than minimal manipulation. The U.S. Food and Drug Administration (FDA) uses a slightly different paradigm that distinguishes between structural and non-structural tissue; however, it achieves a similar regulatory objective.

We also encourage CDSCO 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 more than minimal manipulation. This would harmonize CDSCO's regulations with the FDA's guidance regarding minimal manipulation (example 14-1), TGA's regulation of autologous human cell and tissue products (Adipose tissue example b) and the ICMR Guidelines (levels of manipulation 7.2.1).

Definition of Minimal Manipulation

The ISSCR is concerned that CDSCO's proposed list of processes considered minimal manipulation is broader than the definitions of other global regulators who have recently modernized their regulation of cellular therapies. We recommend removing "overnight culturing" from the definition of minimal manipulation, since cell culturing can result in changes to a cell's genetic and epigenetic signature, resulting in underlying functional changes in the biology. 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. Collectively, these changes illustrate the need for a higher level of regulation. We also encourage CDSCO to remove "disintegration of tissue," "separation of cells," and "isolation of a specific cell" from the definition of minimal manipulation, since this level of processing can result in changes to the original and relevant physiological or structural properties of the cell or tissue.

Homologous Use

In addition to evaluating the level of manipulation, we urge you to consider whether products will be used in a homologous or non-homologous application. By revising the current draft to specify that all cellular-based products intended for non-homologous uses will be regulated as drugs or biologics, India's rules will be more consistent with those of other global regulators. We also encourage you to include unambiguous examples of homologous and non-homologous use to illustrate how non-homologous use of cells poses greater risks to patients and must be regulated as a drug or a biologic. 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 are cells that are most commonly advertised by private businesses marketing unproven "stem cell" interventions. The FDA's guidelines for Minimal Manipulation and Homologous Use (Example 19-6) clearly delineate between homologous and non-homologous use. The guidelines include 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, both the EMA's and TGA's guidelines included adipose tissue examples to delineate homologous and non-homologous use.

Same Surgical Procedure

While we appreciate that your proposed same surgical procedure exemption is limited to autologous cells that have been rinsed, cleaned, or sized, we urge you to futher limit the exemption to cell-based products for homologous uses. The use of autologous cell-based products as a non-homologous treatment or therapy is complex and speculative; 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 recommend including specific examples that clarify the minimal processing allowed through CDSCO's same surgical procedure exemption. For example, the FDA's new guidance regarding its same surgical procedure exception clarified that processing adipose tissue to isolate cells (Example 7-2, stromal vascular fraction) would disqualify the process from the same surgical procedure exemption. By including a similar example, your rules will protect patients from being exploited by clinics marketing unproven interventions as stem cell treatments.

Finally, the ISSCR is concerned about the news reports from the SCSICON 2018 conference that suggest your regulations intend to "demarcate" cellular-based therapies from cellular-based drugs. Instead of creating an arbitrary loophole to allow medical practitioners to provide unproven therapies under the auspices of practicing medicine, we urge you to take a risk-based approach to your regulations that is similar to the other global regulators as outlined by our comments above.

Thank you for considering our recommendations as you finalize your rules for regulating stem cell and cell-based 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,

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