Perinatal Society's Position Paper on the Regulatory Landscape for Perinatal Stem Cell and Tissue Products

The International Perinatal Stem Cell Society, Inc., a 501(c)3 patient focused non-profit organization founded in 2013, is dedicated to advancing perinatal stem cell and tissue products from the laboratory to clinical applications. Perinatal stem cells and tissue products are ethically sourced from perinatal tissues such as the amnion, amniotic fluid, cord blood, decidua, Wharton's jelly/cord tissue, and placenta blood and tissue, which are collected from consenting mothers following the birth of a child without posing any risk to the mother or newborn.

The Perinatal Stem Cell Society has drafted this position paper to state the Society's position regarding the current U.S. regulatory landscape for various products and how updates to the regulatory framework can be strengthened. Guidance from FDA has helped drive innovation in the space, but as the science has advanced, the regulatory framework in the US has not advanced and is now holding innovation back. Countries around the world such as Japan, Colombia, and Mexico have surpassed the U.S. in the stem cell and regenerative medicine fields. Other countries that have advanced ahead of the U.S. both in terms of development of perinatal-derived biotechnology and the availability of advanced healthcare and stem cell products, have done so in part due to updated regulatory pathways that make it feasible for companies to bring advanced medical technologies to market, while also ensuring safety and efficacy. The goal of the Perinatal Society is to support improvements to the regulatory framework that restores the US as the global leader in regenerative medicine and the number one destination for Advanced Cellular and Biotechnology development.

On June 28th the Supreme Court overruled their landmark 1984 decision in the *Chevron v. Natural Resources Defense Council* case. Previously cited in over 18,000 decisions this ruling drastically curtails the power of federal agencies to interpret the laws that they administer and potentially sets the stage for a period of chaos in the cellular and regenerative medicine field. With this fundamental

change in the way that federal agencies enforce the rule of law, it is more critical than ever that updates to the regulatory framework be enacted to include clearly defined pathways that enable companies to successfully bring stem cell and tissue-based products to the market.

U.S. manufacturers develop a wide range of products from perinatal tissue source materials. There are clear and defined pathways for the legal commercialization of certain human cells, tissues, and cellular and tissue-based products (HCT/Ps), including perinatal-derived HCT/Ps, in the United States under Section 361 of the Public Health Service Act and Title 21, Part 1271 of the Code of Federal Regulations.

Additional perinatal tissue derived products, such as conditioned stem cells, or cellular products exerting a systemic effect, are not eligible for the Section 361 HCT/P pathway.

The Perinatal Society advocates for clarity for the existing regulatory pathways and a more streamlined regulatory framework for manipulated regenerative tissue-based products. The Society suggests that the U.S. learn from and adopt aspects of the Japanese regulatory model. Japan has become a world leader in regenerative medicine and their regulatory bodies have successfully navigated many of the same questions and concerns that lack clarity in the United States due to recent FDA statements, and actions that have created confusion among manufacturers regarding what constitutes an HCT/P. While FDA guidances from 2017 and 2020 on HCT/Ps spurred development in the U.S. of many HCT/Ps, Japan far outpaces the U.S. as a leader for biotechnology development especially in the area of regenerative medicine.

In the Japanese model, regenerative medicine products are classified by official Regenerative Medicine Committees that are comprised of experts in the field. The Regenerative Medicine Committee classifies the products as either Class I (High Risk), Class II (Medium Risk) or Class III (Low Risk) regenerative medicine products. The Perinatal Society would like to suggest the U.S. adopt a similar classification system for stem cell and manipulated or conditioned tissue products.

In the U.S., an important guidance document for the current regulatory landscape for all HCT/Ps, including perinatal tissue products is "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use," issued by FDA in July 2020. This Guidance outlines FDA’s regulatory implementation of the regulations in Title 21 of the

Code of Federal Regulations (CFR) Part 1271, specifically the 21 CFR 1271.10(a)(1) criterion for minimal manipulation and the 21 CFR 1271.10(a)(2) criterion for homologous use.

Human cells, tissues, and cellular and tissue-based products (HCT/Ps) can be regulated solely under section 361 of the Public Health Service Act and the corresponding regulations in 21 CFR Part 1271, provided they meet a set of specific criteria. These criteria are designed to ensure the safety and quality of the HCT/Ps without subjecting them to the more stringent requirements applicable to drugs, devices, and biological products. The Perinatal Society does not propose to alter the categorization or regulation of products that currently qualify for a 361 designation. Those are the lowest risk products and already have an established pathway under Section 1271 of FDA's regulations.

As far back as 1997, FDA has recognized that cellular and tissue-based products can be used safely and can be expected to behave in the recipient the same as the tissue behaved in the donor. Thus, premarket clinical trials for safety and efficacy are not necessary or required for HCT/Ps that meet the regulatory requirements outlined in Section 1271. FDA adopted this regulatory framework, at least in part, to make it easier to bring these types of products to market in the U.S., thus advancing availability of healthcare products. Facilities making or distributing these HCT/Ps must be registered with FDA and follow current Good Tissue Practices, as outlined in FDA regulations. Section 1271 outlines four specific requirements for an HCT/P to be eligible for this more streamlined pathway to regulatory marketing.

The first criterion is minimal manipulation, which means that the processing of the HCT/P should not alter its original relevant characteristics. For structural tissues, minimal manipulation implies that the processing does not change the tissue's utility for reconstruction, repair, or replacement. The processing is limited to mechanical processes, not enzymatic or chemical alteration, which may alter the fundamental characteristics of the tissue. Reshaping and resizing of tissue is permissible as minimal manipulation. In the case of cells or nonstructural tissues, like progenitor cells, minimal manipulation means that the processing does not alter the cells' or tissues' relevant biological characteristics. From the Society's perspective, objective evidence of minimal manipulation helps confirm minimal manipulation. Without objective evidence of minimal manipulation, FDA may potentially assume the product is more than minimally manipulated.

The second criterion is homologous use, which requires that the HCT/P be intended for use to perform a same basic function in the recipient as it did in the donor. This is determined by the manufacturer's objective intent, as indicated by the product's labeling, advertising, or other indications. Homologous use does not require that the tissue be implanted in the same anatomic location in the recipient as it came from in the donor. For example, the FDA has given examples in the past that micronized skin can be used to support damaged tissue in the area around a ligament.

The third criterion stipulates that the manufacture of the HCT/P should not combine with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent. Moreover, the addition of these substances should not raise new clinical safety concerns.

Fourth, the HCT/P must not have a systemic effect and not be dependent on metabolic activity of living cells for its primary function, or the HCT/P must be limited to one of three specific situations of autologous use (derived from and used in the same individual), allogeneic use in a first- or second-degree blood relative, or reproductive use.

Under current U.S. regulations, HCT/Ps that do not satisfy these criteria, and do not qualify for any of the exceptions outlined in 21 C.F.R. 1271.15, will be subject to regulation as drugs, devices, and/or biological products under the Federal Food, Drug, and Cosmetic Act and/or section 351 of the Public Health Service Act.

The Perinatal Society believes that the current regulatory framework, specifically section 361 of the Public Health Service Act and the corresponding regulations in 21 C.F.R. Part 1271, provides a suitable foundation for the safe and effective development and commercialization of perinatal tissue products that meet the four characteristics outlined in 21 C.F.R 1271.10.

For complex biologic products, such as monoclonal antibodies and genetically engineered therapeutic proteins, FDA requires product sponsors follow the traditional Biologics License Application pathway under Section 351 of the Public Health Service Act, Section 351 requiring premarket authorization from FDA on the basis of clinical trials to establish safety and efficacy.

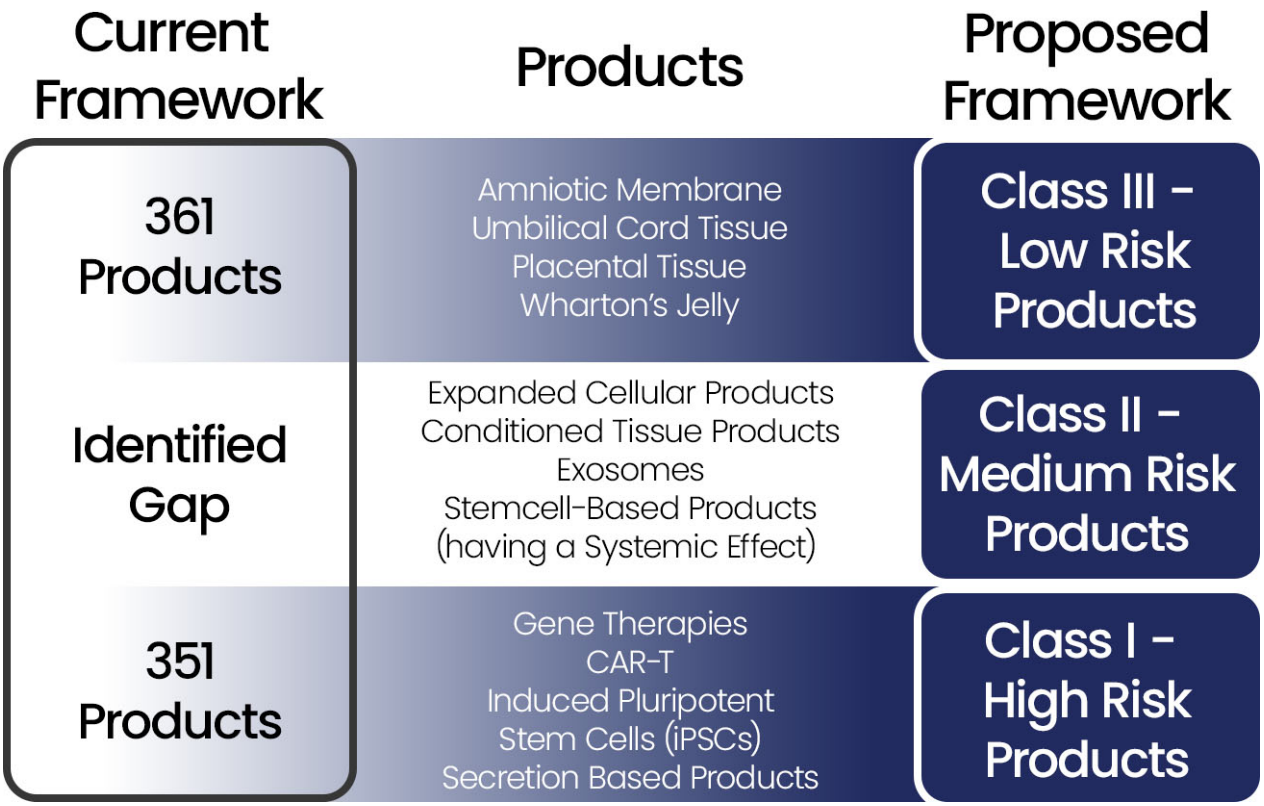
From the Society’s perspective, there is a category of products in the middle between a Section 361 HCT/P, and a complex biologic product, where a new regulatory pathway could both provide assurances of safety and efficacy, and also advance development of biotechnology and availability of regenerative medicine

based healthcare options in the U.S. This category of products includes stem cell-based products, secretion products, and conditioned-tissue products

Over the last several years, Japan introduced a newer type of pathway for these types of regenerative medicine products. Under that pathway for regenerative medicine products, a product sponsor must complete at least a Phase 1 trial to demonstrate safety of the product. Upon approval of the Phase 1 study, the product sponsor can financially support the completion of the Phase 2 and Phase 3 studies through selling patients access to participate in the clinical trials. This approach has worked in Japan to ensure safety of these types of products while also reducing the regulatory and financial burden to bring such products to market.

The impact in Japan has been to attract new development in regenerative medicine, positioning Japan as a global leader in cellular therapy. With a few simple steps, such a pathway can be implemented in the U.S., which likely would set the U.S. on a path to lead the rest of the world in development of regenerative medicine therapies.

Following this concept, implementing the Japanese framework into the current U.S. regulatory framework, Section 361 HCT/Ps would be considered Class III Low Risk, which we believe is appropriate for the following minimally manipulated perinatal tissue products, as long as they meet the requirements outlined in Section 1271.10:



Class III Low Risk Products:

- Amniotic Membrane

- Umbilical Cord Tissue/Wharton's jelly

- Placental Tissue

We recognize that there is a gap in the current U.S. regulatory framework for what would be considered Class II Medium Risk regenerative medicine products under the Japanese system. The Perinatal Society proposes products to be classified as Class II Medium Risk that fall in between the current 361 and 351 designations for perinatal stem cell and tissue products.

Class II Medium Risk Products:

- Expanded Cellular Products

- Conditioned tissue products

- Stem cell-based products having a systemic effect

- Exosomes

- Secretion based products

The Perinatal Society advocates for the development of an intermediate pathway for these Class II Medium Risk Products. In the absence of such a pathway, product sponsors are left to try to fit into imperfect existing pathways that were not developed to apply to these types of products.

Following the basic Japanese model for regenerative therapies, a basic Phase I Safety trial is all that is necessary to begin selling the product, until Phase II and Phase III trials are completed. During this period after the Phase I but before completion of the Phase II and Phase III trials, pharmacovigilance reporting, reporting on progress of Phase II and Phase III trials, and oversight of an independent medical review board can all be included as protections to ensure consistent monitoring of any safety or efficacy concerns.

Lastly, products classified as Class I High Risk would continue to be regulated under the existing 351 pathway and be required to follow the current clinical trial and BLA approval process but would also be eligible for patient financially supported Phase II and III clinical trials.

Class I High Risk Products:

- Gene Therapies

- CAR-T

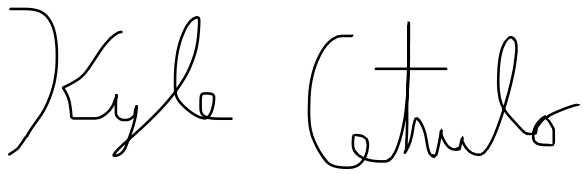
- Induced Pluripotent Stem Cells (iPSCs)

The goal is to provide a basis to ensure safety and efficacy of medical products being sold in the U.S. marketplace and used by healthcare providers for U.S. patients and not to allow regulatory hurdles to prevent safe and effective products from coming to market. That was the basis for FDA in adopting the HCT/P framework for minimally manipulated tissues outlined in 1997 and ultimately adopted in a Final Rule in 2001. Full clinical trials are not necessary to ensure safety and effectiveness of those types of products, and requiring full clinical trials served as an impediment to making such products available in the U.S. marketplace. The same can be said for conditioned tissue and stem cell products today. Japan has found a way to mitigate that regulatory hurdle while still ensuring safety and effectiveness of products being used in Japan, and in so doing has

created a favorable environment for biotechnology development. For the health of the U.S. population and advancement of investment in biotechnology, the U.S. should work towards a similar approach.

Additional Funding Mechanisms:

The Perinatal Society advocates for a new funding mechanism, similar to the Japanese model, which allows clinical trial sponsors to charge patients for participation in Phase II and Phase III clinical trials. Further details about this approach can be found in the Perinatal Proposed Legislation and on our website. We would like to see these same funding mechanisms applied to both the Class II and Class I risk products and the associated clinical studies.



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