

CBA Testimony on Cellular Products and Therapies

U.S. Food & Drug Administration Public Hearing

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**Presented by Joanne Kurtzberg, MD
President**

Good morning.

My name is Dr. Joanne Kurtzberg and I am honored to speak on behalf of the Cord Blood Association.

I am qualified to speak in this capacity as a pediatric transplant, cord blood banker, cell therapist and president of the CBA. The CBA is a young and vigorous, international, nonprofit organization. CBA members include both public and family banks, industry partners, foundations and individuals in, and served by, the cord blood community.

Cord blood was first used, in 1988, as a source of HLA-matched-related donor cells in a 5-year old patient with Fanconi Anemia undergoing transplantation to treat bone marrow failure. The transplant, a first-in-man experiment, performed in a child with minimal pre-clinical data, was successful. The patient, now 33 years old is living a normal life, 27 years later. Importantly, his blood and immune systems are fully comprised of his sister's cord blood cells.

This transplant paved the way for the fields of cord blood banking and transplantation. Today, there have been more than 35,000 cord blood transplants performed and more than 160 cord blood banks, with a total public inventory of approximately 700,000 units and a private inventory more than 4 million, worldwide.

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Cord blood was the first hematopoietic stem cell product to be regulated by the FDA. To date, seven public cord blood banks have successfully obtained BLAs. Lessons learned from the cord blood BLA process should inform regulation of other cell therapies going forward. For example:

1. Cells do not necessarily expire.
2. Stability protocols, performed to extend expiration dates, sacrifice unique cell products that cannot be replaced.
3. Excessive environmental monitoring adds little, if any, value to manufacturing that is performed in a closed system when appropriate qualification testing is performed and specifications are met.
4. The delivery of babies, although sanctioned by nature, is not sterile, not controlled, and is a highly variable process. Cord blood and cord tissue are sourced from this disadvantaged position. Regulatory flexibility is critical to enable the use of these valuable products.

Cord blood and cord tissue-derived products have enormous potential for the development of novel cell-based therapies that will have a critical role in the fields of cellular therapies and regenerative medicine. To this end, the CBA emphasizes the following points related to the proposed guidances:

Excessive environmental monitoring adds little, if any, value

1. Cord blood is not a bag of stem cells. While it does contain small numbers of blood stem cells, the majority of cells are differentiated blood cells. Some of these other cells have

therapeutic value but do not act through engraftment, tissue integration or differentiation. Rather they are effector cells acting through paracrine signaling. As such, we strongly encourage the FDA to consider these mechanisms of action as homologous.

2. The current regulatory framework, which is largely focused on review of drugs, is not sufficient for review of cellular therapies. We encourage the FDA to modify these regulations to address the unique properties of cells.
3. The designation of minimal or more than minimal manipulation should be risk-based, with consideration of clinical indication, route of administration and the complexity of manufacturing of the product. We suggest that if the cells are prepared aseptically and only exposed to FDA approved-for-human-use reagents and or devices, manufacturing should be considered minimally manipulated.
4. The designation of 1271 products including autologous cells or tissue as well as cells and tissues from first and second degree relatives is outdated. If HLA match is the operative in this reasoning, then the guidance should state that related HLA identical or haplo-identical products are included.
5. The FDA should consider a pathway for cellular therapies similar to that already established for hematopoietic stem cell and solid organ transplantation. Emerging therapies could be prepared and delivered in accredited facilities, monitored under IND if indicated and outcomes could be reported to a registry such as the CIBMTR. Expanded access studies could also be used to monitor safety. This is one way to get therapies to patients more quickly while continuing to monitor safety efficacy.

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The CBA has the following specific comments related to two of the guidances under discussion today:

First, the guidance for HCT/PS from adipose tissue doesn't acknowledge mesenchymal stromal cells (MSCs), the primary cell therapy extracted from adipose tissue. These cells represent a major therapeutic resource and should be considered homologous when used to exert paracrine effects. This has relevance not only to MSC derived from adipose tissue, but MSC from cord tissue, bone marrow and others.

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I will end with comments about the homologous use guidance which is particularly relevant for cord blood bankers: An example would be the treatment of young children with cerebral palsy with autologous cord blood.

In the draft guidance for homologous use, FDA states in section 3-1.c: "A manufacturer provides HPCs derived from cord blood with a package insert stating that cord blood may be infused intravenously to differentiate into neuronal cells for treatment of cerebral palsy. This is not homologous use because there is insufficient evidence to support that such differentiation is a basic function of these cells in the donor."

In this instance, the FDA incorrectly assumes that the mechanism of action of cord blood therapy in children with cerebral palsy is through integration of cord blood “stem” cells capable of differentiating into neuronal cells. If this were the case, we would agree that it would be non-homologous use. However, in this therapy autologous cord blood cells are acting through signaling mechanisms that are innate properties of the infused cells and that act on endogenous cells in the patient through paracrine and homologous mechanisms.

Lastly, consider this dichotomy: We have an autologous, not more-than-minimally-manipulated product for homologous use? Or non-homologous use?

If the FDA accepts that this use is homologous, then administration of autologous cord blood which is not more than minimally manipulated would be viewed as practice of medicine and regulated under 1271 as a 361 product. However, if the FDA designates the use as non-homologous and expects a BLA, who gets the BLA? Does each family/private bank go through the BLA process? Does the treating institution obtain the BLA? Does a public bank get the BLA? The list of questions goes on and on . . . and the CBA welcomes the opportunity to engage in meaningful conversation with the FDA regarding these questions.

The Cord Blood Association is committed to bringing effective cord blood and cord tissue-derived therapies to patients as safely and efficiently as possible, and we thank the FDA for the opportunity to raise these issues. We look forward to the FDA’s feedback on our comments.

Thank you.