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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Proposed Rule for Suitability Determination for Donors of Human Cellular and Tissue-Based Products
(FR 64:52696; September 30, 1999)

To the Food and Drug Administration:

The International Society of Hematotherapy and Graft Engineering (ISHAGE) is a professional society representing over 1000 physicians and technical staff involved in the procurement and use of hematopoietic stem cells in medical practice and in industry. We are writing in response to the proposed rule for donor suitability determination as published in the Federal Register on September 30, 1999.

ISHAGE previously recognized the need for standards for selection of donors of hematopoietic tissues and has played a leadership role in the development of such standards in conjunction with the Foundation for Accreditation of Hematopoietic Cell Transplantation (FAHCT). Thus, we support the efforts of the FDA to assure the safety of human cellular and tissue-based products. However, we wish to bring to your attention two major and several minor points in the proposed rule with recommendations for revision.

Our first major point regards the differential application of the rule based on the degree of relatedness of the donor and recipient. The FDA proposes to exclude from regulation a product that is minimally manipulated and not for autologous or family-related use (§1271.15). In discussing the purpose of this rule (§1271.1), the FDA states that the objective is to prevent the spread of communicable diseases. We know of no data to support the notion that, when using the current industry standards for donor screening and testing, the risk of transmission of infection via hematopoietic stem cells from an unrelated donor is any greater than when the donor is related, whether the graft is manipulated or not. We therefore support the FAHCT standards which require screening and testing of all donors to ensure the safety of the product for all recipients and for the technical staff involved in cell processing.

Our second major point regards the differential application of the rule based on the source of the hematopoietic stem cells. In the proposed rule, cord blood and mobilized peripheral blood are considered human cellular products but marrow is not (§1271.3). There are no data to suggest that the risk of transmission of infections is higher with cord blood or mobilized blood stem cells than with marrow. The major potential complications from unmanipulated hematopoietic stem cell allografts result from the degree of incompatibility at the major histocompatibility loci rather than from the source of stem cells, and the incidence of such complications after marrow, blood stem cell and cord blood transplantation have been reported extensively in the literature. We believe that determining the acceptability of these risks falls under the practice of medicine and is not in the purview of the FDA. Hematopoietic cells from all of these sources are considered safe and appropriate for reconstitution of hematopoiesis for patients with primary or secondary marrow failure when donor selection and component collection are performed within the current standard of care. It is the position of ISHAGE that the FAHCT standards meet or exceed the requirements in the FDA proposed rule for donor selection, collection, labeling and storage of unmanipulated cord blood transplants and unmanipulated mobilized blood stem cell transplants, and that if FAHCT standards are followed, an IND should not be required for these activities.

Attached please find a detailed listing of our recommendations for revisions of the proposed rule to address these two major points and the minor points. Should you require further clarification of our position, we would be pleased to provide further information.

Sincerely,

Malcolm K. Dreiner, M.B., Ph.D.
President, ISHAGE


Donna Przepioroka, M.D., Ph.D.
Chairman, ISHAGE Legal and
Regulatory Affairs Committee

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ISHAGE's Recommendations for Revision of the Proposed Amendment to Part 1271

1. §1271.3: Add definition of homologous.

Rationale - This term has a broad definition, and its use in different contexts within the proposed rule may be misinterpreted.

2. §1271.3-(y.2.iii): Define "significant" health risk.

Rationale - We agree that screening and testing for newly recognized infectious agents should be broadened at the earliest possible time, but this term is vague and subject to misinterpretation. In the absence of a clear directive from the FDA, this leaves the establishments totally liable for a judgement decision.

3. §1271.3-(z): Add "and the risk of morbidity with use of the product is considerably less than without the product."

Rationale – We do not support use of a product from an unsuitable donor when the risks from the product are greater than the risks from the underlying disease.

4. §1271.10-(d.2): Delete (i) and (ii), and replace with (i) is for hematopoietic reconstitution.
§1271.15-(d): Delete (1) and (2), and replace with (i) is for hematopoietic reconstitution.

Rationale – It is the position of ISHAGE that donor selection, collection, labeling and storage for unmanipulated cord blood transplants and unmanipulated mobilized blood stem cell transplants are neither experimental nor investigational. As such, these may be subject to listing as are marrow transplants, but these activities should not require an IND if FAHCT standards are met.

5. §1271.55-(a.1.i): Delete "a copy of the donor's relevant medical records"
§1271.55-(b): Add "...from the FDA or any party involved in the collection, processing or transplantation of the component."

Rationale – Copies of actual records, even with the name of the donor deleted, may contain sufficient information for a third party to identify the donor, thus breaching donor confidentiality. A summary of the evaluation and the test results should be sufficient. We agree that the primary source documentation should be readily available at the collection center for reference when needed.

6. §1271.65-(b.1.i): Delete

Rationale – The rationale for use of stem cells from an unsuitable donor is based on the risk-benefit ratio rather than relatedness. Paragraph b.1.iii would apply for both related and unrelated donors.

7. §1271.80-(a): Add to the last sentence “using assays validated to be predictive of transmissibility of infection in the fetal or neonatal tissue.

Rationale – Serologic testing of the mother may not provide the highest degree of accuracy in identifying infectious agents in cord blood cells once nucleic acid testing is available, and it should not be considered “generally acceptable” without the caveat.

8. §1271.80-(b): Revise to “... up to 30 days prior to recovery if the complete donor screening is negative at the time of the procedure.”

Rationale – Current medical practice recommends against retesting for infectious disease markers within 6 months in the absence of risk factors. If the time period were shortened to 7 days, there would not be enough time to evaluate suitability of the donor. Use of the 7-day window would place additional travel and living expenses on the donor and duplicate the cost of testing. Using the current practice of testing within 30 days and performing a complete rescreen, there have been no unexpected cases reported of transmission of infections with hematopoietic stem cell transplantation.

9. §1271.90-(b): Add “Such products should be handled as untested in accordance with §1271.60.”

Rationale – Untested autologous products have the same risks as untested products from other donors and should not only be labeled but quarantined in the same fashion.

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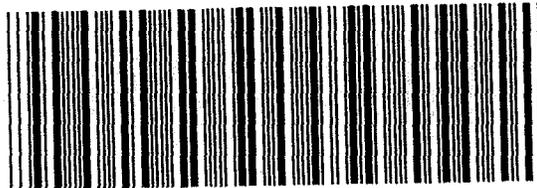
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