International Society for Cellular Therapy
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TO: FDA

FROM: International Society for Cell Therapy

SUBJECT: Comments and questions concerning FDA's Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSC)s

The following comments and questions are provided to FDA for consideration in finalizing the July 2007 FDA Draft Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSC)s.

COMMENTS and QUESTIONS:

1. The FD&C Act defines a device as an instrument apparatus, implement, machine, contrivance, implant, in vitro reagent or similar or related article which is

   - Recognized in the official National Formulary or USP
   - Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
   - Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes

   This guidance document claims that the cell selection devices fit the definition of a device but offers no explanation. In accordance with the 351 regulations, it is not the device that is curing, mitigating, treating or preventing a disease but the cells that are made with the equipment. Therefore, the cell selection devices used in the manner outlined in the document are equivalent to manufacturing equipment. Please provide further explanation as to how these cell selection devices fit the legal definition of a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

2. The draft guidance document explains that the recovery, processing, and direct administration of the cells should occur in a matter of hours without shipping. Many times the cell recovery, processing and administration will be done at three different locations but generally within the same city. However, it may take 20-30 minutes to get the cells between the different locations. Please provide a clear explanation as to what is meant by shipping.

3. The draft guidance documents indicates that the processing should take place at and by the same clinical site in which the patient is receiving care and that the physical location of the cell processing proximate to the patient (within easy walking distance). However, the document is silent on the location of the cell recovery with respect to the location of the processing.

   - Does the cell recovery site need to be within easy walking distance of the cell processing site?
   - Must a quality system be in place for controlling the handling of cells after they leave the device to assure there is not such loss of viability that the dose becomes ineffective?

- If a quality system for post device cell handling should be in place how can the device supplier assure that, and if not then who does?

4. 21 CFR 1271.15(b) indicates that you are not required to comply with the requirements of this part if you are an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure. This document clearly outlines that the same surgical procedure no longer means that everything has to be done in the surgical suite but broadens this exemption to include cell processing outside the surgical suite and at a different locations. The document goes on to explain that this exemption only applies if using devices that are cleared or approved for such use. This added stipulation puts additional restrictions on the exemption that are not outlined in the rule. This added stipulation to the exemption should go through rule making with public comment.

5. Please clearly define what is meant by manufacturing steps? In the use of cell selection devices, many times the cell product needs to be concentrated by some method not part of the device and placed in the final formulation for administration. Is formulation a manufacturing step? In other drug/biologics, it is considered a manufacturing step.

   - Please explain why a different standard to define manufacturing steps is used in this document.

   - Does the cell selection device have to put the cells in the final formulation?

6. One of the criteria outlines that the cells are to be used within a short period of time (i.e. not stored or shipped).

   - Please define in more detail what is meant by a short period of time. Is storing the cells in the refrigerator in the surgical suite considered storage?

   - What is the acceptable temperature range? Since no validation of transport is required, will carrying a bag of cells for 30 minutes in extreme temperatures be acceptable?

   - Does no shipment /storage mean direct infusion after the last manufacturing step or does this mean from the device straight into the patient?

**7.** The last criteria outlined in the draft guidance document indicates that the device and cells are only used at the point of care (i.e. cell processing is performed at and by the clinical site where cells are directly administered). However, many hospitals are campuses and not single buildings. In addition, there is no indication that the cell recovery needs to be performed at and by the clinical site.

   - Please clarify the relationship between the cell recovery, processing and administration.

   - We would recommend that if FDA plans to go forward with this guidance document that point of care needs to be defined in such a manner as to be consistent with the hospital environment.

   - One recommendation would be that the device company must submit information of the transport of the cells between locations.

   - In addition, the point of care should be defined as entities that are either within the institution or under contract similar to what is defined in the GTPs.

**8.** 21 CFR 1271.3(d) clearly defines the cells made using the cell selection devices as HCT/Ps and gives the example of hemaopoietic stem cells derived from peripheral and cord blood. In addition, 21 CFR 1271 indicates which HCT/Ps needs further regulation based on the intended use being homologous or nonhomologous. This guidance document describes a regulatory path whereby the cells will be regulated though the use of a device to manufacture the cells and not regulation of the cells directly. Therefore, depending on your business model there are now 2 regulatory pathways for the very same cellular therapy for the same indication with very different regulatory requirements. This guidance document establishes an uneven regulatory

pathway for two different types of companies. We recommend that the clinical effectiveness and cell characterization requirements for both approval pathways should be the same. We have outlined below 2 areas of the regulations that are clearly different between drug/biologic regulations and device regulations.

- For example, it is not clear from the draft guidance document what will be that standard for clinical effectiveness that will be applied. For the drug/biological standard of clinical effectiveness, the sponsor must establish substantial evidence of effectiveness and adequate safety of the drug or biologic/device under study for it to be approved and labeled for proper use with adequate and well controlled studies. FDA has generally interpreted studies to mean more that one. **This is clearly outlined in the clinical effectiveness guidance document.** For device standard of clinical effectiveness, the sponsor must demonstrate the potential for the device to be effective and safe. This generally means that the sponsor will perform a feasibility study and one pivotal trial. This difference means a shorter path to approval under the device regulations as well as a big difference in finances for a company. Please clearly outline in the final guidance document the regulatory requirements for demonstration of clinical effectiveness.
- The second example is the requirement for potency. In 21 CFR 610.10, a biological product can not be licensed without a lot release test for potency. FDA has currently interpreted this regulation to mean a functional assay that is representative of the mechanism of action. This has been a major development hurdle for many cell therapy manufacturers. This requirement is not part of the device regulations. In fact, the sponsor of a device only needs to prove that the device functions and performs as intended. Therefore, many have interpreted this to mean that the level of testing on the cells would be very minimal compared to if the cells were regulated as a biological product. Please clarify the cell characteristic requirements that FDA will be applying to the device.

9. The Guidance states, “In order to establish the performance characteristics of a device covered by this guidance, the manufacturer should provide data demonstrating that the device is capable of reliably producing the intended cells under routine use conditions.” At the Somatic Cell meeting, Stephanie Simek stated that data would be required to demonstrate the efficacy of the cell product. CBER/FDA has cleared for marketing, using device authority, apheresis devices (cell separators) that were demonstrated to be effective by virtue of the properties of the biologic products prepared with these devices. The products were licensed biologics with known standards – they were platelets (human), red cells (human) and source plasma (human). The devices are also capable of producing granulocytes and lymphocytes, but are not cleared for such use – FDA has sought scientific consensus on criteria for efficacy of these products, but has not obtained this and has not asked for device applications for those indications. Off label use of the devices for such production is widespread.

   - There are potential indications for the cell products derived from the subject devices other than bone marrow reconstitution. Many such indications involve tissue/organ regeneration. There is not consensus within the relevant scientific communities sufficient to develop criteria for efficacy – FDA has stated as much by indicating that there are many pertinent INDs, but no BLAs have been filed. If clearance of a PMA will require demonstration of efficacy of the cells produced, how will the data required differ from that which would be required to support a BLA for the cells themselves?

10. If a device is used in the manner outlined in the draft guidance document and thus the cells are exempt from regulation, how will FDA regulate the cells if instead of administering the cells immediately DMSO is added to the PBSCs and frozen for later use? Since DMSO is an accepted cyropreservation agent, the addition of DMSO would not kick up the HCTP into being regulated as a 351 product. Therefore would the cells still fit the exemption or would they be regulated under 21 CFR 1271?

11. Please clearly define the different cell selection devices that may fall into this category ( i.e. closed systems, positive or negative selection with antibodies, antibody coated beads that are magnetically removed, etc)?

12. Is the final collection bag considered as a separate entity not part of the same device?

13. What type of establishments are covered under this guidance?
14. To obtain sufficient PBSCs for therapy, the autologous donor usually needs a 3-5 day course of mobilizing agent and an apheresis procedure to harvest the "minimally manipulated" PBSC. The apheresis procedures are generally performed many days in advance of the infusion or "implantation" of the cells. In addition, the apheresis procedures are frequently performed in a blood collection facility or apheresis center that is not connected with a surgical suite. The scenario presented in the Draft Guidance is more often performed with an autologous bone marrow harvest at the same time the patient is in the surgical suite for the "implantation" procedure. The Draft Guidance does not mention autologous bone marrow.

    - Does this Guidance directly apply to autologous bone marrow stem cells as well?
    - Does the guidance apply to a mobilized source or only to non-mobilized sources? Does the addition of the mobilizing agent (i.e. G-CSF) constitute a combination product with the addition of the drug to the harvesting of the cells?
    - Does the device manufacturer have to specify the mobilization agent? Do studies need to be performed with all types of mobilization agents that are currently approved by FDA?
    - If a new mobilization agent/procedure becomes available, what would be required of the manufacture of the new mobilizing agent to make the new agent/protocol with an already approved device acceptable? What happens if a device company is not interested in changing the label for the device?

15. The Draft Guidance specifically mentions (II. Background Section, 1st paragraph) using autologous PBSCs for specific clinical conditions, "such as ischemic heart disease, peripheral vascular disease, and bone fracture". According to the FDA's Proposed Approach to Regulation of Cellular and Tissue-Based Products announced in February 1997 and the subsequent tissue rules of 21 CFR Part 1271, autologous cells and tissues administered for nonhomologous clinical use require the filing of an IND or IDE and premarket approval.

    - Does the regulation pathway outlined in the document only apply to the listed indications?
    - Does FDA consider the infusion/implantation of autologous PBSCs for treatment of ischemic heart disease, peripheral vascular disease, and bone fracture as homologous use? See Attachment A: ISCT White Paper on Homologous Use.
    - If FDA does not consider PBSC therapy of ischemic heart disease, peripheral vascular disease, and bone fracture as homologous use, who is responsible for filing the IND or IDE for the clinical study? Is the clinical investigator or the device manufacturer required to file the IND or IDE?
    - Does the off label use of a catheter to deliver cells render the cell therapy as a 351 product?

16. Device manufacturers may intend to develop or may currently market FDA cleared or approved cell processing devices for cord blood, bone marrow, or PBSC for the intended use of laboratory processing and banking of the product, but not for point-of-care use.

    - If a clinician uses a cell processing device that has **not** been approved for point-of-care use in an off-label, point-of-care setting, is the device manufacturer or the clinician responsible for reporting adverse events associated with the device and the procedure?

17. The PBMCs are selected using an approved device for an approved indication as outlined in the draft guidance document. The output of CD34 positive stem cells in absolute number at the point of administration is not solely dependent on the selection device, but also on (a) how much of the source there is (TNC) and (b) the frequency of CD34+ selectable cells in the input source and (c) how long the device Is run or how much of the source is processed.

    - How is the device supplier to assure that choices are made (a, b, c) in order to make an appropriate dose for the patient?

- If there is no mechanism for the device supplier to assure an effective dose whose responsibility is it?

18. In light of the scenario above one should also consider that an effective dose for any indication may come from administration effects i.e. effective cells = (quantity of useful cells at the point of administration) * (effectiveness of the infusion mechanism) * (viability loss from infusion mechanism) to reflect that, for example, catheters might do better than systemic infusion with regard to homing issues, but might themselves inflict a loss in viability.
    - Who assures appropriate infusion system?
    - Are some systems permitted under the guidance and others not?

# Attachment A

# ISCT Working Group on Homologous Use

# White Paper on Homologous Use (21CFR1271.3(c))

**Executive Summary:**

This white paper identifies a number of issues arising from the FDA's current approach for interpreting what constitutes *"homologous use"* for human cells, tissues and cellular and tissue-based products (HCT/Ps). These issues have been identified by the HCT/P community who are members of the International Society for Cellular Therapy (ISCT).

As identified in this white paper, it does not appear that the FDA has developed consistent criteria for determining what uses or functions inherent to some cell populations, are considered homologous between donor and recipient. It also does not appear that the FDA has established a formal process for reassessing prior determinations of homologous or non-homologous use in light of increased understanding of an HCT/Ps' inherent functions as described in peer-reviewed scientific literature. Finally, despite stated intentions, the FDA appears to have broadly interpreted what it considers to be non-homologous uses of HCT/Ps.

ISCT believes that the substance of the FDA decision-making process may be resolved by open, public communication. The ISCT proposes that the FDA implement a formal process for periodic evaluation of evidence from current peer-reviewed scientific literature to reassess the interpretation of "*homologous use*" for specific types of HCT/Ps. ISCT believes that this can best be accomplished in a public forum, such as the Cellular, Tissue and Gene Therapies Advisory Committee, appropriately supplemented with individuals with scientific and clinical expertise for the subject HCT/P(s) under discussion.

The ISCT further recommends that the FDA issue written guidance for HCT/P stakeholders that reconciles the Agency's stated intent to narrowly interpret nonhomologous uses of HCT/P, with the currently perceived practice of presuming that the use of an HCT/P is non-homologous until demonstrated otherwise.

**Background:**

The membership and leadership of the ISCT have determined that the interpretation and application of the new 21 CFR 1271 regulations need further clarity, specifically 21 CFR 1271.3(c) and 21CFR 1271.10(a)(2) on "*homologous use*." To that end, ISCT has organized a Working Group and Advisory Panel to recommend means for clarification. Members of the Working Group and the Advisory Panel include representatives from industry and academia and other concerned organizations; AABB, AATB, ASBMT, ASFA, ASH, and FACT (see appendix A).

The FDA's stated intention with the HCT/P regulations is to "improve the protection of the public health without imposing unnecessary restrictions on

research, development, or the availability of new products". However, in some cases, such as the interpretation of *"homologous use*," it is clear that these new regulations have had a restrictive effect on the pace of industry and academic research.

**Statement of Problem and Discussion:**

The interpretation of the term *"homologous use"* is one of the criteria established to determine the regulatory approach for evaluating human cells, tissues and cellular and tissue-based products (HCT/Ps), that are minimally manipulated and for autologous or allogeneic, family-related use (see box 1). To date, the ISCT membership has found the FDA interpretation of this criterion to be unclear and inconsistent with the stated regulatory intent.

Given the rapidly evolving nature of scientific understanding of the functions inherent to many cells and tissues, it is essential that the FDA, as a sciencebased regulatory agency, establish and provide clear, consistent guidance to cell therapy manufacturers about the regulatory pathway appropriate to their HCT/P. We would like the FDA to provide a meaningful algorithm that HCT/P manufacturers can apply during product development.

ISCT membership is aware that as stewards of public health and safety, the FDA must honor their mandates when there is inadequate scientific evidence of the safety of an HCT/P. However, we would like to see guidance as to the type of data and experience that might be required to allow a change in designation of an HCT/P from a 351 to a 361 product.

Establishing a path for re-evaluation of a non-homologous use assessment may provide an advantage to academic or industry HCT/P development that follows the forerunner. However, over time, this approach would benefit all HCT/P manufacturers. The ISCT Working Group is offering to work with the TRG or Cell, Tissue and Gene Therapy Advisory Committee to publicly develop a risk scale, to define stages and to define criteria for re-evaluation of HCT/Ps once data is available. Then a regulatory algorithm can be developed to short circuit the more intense regulatory pathways.

It is important to note that even with an expanded interpretation of *"homologous use"*, HCT/Ps would still be subject to the other regulatory compliance criteria described in 21 CFR 1271.10 (see Box 1). These criteria when evaluated together determine the appropriate regulatory pathway for products that have a higher risk for patient safety.

**Box 1. Criteria for Regulation under section 361 of PHS Act**
An HCT/P may be regulated solely under section 361 of the PHS Act if the product meets all of the four criteria (21 CFR 1271.10(a)):

- The HCT/P is minimally manipulated;
- The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
- The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
- Either the HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function, or the HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and
  - Is for autologous use;
  - Is for allogeneic use in a first-degree or second-degree blood relative; or
  - Is for reproductive use.

The *"homologous use"* definitions and requirements in the regulations are as follows:

- *Homologous use* means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor (section1271.3(c)).
- The HCT/P is intended for *homologous use* only, as reflected by the labeling, advertising, or other indications of the manufacturer's

Scientists and clinical experts in both academia and industry have frequently struggled to reconcile the FDA's interpretation of what constitutes *"homologous use"* with their own understanding based on current scientific literature of *"homologous use"* or homologous function(s) of specific types of HCT/Ps.

Several examples of homologous uses for HCT/Ps were provided in the 1997 "Proposed Approach to Regulation of Cellular and Tissue-Based Products" and in more recent determinations by the FDA's Tissue Reference Group (TRG), listed on the FDA's website (see Table 1 for selected examples). From a stakeholder perspective, these examples do not provide adequate insight into the decision-making criteria and suggest the lack of a consistent mechanism to allow for an expanded interpretation of what constitutes *"homologous use"* as scientific understanding increases. For example, in the FDA's "Proposed Approach" document, uses of hematopoietic stem/progenitor cells (HPC) for hematopoietic reconstitution in individuals with marrow aplasia, chemotherapy-induced marrow ablation, Fanconi's anemia or severe combined immunodeficiency (SCID) are

considered homologous. This recognition embraces the widely accepted findings in the scientific literature that the donor cell product contains progenitor cells capable of providing complete or partial replacement of the recipients' defective populations of erythromyelopoietic progenitors (Fanconi's anemia), as well as their lymphoid cells (SCID). However, treatment of adrenal leukodystrophy (congenital metabolic deficiencies) using HPC was identified as an example of non-homologous use. Recent scientific evidence has now been accumulated to demonstrate that HPC have inherent lympho-reconstitution and immunomodulatory capabilities, in addition to erythromyelopoietic reconstitution. Consequently, uses of HPC to replace or supplement these functions in a recipient should be interpreted as *"homologous use."* The references #1 - 6 in the appendix support the position that adult hematopoietic stem cells are functionally homologous when used for reconstitution of erythropoietic, myelopoietic, and lymphopoietic tissues.

Even if scientific questions remain on whether the function of the HCT/P in the recipient is homologous with its function in the donor, the FDA has clearly stated in the Preamble that "*In the absence of advertising, labeling, or other indications of the manufacturer's intent for such use, we would not require premarket submissions*." Additionally, the stated intent of 21 CFR 1271 is, "to prevent the introduction, transmission, and spread of communicable diseases by HCT/P's." The regulation does not address patient benefit or HCT/P effectiveness.

Failure of a given HCT/P to meet any of the 21 CFR 1271 inclusion criteria (see the algorithm in Appendix D) imposes additional regulatory filing requirements (IND or IDE), additional pre-clinical testing, additional manufacturing facility requirements, and an extensive clinical trial development pathway. It also implies adherence to the commercial approval mechanism created for drugs/biologics via the Biological License Application or devices through a Pre-Market Approval (PMA). The additional regulatory burden may delay and ultimately prevent the clinical development and potential commercialization of HCT/Ps. The interpretation implied in the preamble has not been applied. Rather, the FDA has insisted that academic centers and industry take the more conservative, restrictive and costly IND route (21 CFR Part 312), when all the other PHS Act 361 criteria have been fulfilled. See Appendix B for IND references.

The ISCT and the HuWG believe the OCTGT uses the interpretation of the *"homologous use"* criterion to acquire clinical benefit data by requiring an IND. This strategy is contrary to the stated intent in the preamble and to the FDA's Critical Path Initiative. Alternative mechanisms are necessary to resolving the conflicting objectives. One resolution would be the development of a guidance document providing a decision algorithm. The decision criterion would go beyond homologous/non-homologous to address specific HCT/P risk factors and subsequent requirements for clinical data. The acquired clinical experience would provide a precedent that can be applied to other developing HCT/Ps.

**Table 1: Homologous Use Examples** *

| **21 CFR 1271.3(c)** | **Homologous** | **Non-Homologous** |
|---|---|---|
| Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor. | Use of bone for repair, replacement, or reconstruction anywhere in the skeleton of the recipient (including the vertebral column).<br><br>Acellular dermis used as a urethral sling to treat female urinary stress incontinence due to intrinsic sphincter deficiency or urethral hypermobility.<br><br>Use of amniotic membrane for ocular repair.<br><br>Use of processed dermis for the treatment of chronic eardrum perforations. | The use of dermis as a replacement for dura mater<br><br>The use of cartilage in the bladder.<br><br>Amniotic membrane cultured with stem cells for ocular repair<br><br>The use of autologous hematopoietic progenitor cells in cardiac tissue. |
| **21 CFR 1271.10(a)(2)** | | |
| The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent. | In the absence of advertising, labeling, or other indications of the manufacturer's objective intent for non-homologous use, pre-market submissions would not be required. The physician's use of the HCT/P would not be the criteria, the criteria is the manufacturer's intended use. | "Promotion of an HCT/P for an unproven therapeutic use such as curing cancer." (ref. preamble) |

*(Weber D.J, "Navigating FDA Regulations for Human Cells and Tissues," Bioprocess International, Sept 2004 pp: 2-7.)

The manufacturer of the HCT/P may determine that the product meets the requirements for regulation solely under PHS 361, 21 CFR 1271 but the FDA can determine otherwise. When disagreements are filed, the FDA has assigned the Tissue Reference Group (TRG) to arbitrate the assignment of 21 CFR 1271 applicability. The criteria used in the decision-making process by the TRG are not clear. As there is no publicly accessible source of such information or documentation, this process will likely remain unclear.

For further descriptions and examples for the application of "*homologous use"* an HCT/P manufacturer can access the FDA preamble to the final rule (Box 2). Again, these examples do not provide adequate decision-making criteria and, as seen below, the FDA decision is subject to change.

In the preamble to the Establishment Registration and Listing final rule, published in the Federal Register on January 19, 2001, the FDA described at length its intent to narrowly interpret what constitutes non-homologous use of an HCT/P. As stated, emphasis was to be placed on the intent of the HCT/P manufacture to advertise, label or otherwise promote a non-homologous use for an HCT/P. The preamble went so far as to state that an entire transplant program could use an HCT/P in a non-homologous manner and still be consistent with regulation under section 361 of the PHS Act (see preamble excerpt in Box 2).

**Box 2. Excerpts from Preamble of HCT/P Establishment Registration and Listing Final Rule (January 19, 2001) Regarding Interpretation of "Nonhomologous" Use.**

Below, in comment 29, we discuss our decision to look not at the actual use of an HCT/P, but at the manufacturer's objective intent for a nonhomologous use. Under this approach, a practitioner could use an HCT/P, such as hematopoietic stem cells or fascia lata, for a nonhomologous use in the treatment of the physician's patients. Thus, we would not look at the surgical use of HCT/P's such as fascia lata or pericardium allografts, but instead at whether they were advertised, labeled, or otherwise objectively intended by the manufacturer for a nonhomologous use. In the absence of advertising, labeling, or other indications of the manufacturer's intent for such use, we would not require premarket submissions.

We intend to interpret ''nonhomologous'' narrowly. Examples of uses that would be considered nonhomologous include: The use of dermis as a replacement for dura mater, the use of amniotic membrane in the eye1, and the use of cartilage in the bladder. As noted above, an HCT/P that is intended by the manufacturer for one of these uses would not be regulated solely under section 361 of the PHS Act and these regulations, but as a drug, device, and/or biological product.

[1]

[1] After a manufacturer of amniotic membrane presented significant data pulled from the clinical literature (no controlled clinical studies have been reported in the literature) FDA opted to change its mind and consider amnion used in the eye to actually be homologous use and subject only to tissue rules. While such action is encouraging, this action took place behind closed doors and little information is publicly available as to the documentation necessary to cause the FDA to reverse its prior statements.

(**Comment 29**) We received approximately six comments agreeing with our focus in proposed § 1271.10(b) on the promotion or labeling of HCT/P's for nonhomologous uses, rather than on their actual use. One of these comments noted that the use of a product should be determined not by the practice of surgeons but by the promotion, labeling, and objective intent of the manufacturer. Another noted that the manner in which we intend to determine homologous use is consistent with the way we determine the intended use of other products under our jurisdiction. Two comments interpreted proposed § 1271.10(b) as relieving clinicians from restrictions on use of tissue, and one of these comments asserted that the exception should be extended to certain clinical transplant programs. Another supportive comment questioned how we will regulate the labeling of 361 HCT/P's. Among other things, the comment asked whether we will require 361 HCT/P's to be labeled for their homologous use. The comment also queried whether cutting, shaping, or processing a product in a manner that makes it amenable to nonhomologous use would be considered promotion, in the absence of labeling or advertising. We appreciate the comments on this issue, and we have decided to maintain the regulation's focus on the objective intent of the HCT/P's manufacturer for a nonhomologous use, rather than on the intent of the practitioner who uses the HCT/P. We believe this approach will lead to more efficient use of our resources. The focus on labeling, advertising, and other indications of the manufacturer's objective intent does not relieve clinicians from all restrictions on the use of HCT/P's. However, it does mean that clinical use of an HCT/P in a nonhomologous manner, whether by an individual practitioner or a transplant program, can be consistent with regulation of the HCT/P solely under section 361 of the PHS Act and the regulations to be contained in part 1271. In order to clarify this provision, we are revising proposed § 1271.10(b) to read, in new § 1271.10(a)(2), as follows: ''The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent. By labeling, we refer to the HCT/P label and any written, printed, or graphic materials that supplement, explain, or are textually related to the product, and which are disseminated by or on behalf of its manufacturer. We will address specific labeling requirements after reviewing comments to the GTP proposed rule. In order to be more consistent with terminology used by the rest of the agency, we have replaced the word ''promoted'' with ''advertised.'' The terms ''advertised,'' ''advertisement,'' and ''advertising'' include information, other than labeling, that originates from the same source as the product and that is intended to supplement, explain, or be textually related to the product (e.g., print advertising, broadcast advertising, electronic advertising (including the Internet), statements of company…

The definitions, illustrations and comments from the FDA's own documents pertaining to *"homologous use"* and interpretation of non-homologous use convey a flexible approach. However, the general experience of many stakeholders is that the default FDA position is to view the use of an HCT/P as non-homologous, unless demonstrated otherwise. Unfortunately, what

constitutes adequate demonstration of *"homologous use"* is not clearly articulated. ISCT membership would like to actively participate in development of an HCT/P guidance document that provides an effective decision algorithm based on scientific knowledge and clinical patient risk.

At the present time, the FDA appears to place significant weight on site of collection of an HCT/P or the placement of the HCT/P within the recipient when making determinations of whether the use of an HCT/P is non-homologous. While such a criterion may be important for more 'traditional' tissues such as bone or skin, its applicability to stem and progenitor cells is tenuous at best. It is widely recognized in the scientific community as well as at the FDA that the microenvironment[2] in which stem/progenitor cells reside within a recipient largely dictate the attributes or functions of which the stem/progenitor cells are capable. Therefore, uses of stem/progenitor cells should not be deemed non-homologous based on where they are used in the recipient, even if collected from a different location in the donor. Rather, the determination of homology should be based on their recognized functions as described in peer-reviewed scientific publications.

There is strong evidence to suggest that cells should be classified as homologous by features other than collection site in the donor or placement in the recipient. References #7 - 15 in the Appendix C define the homologous nature of bone marrow and umbilical cord blood by phenotype, as defined by physical and chemical reactions, and by function as evidenced by direct growth in culture and the performance of these cells in the patient. The paper listed by Cai et al (ref # 14) from the NIH identifies neural stem cells using chemical phenotype and makes the point that stem cells in different parts of the body have characteristics in common, no matter where they are found.

The use of stem/progenitor cells from various sources to repair heart damage has been an active research topic for over 10 years (references #16 - 23). Qun Shi et al, reference # 16, found that vascular grafts were endothelialized by progenitor cells naturally circulating from the bone marrow of dogs. The labs of Jeff Isner, Piero Anversa, and Silviu Itescu published some of the earliest work showing that cells from bone marrow migrate to ischemic regions of the heart and induce neo-vascularization. Subsequent work, including a randomized, placebo controlled, double-blinded clinical study in Germany has shown that bone marrow cells have a clinical benefit in humans following acute myocardial infarction (reference #19).

Some of the strongest evidence that stem/progenitor cells in the bone marrow have a systemic role in repairing damaged tissue comes from the CNS literature. (See references #24 - 26). Eva Mezey (ref. # 24) found that bone marrow cells naturally circulate to the brain and develop neural phenotypes. Michael Chopp's lab (ref. #25) found that bone marrow endothelial progenitor cells, administered intravenously home preferentially to the infarct site in mice following mid-cerebral artery occlusion (MCAO, a stroke model) and aid in neovascularization and improved functional outcome. Paul Sanberg's lab (ref. #26) showed that

[2] The concept of how microenvironment influences function was discussed at an FDA advisory committee meeting on stem cells for neurological indications in July 2000.

mobilized human peripheral blood stem cells behave similarly when given intravenous to MCAO mice. The homing appears to be mediated by SDF-1: CXCR-4 interactions.
These examples serve to reinforce the concept that stem cells should be classified as homologous or non-homologous by features beyond the harvest or injection site. The risk factors for HCT/Ps need to be defined and described by the application of a decision-making algorithm and guidance document.

**ISCT Recommendations:**

In summary, the ISCT makes the following recommendations:

1. The FDA's Office of Cell Tissue and Gene Therapy, which has regulatory oversight of most HCT/Ps, should implement a formal process for periodic evaluation of currently available evidence in the peer-reviewed scientific literature to assess the current interpretation of *"homologous use"* for specific types of HCT/Ps. ISCT believes that this can best be accomplished in a public forum, such as the Cellular, Tissue and Gene Therapies Advisory Committee, appropriately supplemented with individuals with scientific and clinical expertise for the subject HCT/P(s) under discussion. Alternatively, a peer-review process, similar to that employed by the NIH Recombinant Advisory Committee (RAC) should be considered. It is understood that the Tissue Reference Group (TRG) has been initially tasked with this activity. However, if the workings of this internal FDA decision-making group cannot be made more transparent to HCT/P stakeholders, the ISCT believes further vetting of TRG decision-making in a regulatory science-based public forum is in the best interest of the Public Health. In this manner, listings of decision precedents and the discussion involved in the decision-making process can be made public. We strongly believe this approach will facilitate the ability of developers of therapies based on HCT/Ps to provide the FDA with the appropriate information to address regulatory concerns, while also making available these promising therapies to patients.

2. The ISCT believes there is a critical need for the FDA to issue written guidance for HCT/P stakeholders that reconciles the Agency's stated intent to narrowly interpret non-homologous uses of HCT/P with its currently perceived practice of presuming the use of an HCT/P is non-homologous until demonstrated otherwise. We believe the current approach adopted by the FDA is contrary to the intent of the regulation as reflected in the Preamble. Independent of the issue of *"homologous use,"* all HCT/P manufacturers are required to register with the FDA and to establish systems to be compliant with Part 1271 and are subject to inspection and potential corrective action. Where there is no objective intent to promote an HCT/P for a non-homologous use and the HCT/P meets the other criteria in 1271.10 for regulation solely under section 361 of the PHS Act, the ISCT believes sufficient oversight exists at the local level (IRB), and that submission of an IND is an unnecessary regulatory burden for both the HCT/P manufacturer and the FDA.

The ISCT appreciates this opportunity to raise these important issues concerning homologous and non-homologous uses of HCT/Ps and looks forward

to further discussion with the FDA to facilitate implementing these or other negotiated recommendations.

## Appendix A: Membership

**Homologous Use Working Group**

| Nominee | Credentials | Nominated By | Organization |
|---|---|---|---|
| Cardwell, Lizabeth J. | MT(ASCP)MBA | Chair, Working Group | |
| Heimfeld, Shelly | PhD | | Assoc. Member FHCRC |
| Keating, Armand | MD,FRCP | ASBMT | Princess Margaret Hospital |
| Szczepiorkowski, Zbigniew | MD, PhD, FCAP | ASFA | Dartmouth-Hitchcock Medical Center |
| Haley, Rebecca | MD | AABB | Aldagen |
| Ricordi, Camillo | MD | American Society of Transplant Surgeons | Diabetes Research Institute |
| Alpdogan, Onder | MD | ASH | Memorial Sloan Kettering Cancer |
| Mills, C. Randal | PhD | AATB | Osiris Therapeutics Inc. |
| Atkins, J. Wade | MT(ASCP)SBB | | National Institutes of Health |
| Czarniecki, Christine | PhD | | NIAID |
| Garrison, Connie | MBA,MT | | Miltenyi Biotec Inc. |
| Macpherson, Janet | PhD | | Johnson & Johnson Research |
| Peterson, Dale | PhD | | The Vertical Group |
| Weber, Darin | PhD | | Biologics Consulting Group, LLC |

**Homologous Use Advisory Group**

| Nominee | Credentials | Nominated By | Organization |
|---|---|---|---|
| Heimfeld, Shelly | **PhD** | **Chair, Advisory Group** | Assoc. Member FHCRC |
| Cardwell, Lizabeth J | **MT(ASCP)MBA** | **Chair, Working Group** | |
| Brecher, Mark | **MD** | **ASFA** | UNC Hospitals |
| Read, EJ | **MD** | **AABB** | **NIH** |
| McMannis, John | **PhD** | **AABB** | MD Anderson Cancer Center |
| Silberstein, Leslie | **MD** | **ASH** | Children's Hospital of Boston |
| Gastineau, Dennis | **MD** | **FACT** | Mayo Clinic |
| Frey-Vasconcells, Joyce | **PhD** | **CBER** | PharmaNet Consulting |
| Heslop, Helen | **MD** | **FACT** | Baylor College of Medicine |
| Witten, Celia | **PhD,MD** | **FDA/CBER** | CBER,Office Director OCTGT |

**Appendix B: Sponsor INDs**

1. BB-IND 11839: “A Randomized Open-Label Phase II/III Multicenter Study of High-Dose Immunosuppresive Therapy Using Total Body Irradiation, Cyclophosphamide, ATGAM, and Autologous Transplantation for the Treatment of Severe Systemic Sclerosis.”

2. BB-IND 12164: “A Phase II Study of High-Dose Immunosuppressive Therapy (HDIT) Using Carmustine,Etoposide, Cytarabine, and Melphalan (BEAM) + Thymoglobulin, and Autologous CD34+ Hematopoietic Stem Cell Transplant (HCT) for the Treatment of Poor Prognosis Multiple Sclerosis.”

3. BB-IND 12114: “A Randomized, Open Label, Phase II Multi-Center Study of Non-Myeloablative Autologous Transplantation with Auto-CD34+HPC Versus Currently Available Immunosuppressive/ Immunomodulatory Therapy for Treatment of Systemic Lupus Erythematosus.”

4. BB-IND 12875: “A Phase I-II Randomized Comparison of Autologous Bone Marrow Derived Aldehyde Dehydrogenase-Bright (ALDHbr) Enriched Mononuclear Cells Randomized Against Unfractionated Autologous Mononuclear Bone Marrow in Patients with Rutherford 4 or 5 Peripheral Arterial Occlusive Disease.”

5. BB IND 12706: “Randomized Controlled Double-Blind Trial of Intramyocardial Injection of Autologous Aldehyde Dehydrogenase-Bright Stem Cells Under Electromechanical Guidance for Therapeutic Angiogenesis.”

**Appendix C: References**

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## Appendix D: Decision Algorithm

### Figure 1: Current Algorithm

Human cells, tissues, and cellular and tissue-based products (HCT/P)

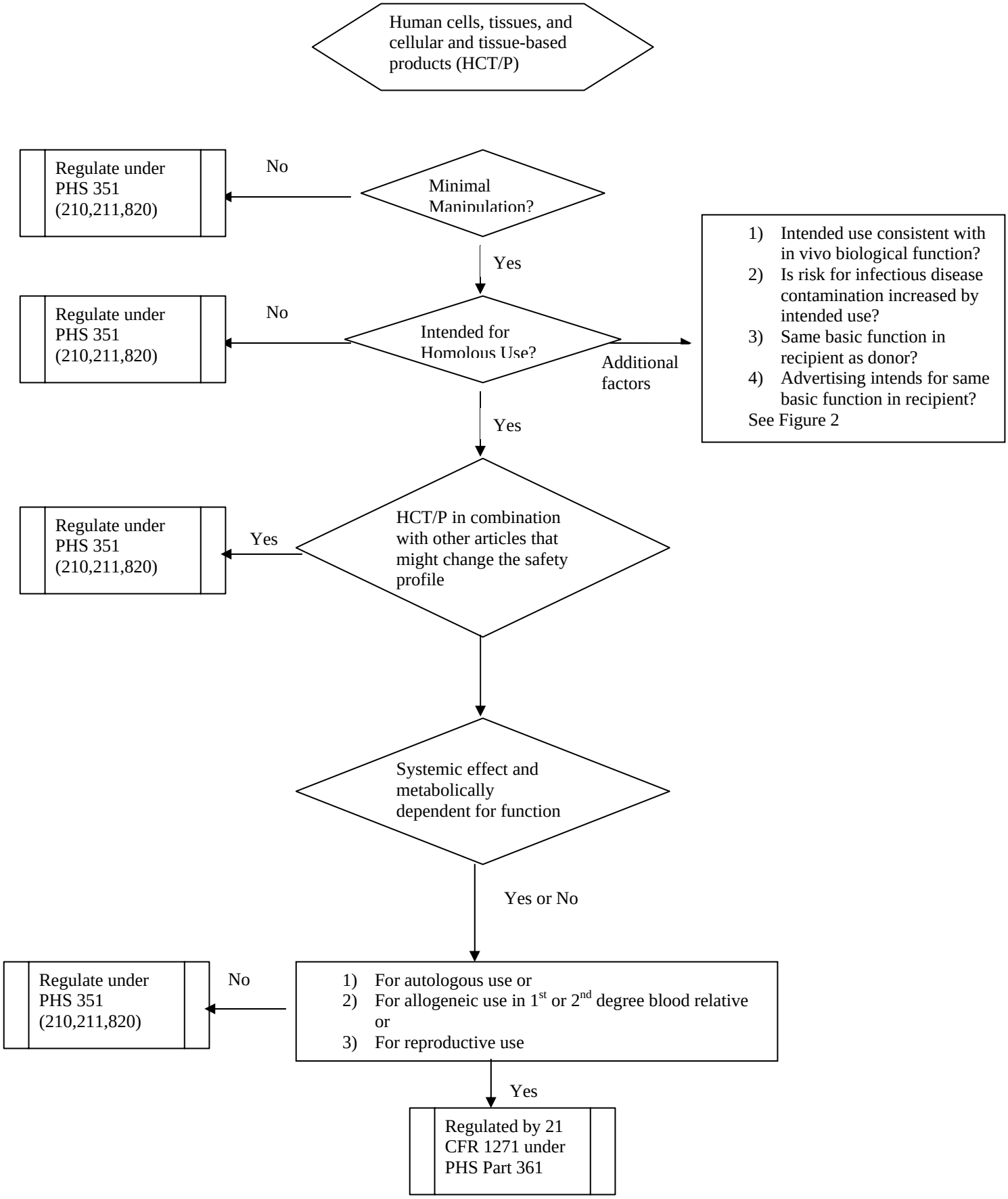
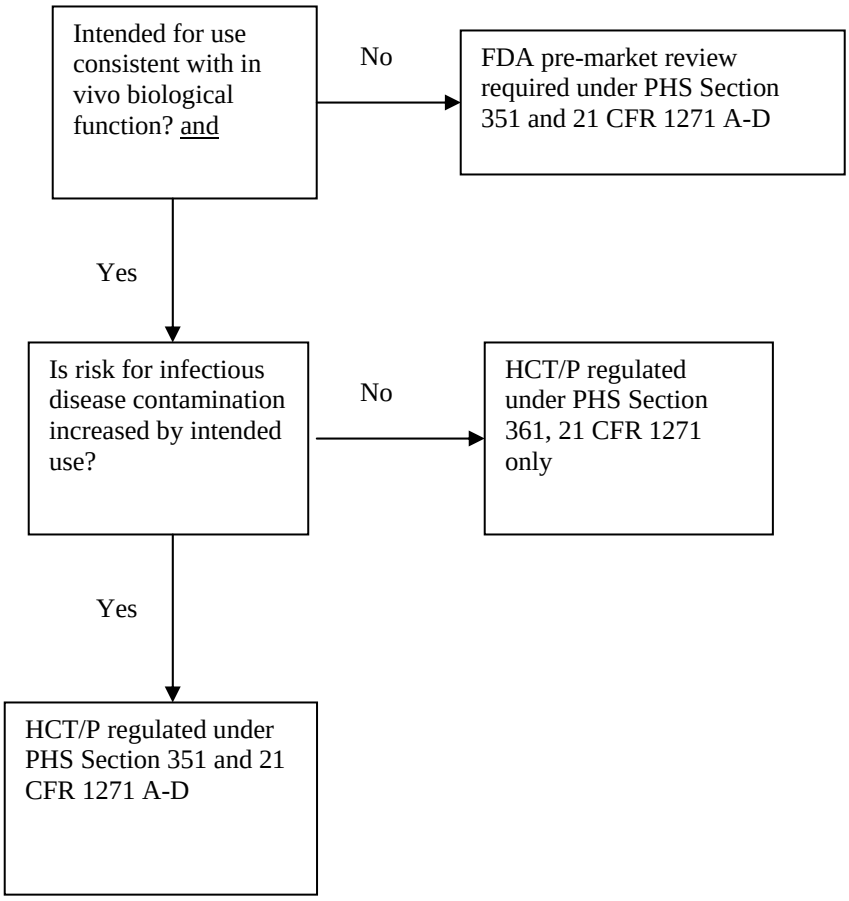


**Figure 2: Homologous Use Algorithm**




"The intended function in the recipient

- Is similar to
- Is analogous to or
- Corresponds to

Function in donor