ASBMT

American Society for Blood and Marrow Transplantation

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Food & Drug Administration Docket
Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fisher's Lane, Room 1061
Rockville, MD

Re: 21 CFR Part 1271 [Docket No. 97N-484P]: Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement

Dear Sirs/Madams:

I am writing as President of the American Society of Blood and Marrow Transplantation, an organization dedicated to the continued development of blood and marrow transplantation approaches, their increased safety and efficacy when applied to lethal disorders of the hematopoietic system, and other sensitive tumors. This organization represents nearly 1,000 members in the transplant community derived from over 250 transplant centers in the United States and in North and South America.

Our group has extensively reviewed the proposed regulations for 21CFR part 1271 in entitled, "Current Good Tissue Practice For Manufacturers of Human Cellular and Tissue Based Products; Inspection and Enforcement; Proposed Rule." For most of the proposed rules, we congratulate the FDA for its balanced approach and its development of appropriate and practicable standards for the production of hematopoietic stem cells for transplantation purposes.

We are also impressed that the vast majority of the rules proposed have already been incorporated in the standards and guidelines proposed by the American Society for Bone Marrow Transplantation and the International Society of Hematopoietic Graft Engineering (ISHAGE) through its accrediting body, the Federation for the Accreditation of Hematopoietic Cell Therapy (FAHCT).

As you know, FAHCT was established in 1994 to specifically provide standards and guidelines for the transplantation community. To insure appropriate evaluation and accreditation, FAHCT has established training programs and has also selected and developed a panel of 300 laboratory and clinical experts in hematopoietic stem cell preparation and transplantation to conduct the inspections of each center applying for

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accreditation. The guidelines developed and adopted by FAHCT form the basis for each center's accreditation. These guidelines are now widely accepted throughout this country and Europe and indeed have been approved by most of the major cooperative treatment groups participating in multicenter trials of transplantation in the treatment of malignancies under the auspices of the NIH and the National Cancer Institute.

In reviewing the proposed rules, we also note, however, several important discrepancies and differences between the standards and guidelines formulated and adopted by FAHCT and those proposed in the new rules by the FDA. The joint response of FAHCT, ASBMT and ISHAGE has already detailed the several points in the proposed FDA rules which either deviate from or are not required by the FAHCT Standards, which raise concerns in the laboratories providing hematopoietic stem cell grafts. Because ASBMT uniquely represents the physicians who administer transplants and care for these patients prior to, during, and after transplantation, we feel it important to summarize those components of the rules proposed by the FDA that exceed the requirements in the FAHCT Standards that will have an untoward impact on the practice of transplantation medicine and potentially inhibit effective application and continued development of allogeneic hematopoietic stem cell transplants in the treatment of patients.

These points of concern, in the order of their presentation in the proposed rules, are:

1) Sections 1271.160 (b) Functions (7) paragraph 2 and Sections 1271.320 (b) Complaint File.. File review and copying by the FDA.

The requirement for reports of periodic reviews and analyses of product directions and for maintenance of a complaint file for review upon request by the FDA reflects the need for quality management tools by facilities producing hematopoietic stem cells for transplantation. We accept this need. However, it is essential that these functions permit open and frank reviews. Such reviews within individual centers are privileged, confidential, and not a part of the public record. The FDA should specify in the final rule that the FDA and its employees will guarantee the confidentiality of these reports and that these reports will not become part of the public file regarding a center producing or distributing the cell product.

2) Section 1271.60 (c and d) Authority Over Program and Audits

The requirement for oversight and audits by individuals not engaged in the work of the hematopoietic stem cell processing laboratory will be difficult and may not be practicable for small facilities, where only 1-2 individuals may do this type of work. If independent oversight and audits are required, individuals at a center not expert in the issues would likely be recruited. Alternatively, outside experts would need to be recruited at a cost that would likely be prohibitive. These requirements are onerous and might well significantly reduce the number of donor centers currently participating in the National Marrow Donor Program, which currently provides up to 30% of the transplants administered worldwide. For these reasons, we would recommend that this requirement be dropped.

3) Section 1271.180 Procedures: "Any deviation from a procedure shall be authorized in advance by a responsible person, recorded and justified." Because of donor to donor variation in yields of

hematopoietic stem cells and occasionally, the responses of blood cells to standardized fractionation procedures, it is not possible to predict and authorize deviations in advance. In the context of a hematopoictic stem cell transplant, this is particularly the case, since the transplant from a given identified donor must be administered within 1-2 days of completion of myeloablative cytoreduction. Given these circumstances, we would respectfully recommend that this rule be deleted.

4) 1271.195 Environmental Control and Monitoring (a) General and (e) Records.

The intent of these rules is appropriate, and most of the specific requirements are already part of the FAHCT guidelines. However, certain features of the rules need to be revised to make them practicable and not inappropriately burdensome.

Given the fact that the papers cited by the FDA regarding the incidences of contamination of both manipulated and unmanipulated hematopoietic stem cell preparations derived from marrow and blood quote rates which are not different from those published for conventional blood products such as platelets and red cells, vide infra it is unduly onerous to require the cleaning and disinfection of rooms and equipment that is required for drug manufacture for facilities processing multiple individual hematopoietic stem cell products when other control systems such as HEPA filtered laboratory hood, are in place to prevent contamination. Procedures and systems such as are called for by FAHCT and AABB for blood cell processing facilities are and should be sufficient.

Similarly, the demand for record keeping which may be useful in the manufacture of large lots of drugs is unduly burdensome and non-practicable for a facility producing small or large numbers of individual hematopoietic stem cell components. The processing records for each stem cell preparation should, as requested by FDA and FAHCT Standards, identify supplies and reagents used for processing. The converse, that is, to have separate records of each transplant prepared with each reagent and with each piece of validated equipment, is prohibitively time-consuming. Again, we believe this requirement should be dropped and that the guidelines recommended by FAHCT would be sufficient.

5) 1271.220 Process Controls (b) Processing Material and (c) Pooling.

(b) The section on Processing Material should be amended to state that validated procedures shall be established to insure the appropriate use and removal of processing material and that the use of these procedures in the preparation of the stem cells be documented. It is not possible for a center to test, on a case by case basis, that processing materials have actually been eliminated.

(c) The section on pooling is appropriate for hematopoietic stem cell fractionation as it is currently practiced. However, with the current development of several strategies for inducing transplant anergy and, conversely, for generating donor type alloreactive T-cells and T-cells specific for a patient's cancer for adoptive cell therapy, this rule will soon be outdated and restrictive . Rewording of the rule to include the phrase "Unless required by a specialized approved protocol...." Would avoid these future restrictions and facilitate rather than inhibit progress.

6) 1271.250 Labeling Controls

These rules need to be streamlined along lines required by FAHCT and AABB which provides for coded identification of donor, identification of intended recipient and critical information regarding donor suitability and the type of processing used. The information called for in the rule is exorbitant for identification of individual transplant products.

7) 1271.260 Storage

Expiration dates are appropriate for conventional blood products, or drugs with defined shelf-lives. At present, the shelf-life of appropriately cryopreserved hematopoietic stem cells from peripheral blood, marrow or umbilical cord blood is not established. The rule needs to be revised to reflect this. Arbitrary assignment of expiration dates for such cryopreserved transplants is, at this stage, unjustified.

08) 1271.350 (a) Adverse Reaction Reports

The requirement for reporting any adverse reaction that necessitates medical or surgical intervention goes well beyond current FDA guidelines for reporting adverse drug reactions. Furthermore, since transplants of marrow, peripheral blood stem cells and umbilical cord cells can be rejected and conversely, often cause reactions such as graft vs. host disease, which can be fatal, this rule needs to be revised and better targeted.

9) 1271.420 Human cellular and tissue-based products offered for import (b)

This rule specifies that imported hematopoietic stem cell transplants would each have to be held until released by the FDA.

The rule is not acceptable to the hematopoietic stem cells transplant community. Unless there is an FDA officer available every minute of every day and night to immediately approve the 2000-3000 unrelated marrow and PBSC transplants that enter or leave this country each year, it cannot and must not be enacted. Marrow and peripheral blood stem cells are highly perishable. More importantly, the potential recipient of such a transplant will have completed supralethal myeloablative conditioning by the time the transplant arrives. To have such a transplant on hold, while an official at an airport tries to contact an FDA official to approve its import is, at this stage in the history of unrelated hematopoietic stem cell transplants, unethical and serves no useful purpose.

In addition to the enclosed specific comments, requests and suggestions regarding the proposed rules, we also wish to express, for the record, the serious concerns and reservations of the transplant community regarding the accuracy of the FDA's estimates of the risks associated with hematopoietic stem cell transplants in the absence of the proposed rules and the costs and benefits of implementing these rules as proposed.

While we completely concur with the FDA's objective of providing safe transplants with the lowest possible risk of microbial contamination, a perusal of available literature and a critical review of the papers cited on page 1547 of the proposed rules indicates that the risks to transplant recipients are greatly overestimated.

First, it should be noted that the peripheral blood progenitor cells and marrow cell samples described in the papers by Webb et al and by Espinosa et al were largely derived from autologous donors who had received multiple prior therapies, and, indeed, often required multiple harvests to obtain targeted doses of stem cells (82% in the series quoted by Webb et al., 97% in that of Espinosa et al). This is an important aspect of these studies, since many of these patients likely had low counts at time of harvest, would be likely to have had an indwelling catheter for extended periods prior to harvest, and would be at high risk for catheter infection at time of harvest. Thus, the risks of contamination quoted for PBMC (2.4% for Webb et al.; 0.2% for Espinosa et al.) would be expected to be at the highest end of frequencies. In fact, the incidences quoted are, in one case, no higher than, and in the other, lower than the incidences of contaminated blood products reported in several series for platelet or red blood cell transfusions. Strikingly also, the rate of contamination for monoclonal antibody treated and CD34 selected cells reported by Webb et al did not differ significantly from that of unmanipulated peripheral blood stem cells collected like a normal leukapheresis in a totally closed system.

Based on the data presented, there is no convincing evidence to suggest that the added rules called for will significantly alter the incidence of contaminated peripheral blood progenitor cell and marrow cell samples, since it is no higher than that recorded for current transfusion practice.

As an aside, it should also be noted that the autologous stem cell factions described by Webb et al and Espinosa et al would not be subject to the proposed FDA rules.

Secondly, the rates of infection quoted in the FDA document are inflated. While 13.7% of patients developed fever in the early post transplant period, only 2.73% were actually culture positive. In the two cases reported, the organism in the stem cell graft was subsequently cultured from the patient. As in all other reported series, the infection was effectively treated by antibiotics. In no other case was a positive culture documented. Given the high rate of fever in patients treated with chemotherapy without a stem cell graft at this stage post treatment, the 2.73% incidence is the more accurate figure.

Thus, if the true rate of infection is applied, even using the high rate of 2.4% for contaminated samples reported by Webb et al, the actual number of potential lethal infections is:

$$8000 \times 0.024 \times 0.0273 \times 0.58 \text{ PBSC} = 3 \text{ patients.}$$

If the rate of 0.2% reported by Espinosa is applied, the number is:

$$8000 \times 0.002 \times 0.0273 \times 0.58 \text{ PBSC} = 0.25 \text{ patients.}$$

These numbers are strikingly lower than the 15 patients quoted by the FDA.

Thirdly, it must be noted that the added inpatient costs for treatment of these infections are grossly inaccurate, since each of these patients would be expected to be in the hospital as an inpatient during the same time to receive support following myeloablative therapy.

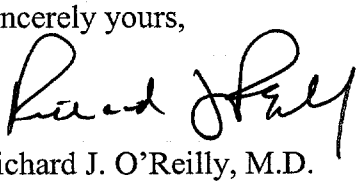
I will not reiterate the cost accounting provided by FAHCT in its assessment of the added costs of the FDA rules beyond those incurred by practices already required by FAHCT for accreditation. Suffice it to say they are significantly higher than the FDA estimates and likely not sustainable by smaller centers. Page 6.

In summary, while we applaud the efforts of the FDA, and appreciate their responsiveness to FAHCT as reflected by the similarities between the proposed FDA rules and the existing FAHCT standards and guidelines, we cite several new rules that will have a negative and potentially severe impact on the clinical practice of transplantation. By placing unduly burdensome requirements on transplant collection centers, certain of these rules may also force the closing of many small collection centers in the United States and likely limit access to hematopoietic stem cell transplants for patients in our own and other countries participating with the National Marrow Donor Program. The latter problem is particularly worrisome since it would reduce the potential pool of unrelated donors for its current level of 7 million to 4 million, and deny hundreds of patients a potentially curative graft. Lastly, we question the risk/benefit ratio proposed since, 1) the actual rates of contamination of stem cell transplants cited do not exceed those reported for unmanipulated platelet and red cell transfusion, 2) the number of severe infections to be presented is strikingly smaller than estimated and, more importantly, not likely to be affected by the rules proposed and, 3) the additional costs, which are not likely to be deferred by third party insurers, are exorbitant.

We respectfully suggest that the rules cited in this letter be deleted or modified. We also suggest that the existing guidelines required by FAHCT are sufficient to insure the safety of hematopoietic stem cell transplants we all wish to provide.

Thank you for your consideration.

Sincerely yours,



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