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of Hematopoietic Cell Therapy**

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May 3, 2001

Food and Drug Administration Docket
Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fisher's Lane, Room 1061
Rockville, MD 20852

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

The following is the response of the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT) to the Food and Drug Administration's proposed regulations for Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement published in the Federal Register on January 8, 2001.

In addition to the specific proposed regulations discussed in this letter, FAHCT and its parent organizations, the International Society of Hematotherapy and Graft Engineering (ISHAGE) and the American Society of Blood and Marrow Transplantation (ASBMT), feel strongly that the risks from the contaminated hematopoietic progenitor cell (HPC) products and the costs of implementing the proposed regulations included in the 21 CFR Part 1271 document are highly flawed and misleading. As we discuss below, the risks to the patient are overstated and the estimates of the costs of complying with the proposed FDA regulations under-estimated.

Risks of Contaminated HPC Products and Cost Estimates of Compliance

The statements made regarding the morbidity and costs incurred because of contaminated hematopoietic transplant products are greatly exaggerated, misleading and fundamentally incorrect. Infections frequently occur following hematopoietic transplantation related to pancytopenia and are not due to contaminated PBSC. The costs involved with hematopoietic transplantation are directly related to supportive care required during the period of chemotherapy induced myelosuppression post transplant. Although

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contamination of the hematopoietic transplant may rarely occur in hematopoietic transplant collections, it generally involves relatively nonpathogenic skin flora. Since it is often not feasible to collect additional transplant products, and the transplant can be life saving, a number of cases have been reported using cells contaminated by *S. epidermidis* without major complication or prolongation of hospitalization; patients are generally treated with appropriate antibiotics during the cell infusion. The toxicity of DMSO is readily managed by limiting the amount of DMSO infused. ICU admissions in transplant recipients are generally the result of high dose chemotherapy and infections unrelated to contaminated cell infusions; it is well documented that these infections are acquired from flora colonizing the gastrointestinal and respiratory tracts, not contaminated transplant products. Thus the calculations regarding lives saved and costs reduced by the proposed measures are fundamentally flawed. We are unaware of evidence that methods currently in use by the medical community has resulted in avoidable morbidity or mortality.

Specifically relating the FDA risk and cost estimates:

- 1) FDA estimates that the average stay for a bone marrow transplant patient in 1994 was 35 days at a cost of \$168,573. Costs and average length of stay in 2001 are much different than in 1994; again, this figure is related to generally supportive care needed for a transplant recipient and is not due to contamination of the graft.
- 2) The FDA attempts to estimate the impact of a contaminated HPC product for immunosuppressed recipients. The marginal risk of a contaminated product over that of infection from other causes in immunocompromised hosts is extremely small in aggregate. As indicated there are many reports of successful transplantation despite low level contamination of the graft.¹
- 3) The dimethylsulfoxide (DMSO) toxicity attributed to large volume peripheral blood progenitor cell infusions is overestimated. The use of DMSO has no impact on cost or toxicity in the vast majority of HPC recipients.
- 4) FDA estimates that 2.4% of peripheral blood progenitor cell products are contaminated and suggest there is a 13.7% incidence of infection in patients receiving contaminated HPC products (net infectious risk: 0.33%). The incidence of infection cited greatly overestimates the risk of infection caused by the HPC product. Further, the vast majority of contaminated HPC products contain skin flora (gram-positive cocci) that are not life-threatening, are easily treated in the outpatient setting, and do not contribute at all to inpatient hospital costs as suggested by the analysis. These infections almost never cause hospital admission or prolongation of hospital stay. In the same reference cited by the FDA,¹ there were **no** irreversible sequelae noted following infusion of contaminated product.
- 5) Intensive Care Unit (ICU) admission. The FDA cited data of a 57% death rate in transplant patients admitted to ICU with infections versus a 13% death rate in patients with no infections is **not** relevant to the cost of infusing contaminated HPC products, but rather the cost and risk of endogenously acquired infection in transplant patients. There are no data to suggest that patients who receive contaminated HPC products require ICU care or have a

higher death rate than similar transplant patients who receive uncontaminated products. The FDA estimates that 15 patients a year could get infection from contaminated HPC products and that 7 of these patients would die. As noted above, death from contaminated product infusions is extremely rare. Of the estimated 15 patients, it is highly likely that the mortality will be zero and that no additional hospital days would be required for treatment. The anticipated additional cost per patient is less than \$500 for the requisite two-week course of vancomycin or similar antibiotic. Transplant recipients generally receive antibiotic prophylaxis as a standard of care and thus, would not receive additional days of antibiotic treatment, even if a contaminated graft was administered. Thus, for an estimated cost of no more than \$7500/yr, and no excess mortality risk, the agency proposes regulation costing millions of dollars per year (see below).

- 6) The FDA document states that the aggregate annual costs for a facility to come in to compliance with their proposed regulations would be \$9,256.81. That calculation was derived from one-time costs of \$3,571,049; annual costs of \$3,194,292 and then total annualized costs of \$3,702,027 calculated for 400 facilities. However, on page 1526, table 2, column 5, the costs of complying with the proposed regulations were broken down by specific regulation, for both compliant (i.e. FAHCT accredited) and noncompliant facilities. We took the FDA's estimated costs from table 2 and determined that for a compliant (FAHCT accredited) facility, the cost per facility per year would be \$27,291 and for noncompliant facilities \$79,437. The annual costs for 300 centers that were determined to be compliant would therefore be \$8,187,300. For the 100 facilities estimated to be noncompliant, the cost would be \$7,943,000. Thus the total annual costs of compliance would actually be \$16,131,000. If this additional cost were associated with additional safety for the patients there would be less concern. However, as discussed below, there are no data to suggest that any of the proposed regulations, particularly for compliant facilities, would end up improving the safety and thus clinical care of our HPC transplant patients.

The following proposed regulations are of concern to FAHCT:

1271.150 (b) paragraph 2: Facility responsible for release criteria

Further clarification of who is responsible is required. It is not clear whether this responsibility pertains to the manufacturing facility or just the distributor. If the distributor is an institutional laboratory that receives a product that was processed at a commercial laboratory, this requirement would be unduly burdensome.

1271.160 (b) Functions (7) paragraph 2: Confidentiality

FDA is requiring in section Sec. 1271.160 (b)(7) that the periodic review and analysis of all product deviations be made available for review upon inspection and for submission to FDA upon request. Furthermore, FDA is requiring in section 1271.320(b) that a complaint file to be maintained shall also be made available for review and copying upon request from an authorized employee of the FDA.

Both the periodic audit of product deviations and the collation of a complaint file are tools of quality management. The proper conduct of quality management activities requires open and truthful review of adverse outcomes within the facility conducting the audit. FDA should state in the final rule that FDA and its employees shall guarantee that the confidentiality of these quality management activities will be strictly maintained by FDA and that records or copies of such records shall not become part of the public record regarding a manufacturer or distributor of cellular or tissue-based products.

1271.60 (c) Authority over program

This is a departure from the requirements that the agency has imposed on other areas such as blood and blood components, where the more general wording of the regulation [21CFR 606.100 (b) (19) (c)] may on occasion lead to a single person doing actual work and final review, separated in time and function. In small laboratories with only a single technician it may not be possible for an independent person to have oversight. This requirement will limit access to care by limiting the number of programs available who could provide additional staffing. The proposed tissue regulation is at least as stringent as cGMP requirements in 21CFR 211.

1271.60 (d) Audits (2) Acceptable personnel

As above, in small laboratories with only a single technician, there may not be an alternative knowledgeable person able to perform the audits. We think it would be inappropriate to limit access to care by limiting programs that had a knowledgeable staff person but not another knowledgeable person to perform the audit.

1271.170 Organization and personnel (b) Competent performance of functions

We recommend that "training and documentation of competency" be used rather than "education and experience." The latter are more vague and do not ensure competent performance of the procedure.

1271.180 Procedures (6) Deviations

Some deviations, such as those occurring in process, cannot be authorized in advance.

1271.180 (last sentence) Archiving records for at least 10 years

This requirement to maintain obsolete procedures for ten years is inconsistent with record retention requirements where documents pertaining to manufacture of a product should be kept for at least 10 years after implantation, transplantation, infusion, or transfer of the product. [Section 1271.270 (e)]. We believe the longer retention of obsolete procedures (i.e., for ten years after transplantation) to be more appropriate and request clarification of FDA intent.

1271.190 (c) Facilities (4) Cleaning and sanitation activities

Clarification of "significant" cleaning and sanitation activities is necessary. Such activities could include mopping the floor or washing the cabinets. We believe it would be unduly burdensome to keep records of mopping the floor for 10 years. Alternatively, changing the air handling filters is a significant cleaning activity that would have more relevance to the quality of the processing procedures and records of such an activity warrant retention.

1271.195 Environmental control and monitoring (3) Cleaning/disinfecting rooms

We interpret this to mean that this type of cleaning and disinfection would not apply to most stem cell laboratories performing routine (minimally manipulated) processing procedures. If that is not the case, it is burdensome to require disinfection of all rooms when other control systems to prevent contamination are in place.

1271.195 (5) Environmental monitoring for "organisms"

There is no consensus from current expert opinion on what "organisms" to monitor. This regulation would have to be more specific to be meaningful.

1271.200 Equipment (c) Calibration of equipment

We object to the requirement for calibration of computers since they do not measure anything. Validation should be sufficient.

1271.200 (e) Records (2nd sentence) Records of recent maintenance, cleaning, etc.

Such records cannot physically be kept on small instruments such as pipettes. A central repository of such records should be sufficient.

1271.200 (e) Records (3rd sentence) Records of the use of each piece of equipment

The instrument used to process a product is already documented on the processing record. To require listing each product process for each piece of equipment does not add to the safety or quality of the product and is unnecessarily burdensome.

1271.210 Supplies (c) Records (3) Records of each supply or reagent

The supplies and reagents used to process an HPC product are already on the processing record. As above, to require listing each product process for each pipette or bottle of medium does not add to the safety or quality of the product and is unnecessarily burdensome.

1271.220 Process controls (b) Processing material

It is not always physically possible to document that the processing material has been removed from the product. For example it is not possible to determine exactly how much ficoll is left in

the HPC product to be issued. It should be sufficient to document that validated procedures were used in processing.

1271.210 (c) Pooling of human cells from two or more donors

This requirement conflicts with the philosophy of the regulatory model which holds that, as technology becomes more standard, the requirements become less burdensome, not more.ⁱⁱ Although currently generation of cellular products such as cytotoxic T lymphocytes or dendritic cells are typically performed under IND, this may not be the case as these procedures become more standard. Such a requirement will stifle technology transfer and ultimately impact adversely on patient care.

1271.250 Labeling controls (3) Documentation required for distributed HPC products

"Distribution" needs to be defined. If the product is going from the HPC laboratory to the clinical unit of the same program, detailed documentation of the donor testing does not need to accompany that product as it can be found in the laboratory. It is burdensome to include all the specific results of the testing and doesn't improve the quality of the product. It is sufficient to provide the statement of suitability including the specifics only when there is a product deviation. If distribution means distribution outside of the institution then such documentation makes more sense.

1271.260 Storage (b) Temperature (2) Temperature limits

All three parameters (ensuring function and integrity, preventing deterioration, and inhibiting infectious agent growth) may not be optimal at the same temperature, and in fact are likely to be optimal at different temperatures. Some HPC products are held at room temperature in the absence of preservatives or antibiotics. That temperature might be optimal for preserving integrity and function, but allow growth of some infectious agents. Each facility will have to prioritize those three parameters and develop standard operating procedures that describe the acceptable temperature limits for the products in their own institution, based on their own validation to ensure integrity, etc.

1271.260 Storage (c) Expiration date

The safe duration of cryopreservation for an HPC product is unknown at this time and will take years to validate.

1271.270 Records (c) Other record keeping requirements (5th sentence) Donor suitability records in English

Clarification is required here, as clearly English translations would not be required for foreign facilities that are processing products to be distributed outside the United States. This should be stipulated for products distributed within the United States.

1271.290 Tracking (d) Product information

The manufacturer has no authority over the content of the medical record. It should be sufficient to provide paper documentation appropriate for the medical record and notice of the Federal Regulations requiring that the information be placed in the medical record.

1271.290 (f) Consignees

The manufacturer has no authority over the content of the medical record and may not have permission to review the content of the record at a later time. It should be sufficient to provide the paper documentation appropriate for medical record in notice of the Federal Regulations requiring that the information be placed in the medical record.

1271.320 (b) Complaint file (3rd sentence) File review and copying by the FDA

Copying files is a breach of confidentiality that is not acceptable. If this is required, the FDA must ensure that patient-specific information does not become part of the public record.

FDA is requiring in section Sec. 1271.160 (b)(7) that the periodic review and analysis of all product deviations be made available for review upon inspection and for submission to FDA upon request. Furthermore, FDA is requiring in section 1271.320(b) that a complaint file to be maintained shall also be made available for review and copying upon request from an authorized employee of the FDA.

Both the periodic audit of product deviations and the collation of a complaint file are tools of quality management. The proper conduct of quality management activities requires open and truthful review of adverse outcomes within the facility conducting the audit. FDA should state in the final rule that FDA and its employees will guarantee that the confidentiality of these quality management activities will be strictly maintained by FDA and that records or copies of such records shall not become part of the public file regarding a manufacturer or distributor of cellular or tissue-based products.

1271.350 Reporting (a) Adverse reaction reports (1) Adverse reaction information (iv) Medical or surgical intervention

This requirement is too vague and nonspecific. Medical intervention could be giving Benadryl and Tylenol. Requiring this type of intervention to be reported is overly burdensome and will not improve the quality of the HPC product or patient care in general.

1271.350 (b) Reports of product deviations (1)

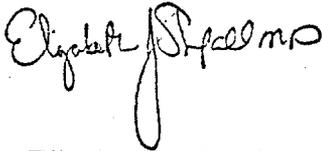
Reporting minor and unimportant deviations should not be required. More specifics on how serious a deviation needs to be to require reporting should be provided.

1271.420 Human cellular and tissue based products offered for import (b) Holding products until release

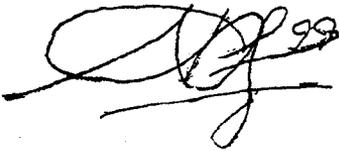
It is medically unsafe to hold fresh HPC products that would need to be processed and infused without cryopreservation, for FDA review. This requirement is not logistically feasible, and has a high chance of jeopardizing the quality of the products and thus seriously compromising transplant patient care. This would require that the FDA be available 24 hours a day 7 days a week to deal with HPC products coming from overseas. Even those products that are cryopreserved will have limited duration before thawing occurs; the FDA could ultimately be responsible for adversely affecting the integrity and function of the products.

In summary, it appears that the proposed FDA regulations offer little additional benefit over the FAHCT Standards that are currently in place. Given that FAHCT is already inspecting to standards which are very close to the proposed regulations we once again offer our services to improve the quality of care and HPC products provided to our patients. We look forward to continued dialog on this and other issues.

Sincerely,



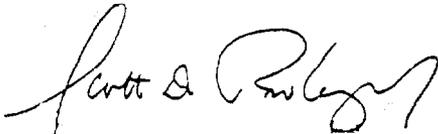
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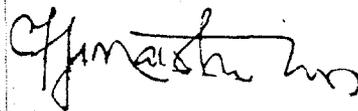
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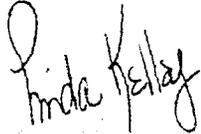
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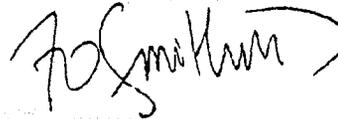
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References:

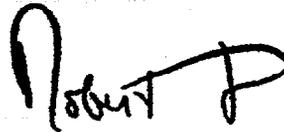
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- ¹ I. Webb, I.J., F.S. Coral, J.W. Andersen, A.D. Elias, R.W. Finberg, L.M. Nedler, J. Ritz, and K.C. Anderson, "Sources and Sequelae of Bacterial Contamination of Hematopoietic Stem Cell Components: Implications for the Safety of Hematotherapy and Graft Engineering," *Transfusion*, vol.36, pp. 782-788, 1996
- ⁱⁱ The Food and Drug Administration: "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products" February 28, 1997.



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