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National Marrow
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Health Resources and Services Administration and
Naval Medical Research and Development Command

Dockets Management Branch (HFA-305)
Food and Drug Administration
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Dear Comments Administrator:

Enclosed you will find the National Marrow Donor Program's® comments to the Food and Drug Administration's proposed rule "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement". (Docket number 97N-484P.)

Please feel free to contact me if you have questions as it pertains to our comments. I can be reached at 612-362-3425.

Sincerely,

Dennis L. Confer
Chief Medical Officer

enclosure

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NATIONAL MARROW DONOR PROGRAM®
COMMENTS TO

21 CFR Part 1271, Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule. Docket no. 97N-484P.

The comments are formatted in the following manner:

The portion of the FDA docket "21 CFR Part 1271, Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule", which is being commented on, is highlighted in bold and is followed by the page number, column and paragraph that pertains to the comment. The proposed rule is cited and is followed by the National Marrow Donor Program's® (NMDP's) comment.

II. Summary of the Proposed CGTP
G. Processing
Page 1516, column 2, paragraph 4

Proposed Rule:

The pooling of human cells from two or more donors during manufacturing would be prohibited.

NMDP Comment:

In some cases, a related or unrelated marrow or peripheral blood stem cell donor can not be found for a critically ill patient. In these cases a cord blood donor may be the only option for the patient. In the case of an adult recipient, because many protocols require the transplantation of an adequate nucleated cell dose to ensure a successful outcome, the pooling of cord blood stem cells from more than one donor may be the only option for an adult cord blood stem cell transplant recipient.[1]

The NMDP understands that the pooling of stem cells from multiple donors, which are then transplanted into multiple recipients may pose additional risk as is relates to infectious disease transmission, however in the example described above, the benefit associated with the pooling of product from multiple donors outweighs the risk associated with the increased chance of transmission of an infectious disease.

The NMDP proposes that the final rule allow the pooling of stem cell products from two or more donors, with the provision that the resulting pooled product may be transplanted into only one recipient.

II. Summary of the Proposed CGTP Regulations
L. Tracking
Page 1519, column 1, paragraph 5

Proposed Rule:

Each establishment shall establish and maintain a method of tracking from the donor to the recipient (or final disposition) and from the recipient to the donor.

NMDP Comment

Assuming each collection, processing and distribution establishment tracks movement of the product through its own process and subsequent transfer or release to the next establishment, it is the recommendation of the NMDP that one designated establishment shall collect this tracking information and maintain the entire history of collection, processing and release. This would enable safety or efficacy problems that appear after the release or transplantation to be fully traced, investigated and reported.

III. Additional Requirements With Respect to 361 Products
A. Reporting Requirements
Page 1520, column 2, paragraph 3

NMDP Comment:

The NMDP requests clarity on who is required to report adverse events to the FDA. It has not been clearly defined if it is the establishment that makes the product available for distribution, or a different establishment that may be involved in the chain of collection, manufacturing, release of the product for distribution, or the establishment that actually distributes the product.

III. Additional Requirements With Respect to 361 Products
B. Labeling and Claims
Page 1521, column 3, paragraph 1

Proposed Rule:

The following would be required to appear on the product label:

- The name and address of the establishment that determined that the product met release criteria and made the product available for distribution

- A description of the type of product
- Expiration date

NMDP Comment:

If the name and address of the establishment that determined that the product met release criteria and/or made the product available for distribution were to appear on the product label, donor/recipient confidentiality would be seriously breached.

Some stem cell transplant protocols include the infusion of the product directly from the product bag. In this case the product, which is brought to the recipient's room, is hung at the bed side where the patient themselves and frequently family members are fully capable of examining the stem cell product bag information. Even without access to the donor information on the product bag the NMDP has experienced occasions where the recipient family has aggressively researched the source of the unrelated stem cell donation and has proceeded to contact the donor without authorization from either the NMDP or the donor.

The NMDP therefore proposes that in the case of the unrelated stem cell product, the information pertaining to the name or address of the establishment involved in collection, distribution or manufacturing must not be provided on the product label. This information must be provided on labeling that accompanies the product and is intended for the transplanting physician and establishment but is not made available to the recipient.

IV. Inspection and Enforcement Provisions
B. Imports
Page 1523, column 3, paragraph 2

Proposed Rule:

As with other imports, when a tissue-based product is offered for entry, the importer of record must notify the director of the FDA district having jurisdiction over the port of entry. The tissue must remain in quarantine until it is released by the FDA.

NMDP Comment:

The NMDP requests clarification on the importation process of stem cells intended for immediate transplantation. It appears that the intention of the agency with the current 1270.42 is related to import of tissue for export and does not address tissue (or cells) that are intended for immediate distribution.

The NMDP urges the agency to consider the following issues as it relates to the importation of peripheral blood and cord blood stem cells into the U.S. for immediate transplantation:

Peripheral blood stems cells are required to be infused into a waiting transplant recipient within a very short time frame; usually within 48 hours of collection. Because of the urgency for transplantation, the stem cells are actually carried by a NMDP designated individual on an airplane, through the airport, and through customs to the designated hospital. Any delay in the product transport process could seriously jeopardize the viability of the stem cells and the success of the transplant into the waiting recipient. Cord blood products, although frozen, have the same viability and transplantation concerns. Therefore immediate clearance through airport customs for both products is required.

The FDA Specifically Requests Comment on the Following:

II. Summary of the Proposed CGTP Regulations
A. General Provisions
Page, 1512, column 1, paragraph 4

Proposed Rule:

"The establishment that determines that a product meets release criteria and makes the product available for distribution, whether or not that establishment is the actual distributor, is responsible for ensuring that the product has been manufactured in compliance with the requirements of subpart C and D of part 1271 and any other applicable requirements".

NMDP Comment:

When considering this requirement it is important to note that more than one establishment may actually make the product available for distribution. With this in mind, the NMDP would propose that the last establishment that releases the product for distribution is responsible for ensuring that all requirements in subparts C and D have been met.

Since the agency specifically requests examples of industry arrangement, below are current actual scenarios.

Peripheral Blood Stem Cell Collection, Processing and Transplantation:

The transplant recipient receives transplant preparative myeloablative therapy prior to the scheduled transplant. Peripheral blood stem cells are collected from the unrelated Filgrastim stimulated donor at an apheresis center according to the specified collection criteria. The product is then hand carried to the recipient's transplant center and is normally infused within 48 hours of collection.

Or

The transplant recipient receives transplant preparative myeloablative therapy prior to the scheduled transplant. Peripheral blood stem cells are collected from the unrelated Filgrastim stimulated donor according to the specified collection criteria. The product is then hand carried to a processing establishment, who then further processes the product to meet the transplanting physician's requirements (such as T-cell depletion). Often this processing facility is located within the transplanting hospital, or sometimes may actually be located in a different state. Finally, the product is hand carried to the recipient's transplant center and is normally infused within 48 hours of collection.

Cord Blood Stem Cell Collection, Processing and Transplantation:

The cord blood unit is collected from a volunteer donor and stored for transplantation into a yet undetermined recipient. Based on a subsequent request by a transplanting physician, the stored cord blood product is released for distribution by the cord blood bank based upon a request from the transplanting hospital. The product is shipped in a frozen state to the hospital. The receiving hospital places the cord blood unit in frozen storage. The transplant recipient receives transplant preparative myeloablative therapy prior to the scheduled transplant. The cord blood stem cell product is thawed and infused by the transplanting hospital.

Or

The cord blood unit is collected from a volunteer donor and stored for transplantation into a yet undetermined recipient. Based on a subsequent request by a transplanting physician, the stored cord blood product is released for distribution by the cord blood bank. The transplant recipient receives transplant preparative myeloablative therapy prior to the scheduled transplant. The product is shipped in a frozen state to a processing establishment, which is sometimes affiliated with the transplanting hospital and located within the hospital complex or is sometimes not affiliated and may be located in a different area of the country. The processing establishment then performs processing some additional according to the transplant physician's specific request. The cord blood unit is then hand carried to the transplanting hospital for immediate recipient infusion.

Another version of this same scenario involves transfer of the release stored frozen product from the transplant center to a processing establishment located in the same hospital complex (or close proximity) and then the return of the thawed product to the transplanting hospital for immediate infusion.

II. Summary of the Proposed CGTP Regulations
K. Records
Page, 1518, column 3, paragraph 3

Proposed Rule:

"The FDA requests comment on whether there are specific types of records for which a retention period shorter than 10 years would be appropriate and would not compromise the agency's ability to prevent the introduction, transmission and spread of communicable disease."

NMDP Comment:

The NMDP feels that a requirement for record retention of 10 years is appropriate.

References

1. Amos, T.A.S; Gordon, M.Y. Sources of Human Hematopoietic Stem Cells For Transplantation-A Review. Cell Transplantation, Vol. 4, No. 6, pp 547-569; 1995.

REFERENCE