American Red Cross

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May 4, 2001

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

RE: Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products: Inspection and Enforcement Proposed Rule [Docket No. 97N-484P, 66 FR 1508 (January 8, 2001)]

Dear Docket Officer:

The American Red Cross (ARC) is pleased to submit comments on the proposed rule (proposal), which outlines the Food and Drug Administration's (FDA) requirements for manufacturers to follow current good tissue practices (GTPs). The proposal includes methods used in, and the facilities and controls used for, the manufacture of human cellular and tissue-based products, recordkeeping, and the establishment of a quality program.

The American Red Cross, through its National Tissue Services, is a large supplier of the nation's tissue needs for transplantation. ARC provides cardiovascular, musculoskeletal, as well as skin, allograft tissue to physicians and dentists for patient treatment.

The Red Cross is also involved in research programs related to cellular therapy, including the potential use of umbilical cord blood to restore a patient's blood and immune system following chemotherapy or radiation treatment, research regarding peripheral blood stem cell (PBSC) transplants and their potential use as an alternative to bone marrow for the treatment of reconstituting the hematopoietic system after marrow ablative chemotherapy, and also has ongoing relationships with The National Marrow Donor Program ('NMDP') for example, to operate marrow donor recruitment centers.

ARC thus has an interest in consistent regulation of human cellular and tissue-based products.

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ARC first wishes to state that we strongly support the proposed rule. It is clear that FDA has recognized the importance of this regulation by carefully considering and including all relevant aspects of manufacturing and processing cellular and tissue-based products when formulating the proposal. The comments contained in this letter, therefore, are primarily technical clarifications. ARC encourages FDA to issue a final rule as quickly as possible.

We wish to highlight our two main concerns for FDA's consideration since we believe that they are relevant to the successful and complete implementation of the regulation.

ARC requests that FDA reconsider *§ 1271.290 Tracking,* which contains requirements for tracking all cellular and tissue-based products from the donor to the recipient and from the recipient or final disposition to the donor. While we appreciate the intent of this section, we believe it is infeasible.

Many factors contribute to this assessment. Examples include the fact that many patients change health care practitioners without notification, and the recently issued federal privacy regulations bar any unauthorized persons from access to a patient's individually identifiable information. Even if these factors did not exist, we know of no efficient way to "ensure" that the thousands of consignees and practitioners to whom we provide tissue are keeping the required information.

ARC also requests that FDA reconsider the provision contained in section *1271.220(c) Pooling* which states that human cells and tissue may not be pooled. We understand FDA's concerns about the potential safety risks of large supplies of pooled products. Therefore we agree that pooling of tissue based products should not be allowed. However, we are concerned that the proposal to prevent pooling of cellular based products during manufacture may restrict future research on new technologies for product processing or patient treatment. We suggest that FDA reconsider this section's complete ban on all pooling.

Our detailed comments further describe these concerns as well as potential alternative regulatory approaches. (See attachment)

In closing, Red Cross appreciates the opportunity to comment on the proposed rule. If you have any further questions on this letter, please contact Anita Ducca, Director, Regulatory Relations of Quality Assurance/Regulatory Affairs at (703) 312-5601.

Sincerely,

Jonathan Jester
Interim Vice President
Quality Assurance/ Regulatory Affairs

Attachment

Comments by
The American Red Cross
On the Proposed Rule
Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products: Inspection and Enforcement Proposed Rule
[Docket No. 97N-484P, 66 FR 1508 (January 8, 2001)]

The American Red Cross is pleased to provide these comments on the proposed regulation (proposal) for Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue Based Products (GTP or GTPs). These comments are identified by the section of the proposed regulation in which the text appears.

1271.3(kk) *Product deviation*

ARC recommends revising the term "Product deviation." The rule states that a Product deviation "means an ***event*** that represents a deviation from current good tissue practice..." [emphasis added]. We agree that a "deviation" from the GTPs should be an event, however, the term ***product*** deviation implies that there is some nonconformance with the product itself. In this instance, we believe that FDA intends to indicate that there is a deviation in the process, not the product. Typically, a deviation in a product would be referred to as a "product non-conformance" whereas a deviation in a process would be referred to as a "process deviation." Thus, the term "product deviation" mixes the two types of possible inaccuracies.

1271.3(oo) *Quality program*

Page 1512 and 1513 of the preamble explains the purpose of section 1271.3(oo):

> Any establishment that manufactures human cellular or tissue-based products needs to have in place a method of ensuring that its manufacturing processes are performed properly and in compliance with applicable regulations....In these regulations, FDA is proposing to use 'quality program' to refer to the set of activities, including management review, training, audits... that represent a commitment... to the quality of its products.

ARC agrees and endorses this concept completely. However, when incorporating the definition of a "quality program" into the proposed regulatory text, the rule defines "quality program" as

"An organization's comprehensive ***system for manufacturing***..."[emphasis added]. Thus, there is a slight difference in the proposed intent of the "quality program" and the actual text of the proposed rule. Where the preamble describes the quality program as "a ***method***..." [emphasis added] the regulatory text describes it as the manufacture itself.

ARC recommends rewording the regulatory text to more closely reflect FDA's intentions as stated in the preamble. Specifically:

> An organization's comprehensive system for *ensuring that its* manufacturing *processes are performed properly and in compliance with applicable regulations*...

ARC notes that the quality program definition includes "tracking." We have included detailed comments on the proposal's tracking requirements under our comments on §1271.290 below.

1271.3(pp) *Recovery*

The proposal states that "***Recovery*** means the ***process*** of obtaining from a donor cells or tissues that are intended for use in human...". [emphasis added] ARC recommends restructuring this sentence to clarify that recovery means actually obtaining the cells or tissue, rather than referring to recovery as a "process." We believe this technical correction is appropriate since a "process" may not necessarily result in obtaining the tissue or the term may be confused with associated paperwork defining procedures.

Hence, we suggest the following alternative language: "Recovery means obtaining cells or tissues from a human donor...".

1271.3(qq) *Storage*

The definition of "storage" refers to "products" awaiting future processing and/or distribution. However, the term "product" usually refers only to the final product that is ready for shipment for transplantation, and would not necessarily refer to the materials awaiting further processing. ARC recommends clarifying that all human derived materials, including those in storage prior to shipment for either processing or for distribution, are included in the definition.

We recommend the following insert into section qq: "holding human cellular or tissue-based *materials or* products for future processing and/or distribution."

1271.150(b)(2) Current good tissue practice: general

Section 1271.150(b)(2) states:

> 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...[is in compliance]

It appears that FDA believes that the firm performing the processing should be held accountable for meeting the GTPs for the aspects of the processing it is performing. In a situation where some or all of the product is prepared by a processing firm under contract, our interpretation of the regulation is that this processing firm would be held accountable for compliance with the segments of the process they perform.

The proposal also states:

> 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...

Contracts between tissue establishments/distributors and tissue processors may include provisions to have the tissue materials obtained by the establishment and processed by another firm. The tissue establishment could then choose to release the product as follows: (1) release to a consignee under the tissue establishment's label, or (2) release to another distributor, or (3) release back to the processing firm which may, in turn, also serve as a distributor. Under the proposal, ARC understands that it is the tissue establishment's responsibility to ensure that the product has been manufactured in compliance for any of the three situations described above, prior to a release decision.

ARC believes it is appropriate for both firms to be held accountable for the product in its possession and for the firm making the release decision to be held accountable for ensuring that the regulation's provisions have been met. This will help avoid having a processing firm caught between two expectations: i.e., that they must comply with FDA's regulations, and the distributing firm's objectives, for example, to meet certain production time schedules incompatible with compliance.

If our interpretation is correct, and is consistent with FDA's expectations, we endorse this section of the regulation.

1271.200(e) Equipment /Records

The proposal indicates that:

> records of recent maintenance, cleaning, sanitizing, calibration, and other activities shall be available ***at*** each piece of equipment. [emphasis added]

ARC agrees that establishments should maintain such records and that they should be in a location easily accessible to those who need them. However, we assume that by stating they must be *at* each piece of equipment, FDA means directly adjacent to the equipment, perhaps in files or other storage medium.

This requirement is unlikely to be feasible at all manufacturing sites and for all pieces of equipment. It is also not advisable, since fitting in storage medium or otherwise placing the records at each piece of equipment could disrupt the physical plant and/or the ability to maintain a controlled environment. There may also be a worker safety concern as workers attempt to "get around" the extra containers to perform tasks. Moreover, it is unclear how this requirement will be implemented if the records are stored electronically.

ARC recommends that FDA allow facilities the flexibility to maintain the records in a location that is easily accessible to the equipment, but not directly ***at*** the equipment site. For example, the establishment could place a small label containing the date of last equipment maintenance and/or inspection on or near the equipment, with an indication of where the detailed records are located, without keeping all the records directly with the equipment.

1271.220(c) Process Controls/Pooling

This section contains a specific prohibition against pooling the human cells or tissue as stated: "Human cells or tissue from two or more donors ***shall not be pooled***...during manufacturing." [emphasis added]

Currently, ARC does not "pool" the types of products we prepare that will be subject to this proposal once final. However, we are concerned that the elimination of pooling of human cellular-based products during the manufacturing process may serve to restrict future research on potential new treatments or manufacturing technologies. While FDA may be willing to consider variances from this provision, the fact that it is directly prohibited by the GTP regulation may seriously deter potential research sponsors, investigators, or those funding the research.

A research program frequently involves taking a significant risk involving financial investments as well as the dedication of facilities or staff to efforts that may not result in a final product or treatment that is efficacious. Knowing that there is an additional hurdle that must be overcome before a product may be produced and marketed is likely to further discourage initiation of research efforts.

Although described in the preamble as a reason for concern about pooling these products, ARC wishes to point out that not all such manufacture involves pooling large volumes of materials where a single donation may contaminate products intended for many recipients. Additionally some human-derived blood products currently on the market are pooled without any restrictions. Solvent detergent treated fresh frozen plasma, cryoprecipitated antihemophilic factor, and random donor platelets are examples of blood components that can also be pooled. Also, it is standard practice for a treating physician to order at least two, and frequently several, units of red blood cells for a single patient. A typical patient receiving a therapeutic apheresis procedure for treatment of sickle cell anemia, myasthenia gravis, or cryoglbulinemia, might receive seven or more units of red blood cells or fresh frozen plasma during the procedure. While the units are not "pooled" during the manufacturing process the effect is the same since the patient is receiving blood products from several different donors.

Moreover, it may one day be determined that pooling at the manufacturing site is beneficial. For example, it is suggested that pooling of multiple units of plasma may reduce viral load through dilution or that neutralizing antibodies may inactivate viruses and thereby reduce the recipient's risk of disease transmission. Future exploration of possible treatments and technologies involving pooling of human cellular and tissue based-products may lead to similar, or better, methods of helping to aid patient safety or treatment. However, we have not pooled our tissue-based products and we continue to support FDA's policy of eliminating the pooling of human tissue donations.

ARC recognizes FDA's concern about the potential safety implications of pooling many donations. Thus, for human cellular-based products, we suggest an alternative to the proposal's complete elimination of pooling for cellular-based products. Specifically, we suggest that FDA modify the regulatory text to allow pooling during the manufacturing process. However, the text could indicate that the establishment must also demonstrate and document, through a validated Standard Operating Procedure, that they have examined the potential safety risks of pooling the product, and have taken measures to reduce that risk to the extent possible.

We believe this change will greatly facilitate future exploration of new treatments and technologies.

1271.225(a) Process changes

This section states that "***any*** such change shall be verified or validated..." [emphasis added]. Red Cross believes that most changes will need to be verified or validated, but does not believe that *every* change will need verification or validation. For example, simple changes such as requirements for additional training or changes in location or storage of records are unlikely to require verification or validation.

ARC does agree, however, that an assessment of the need for verification or validation should be made prior to a change. Thus, we recommend the addition of the phrase "if appropriate as determined by a risk assessment" after the word "validated" in this section.

1271.290 Tracking

ARC agrees that all human cellular and tissue-based establishments should "maintain records of, the disposition of each of its human cellular or tissue-based products, that enables tracking..." (1271.290(b)). This is an appropriate expectation and we plan to fully comply. However, we are concerned with the additional requirements in section 1271.290(f), which states that tissue establishments

> ...shall inform the consignee in writing of the requirements in this section... Upon initial distribution of product to the consignee, the establishment shall document that the consignee has agreed to participate in its tracking method and ***to take all necessary steps to ensure compliance with the requirements of this section.*** [Emphasis added]

ARC finds this requirement particularly problematic. FDA is essentially requiring tissue establishments to "police" their own customers, many of whom are individual practicing physicians and dentists. However, there is little definition as to what constitutes "all necessary steps" making a consistent application of this requirement among all manufacturers of human cellular and tissue-based products difficult, at best. Even if the proposal's expectations were better defined, there are other concerns that seriously mitigate against our ability to "ensure compliance" effectively, including:

- Seeking least burdensome compliance practices - Providers of human tissue and cellular based products may be tempted to develop agreements that are least burdensome rather than most effective in ensuring compliance. They may feel that such arrangements will attract a larger share of the market. Consignees, in an effort to save costs, may be similarly tempted to seek the least intrusive contract arrangements. Further, we know of no means at FDA's disposal to effectively ensure that these contracts and other arrangements are applied consistently.

- Emergencies – If a physician or dentist requires the tissue for an emergency patient need, and does not have an existing contract, ARC would not be able to provide the product until the consignee develops a tracking system, and ARC takes "all necessary steps" to ensure they do so. We cannot believe FDA intends for us to withhold the product from the patient while we carry out such steps. Nor is it reasonable to delay shipment while we document the emergency requiring us to bypass "all necessary steps", in order to avoid a potential FDA inspection finding later on.

- Privacy laws - The Department of Health and Human Services has recently promulgated privacy regulations guaranteeing that patient records and other individually identifying information will not be accessed by anyone other than the patient and their practitioner without authorization from the patient.[1] Individual states also have laws restricting sharing patient information. Although donations of human cellular and tissue-based products are excluded from the privacy rules, recipient patient records containing individually identifiable

[1] 65 FR 82461, Dec. 28, 2000.

information are not. Since tracing by a consignee could not be performed without identifying the link between the recipient patient and the product, it would be very difficult if not impossible for a tissue establishment to ascertain whether the consignee maintains an adequate system if they cannot review recipient patient records. Thus, tissue establishments will be caught between the requirements of two or more regulations in direct conflict with each other.

- Patients change practitioners - Even if the above concerns were nonexistent, patients frequently move localities, change health care providers of their own accord, or are required to do so when employers change insurance plans. They often do so without providing their new location to their former practitioners. Tracking such patients will not be possible.

- Numbers of consignees - There are thousands of hospitals and individual health care practitioners using human cellular and tissue-based products. ARC has, for example, contracts with some 3000 dental offices to provide our demineralized bone product, Grafton. To "take all necessary steps to ensure compliance" could become an unwieldy and unrealistic undertaking given the number of consignees, patients and transactions. One possible method of overcoming this extensive requirement could be to contract with an additional distributor or a few distributors whose sole purpose is to ensure compliance. The net result could be higher product prices or distribution delays due to the need to go through a "middle man."

Given the above, ARC strongly recommends deleting this requirement. Should FDA still believe that tracking of human cellular and tissue-based products is necessary, we suggest that the Agency follow the approach jointly developed by FDA's Center for Biologics and Evaluation and Research (CBER) and the Health Care Financing Administration (HCFA) when proposing the regulations for Hepatitis C (HCV) Lookback.[2]

FDA and HCFA recognized that notification could not reach the actual blood product recipient without adequate recordkeeping and added practices by Hospitals and other consignees. Therefore, HCFA proposed a regulation to require HCV notification and related recordkeeping as a "condition of participation" for consignees receiving payment through Medicare and Medicaid. ARC believes a similar approach to require consignees to track of human cellular and tissue-based products would be more feasible than the approach included in the GTP proposal.

[2] 65 FR 69377, Nov. 16, 2000 and 65 FR 69416, Nov. 16, 2000.

1271.265(a) Receipt and distribution

This section discuss procedures for "receipt, acceptance or rejection, distribution... of ...products." Similar to our comments in section 1271.3(qq) we recommend including the phrase "materials or" before the term "products." This change will clarify that all donated materials are subject to this section, regardless of their processing status.

1271.265(a)(5) Receipt and distribution

ARC notes that we agree with the provision to include the identity of the consignee in this section. This information may seem an obvious requirement, but adding it to the regulation will help avoid potential misunderstandings about our responsibilities to retain such records.

1271.270(c) Other recordkeeping requirements

One of this section's requirements is that the donors' records "shall be in English, or if in another language, shall be translated to English and accompanied by a statement of authenticity by the translator...". ARC has no objection to translating the records into English, but there is no discussion of recordkeeping for the original non-English record. This omission may imply that the original record may be destroyed.

The Red Cross is currently having our tissue donor family questionnaire translated for use in areas of the country with a large Spanish speaking population. The original records of these donors will be in Spanish. We believe it will be important to keep the original records, regardless of the translation, because they will include the original signatures and there may be a need to reexamine the original record or show it to family members again at a later time.

We suggest that FDA revise this section to indicate that the original may be in any language and should be retained, but that a copy, translated into English, should also be kept on file. Thus, it will be clear that both records remain available.

The Red Cross wishes to reiterate its commitment to full compliance with the Good Tissue Practices regulations. We are also pleased to work with FDA further in describing either this letter or in providing other information that may contribute to finalizing the regulation. If you have any questions, please contact Anita Ducca, Director, Regulatory Relations at 703-312-5601.

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