CLEARANT

Thomas J. Lynch
Senior Vice President
Regulatory Affairs and Quality Assurance

Corporate
11111 Santa Monica Blvd.
Suite 650
Los Angeles, CA 90025
Tel 310.479.4570
Fax 310.479.2959
www.clearant.com

Research Facility
14915 Broschart Road
Suite 103
Rockville, MD 20850
Tel 301.738.9199
Fax 301.738.9012
www.clearant.com

01 MAY -8 P3:58

May 8, 2001

Reference: Docket No. 97N-484P
Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products

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

Dear Sir/Madam:

We appreciate the opportunity to comment on the Proposed Rule, published January 8, 2001, Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement (66 Federal Register 1507-1559). The Proposed Rule is part of a comprehensive new program to regulate human cellular and tissue-based products, originally proposed in February 1997. Current Good Tissue Practice is designed to work together with two other rulemaking initiatives: establishment registration and product listing (registration proposed rule, 63 FR 26744, May 14, 1998) and a requirement that most cell and tissue donors be tested and screened for relevant communicable diseases (donor-suitability proposed rule at 64 FR 52696, September 30, 1999). These requirements collectively are intended to prevent the introduction, transmission, and spread of communicable disease through the use of human cellular and tissue-based products. The proposed program for regulating human cellular and tissue-based products is timely and appropriate in its nature and scope. It is an obvious product of much thought and consultation with the industry to be regulated and with the medical and scientific communities. We applaud the Agency's efforts, and the following comments are offered in that spirit.

General Comments

1. As stated in the proposed rule, "donor screening and testing, although crucial, are not sufficient to prevent the transmission of disease by human cellular and tissue-based products. Rather, each step in the manufacturing process needs to be controlled."[1] "CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of human cellular and tissue-based products. CGTP requirements are intended to prevent the introduction, transmission, and spread of communicable disease through the use of human cellular and tissue-based products by helping to ensure that: (1) The products do not contain relevant communicable disease agents; (2) they are not

[1] 66 FR 1507 at 1509-1510.

contaminated during the manufacturing process; and (3) the function and integrity of the products are not impaired through improper manufacturing, all of which could lead to circumstances that increase the risk of communicable disease transmission."[2] The standards articulated in the proposed rule, while satisfying the second and third objectives, do not fully address the first objective, that the "products do not contain relevant communicable disease agents", since pathogen inactivation or removal measures during manufacturing are not included among the measures that could contribute to the safety of these products. Rather, the rule focuses on "[e]rrors in labeling, mix-ups of testing records, failure to adequately clean work areas, and faulty packaging are all examples of improper practices that could lead to a product capable of transmitting disease to its recipient." While eliminating these practices would reduce the risks of using unsuitable raw materials and of product contamination and cross-contamination, these measures do nothing to address the risk of "window" donations (raw materials contaminated with infectious agents at levels below the limit of detection of any testing performed) or the risk of contamination with an infectious agent for which testing is not performed. These latter risks could be mitigated in some cases by the application of appropriate pathogen inactivation or removal procedures.

Comment 1. The Final Rule should incorporate language requiring the use of pathogen inactivation or removal procedures during the manufacture of human cellular and tissue-based products, as and when these procedures become feasible and can be employed without compromising the function and integrity of the products themselves.

2. Proposed Section 1271.220(c) would prohibit the pooling of human cells or tissue from two or more donors during manufacturing.[3] Pooling materials from multiple donors enhances the risk of contamination with infectious agents that is associated with any individual donor. The proposed rule specifically points to the past practice of pooling dura mater, which the FDA's Transmissible Spongiform Encephalopathy Advisory Committee advised against in 1997 in order to reduce the risk of transmitting Creutzfeldt-Jakob Disease (CJD).[4] As stated in the Proposed Rule, this prohibition would be absolute (albeit subject to the procedure for seeking an exemption or alternative under Section 1271.155). This absolute prohibition may have the unintended effect of stifling innovation of products that one cannot clearly anticipate today. Furthermore, the need for this particular risk-reduction measure may be lessened as effective, robust pathogen clearance methods are developed and adopted.

Comment 2. Section 1271.220(c) should be reworded to provide some flexibility in order to accommodate new technological developments. The pooling of human cells or tissue from multiple donors should be avoided unless the manufacturer can demonstrate a favorable risk-benefit ratio to the patient, or that the pooling practice does not enhance the risk of pathogen transmission associated with cells or tissues derived from single individuals.

---

2 66 FR 1507 at 1510-1511.

3 66 FR 1507 at 1516 and 1555.

4 66 FR 1507 at 1516.

Background and Rationale—Viral Clearance

"Because of their nature as derivatives of the human body, all human cellular and tissue-based products pose a potential risk of transmitting communicable diseases. Thus, the donor-suitability proposed rule would require that most cell and tissue donors be tested and screened for evidence of relevant communicable-disease infection. Similarly, the CGTP regulations now being proposed are designed to prevent the introduction, transmission, and spread of communicable diseases."[5]

"Certain diseases, such as those caused by the human immunodeficiency virus (HIV) and the hepatitis B and C viruses, may be transmitted through the implantation, transplantation, infusion, or transfer of human cellular or tissue-based products derived from infected donors. The agency has, in an earlier rulemaking, proposed that most cell and tissue donors be screened and tested for these and other relevant communicable diseases.....***However, donor screening and testing, although crucial, are not sufficient to prevent the transmission of disease by human cellular and tissue-based products.***"[6]

The effectiveness of donor screening and testing is limited in two fundamentally different respects. First, screening and testing can do nothing to prevent the subsequent contamination of a product with adventitious agents. The Proposed Rule addresses this type of risk by establishing manufacturing standards that should reduce the possibility of product contamination and mix-up. Otherwise, the Proposed Rule relies on the effectiveness of donor screening and testing to mitigate the risk of endogenous infectious agents.

The second type of limitation relates to the scope and sensitivity of donor screening and testing. Donor screening, while potentially a broadly effective precautionary measure, is relatively limited in its sensitivity and precision. Testing can be practically performed for only a limited number of infectious agents (testing for ten specific infectious agents are required or recommended for various products by the donor suitability rule[7]). Obviously, infectious agents for which testing is not performed cannot be eliminated by the process. Every test that is performed has a threshold associated with it and a risk that contaminations below this limit of detection will escape as "window" donations. Finally, however sophisticated and automated test methods become, and despite stringent quality standards governing their performance, laboratory tests can never be entirely free from human error.

The limitations to the effectiveness of donor screening and testing produces a residual risk that the use of cells or tissues from a donor harboring an infection will transmit that infection to a recipient. This situation is entirely analogous to the residual risk associated with human blood products for which precautionary measures have developed over the years and which experience has clearly informed the Agency's thinking in this area.

---

5 66 FR 1507 at 1509.

6 Ibid (emphasis added).

7 64 FR 52696 at 52723 (proposed §1271.85). Currently, 21 CFR 1270.21 requires testing only for HIV and hepatitis B and C viruses.

Human blood products include both transfusable components usually derived from single donations, and the plasma derivatives manufactured from many thousands of units of human plasma. A multi-layered system of safety measures has developed over the years to achieve the current levels of safety afforded by these products. Donor screening and testing are performed for all these products, and manufacturing standards have been established to control the subsequent handling of these products. For the plasma derivatives that are subjected to more extensive manufacturing procedures, there is an opportunity to incorporate viral clearance procedures into the manufacturing processes. Viral clearance methods have been developed that are highly effective against the most clinically significant viruses such as HIV, hepatitis B and C (the so-called enveloped viruses).[8] Since the implementation of these methods, there have been no documented transmissions of these viruses in the U.S. through the use of plasma derivatives subjected to effective viral clearance procedures.[9] This safety record is remarkable in light of the large number of plasma donations used to manufacture these products and the residual risk that remains after all donor screening and testing is completed. Indeed, viral clearance procedures are today considered to make a significant, if not the single greatest, contribution to the safety of these products. Consider the following statement by the European Agency for the Evaluation of Medicinal Products (EMEA) in their guidance document for plasma derivatives:

> Products derived from human plasma have been shown to transmit viruses to recipients even where the starting material has been controlled for viral contamination in accordance with state of the art procedures... While selection of donors and testing of donations are essential safety measures, incidents of viral transmission show that they are insufficient alone to insure safety of the product. The manufacturing process itself plays a central role and is a great significance for products derived from plasma.
>
> ***It should be emphasized that the manufacturing process cannot be considered satisfactory unless it is capable not only of generating a product of high-quality but also of effectively inactivating and/or removing infectious agents.***[10]

Very similar sentiments were expressed by the then-acting Commissioner of the FDA in 1998:

> Since the initial safety steps of eliminating blood possibly contaminated with infectious agents is imperfect, ***the most critical safety step remains viral inactivation***. The risk to a patient from any particular agents may vary with the particular plasma derivative. Thus, FDA believes that ***all human plasma derivatives should undergo viral inactivation or removal procedures*** to ensure safety. FDA has been moving progressively toward this goal even for products that have never been documented as transmitting viral agents.

---

8 The effectiveness of current viral clearance procedures again other types of viruses, e.g., the non-enveloped viruses, is limited and occasional transmissions by the use of plasma derivatives (and other blood products) have occurred.

9 Tabor, E. 1999. The epidemiology of virus transmission by plasma derivatives: clinical studies verifying the lack of transmission of hepatitis B and C viruses abd HIV type 1. Transfusion 39: 1160-1168.

10 EMEA, Note for Guidance on Plasma-Derived Medicinal Products, CPMP/BWP/269/95, rev. 2, section 3.3 (emphasis added).

> While all the above safety measures enhance the reduction of risk, without adequate viral inactivation, the other safety measures will not provide the measure of assurance that is necessary for public safety....[T]he final safety step of ***viral inactivation/removal is the most important mechanism which assures the safety of plasma derivatives***.[11]

The concerns of the public health authorities are not limited to infectious agents that are well-known or that have caused significant problems in the past. Instead the standards focus on addressing the risks posed by unknown and/or future agents, especially the non-enveloped viruses, which risks cannot be addressed by donor screening and testing. Moreover, the limitations of the viral clearance methods currently in use are implicitly acknowledged by the European recommendation that each manufacturing process incorporate at least two distinct viral clearance steps:

> [S]ince many instances of contamination in the past have occurred with agents whose presence was not known or even suspected at the time of manufacture, an evaluation of the process [should] provide a measure of confidence that a wide range of viruses including ***unknown, harmful viruses***, may be eliminated.[12]
>
> For all plasma-derived medicinal products, it is an objective to incorporate effective[13] steps for ***inactivation/removal of a wide range of viruses*** of diverse physico-chemical characteristics. In order to achieve this, it will be desirable in many cases to incorporate ***two distinct effective steps*** which complement each other in their mode of action such that any virus surviving the first step would be effectively inactivated/removed by the second. At least one of the steps should be effective against ***non-enveloped viruses***.[14]

The FDA has expressed a similar appreciation of this risk:

> ***The greatest threat to the blood supply is posed by unknown or emerging agents*** that may not be inactivated or removed during processing. Realizing that there constantly will be emerging infectious agents which posed threats to the safety of

---

11 Michael A. Friedman, M.D., Acting Commissioner, Food and Drug Administration, Statement before the Subcommittee on Human Resources, Committee on Government Reform and Oversight, U.S. House of Representatives, September 9, 1998 (emphasis added).

12 EMEA, Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses, CPMP/BWP/268/95, section 1.7 (emphasis added).

13 The definition of "effectiveness" depends on the outcome of the validation studies and the following criteria: (i) the appropriateness of the test viruses; (ii) design of the validation studies; (iii) the extent of viral reduction achieved; (iv) the kinetics of inactivation; (v) the nature of the inactivation/removal step and whether it is selective for only certain types of virus; (vi) the susceptibility of the inactivation/removal step to small variations in the process; and (vii) the limits of assay sensitivity. EMEA, Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses, CPMP/BWP/268/95, section 6.1.

14 EMEA, Note for Guidance on Plasma-Derived Medicinal Products, CPMP/BWP/269/95, rev. 2, section 5 (emphasis added).

> the blood supply, FDA is committed to developing a strategy for each identified emerging infectious agent.[15]

Significant efforts and resources are today been devoted to improving pathogen inactivation technologies in two respects: by increasing the variety of infectious agents which can be effectively inactivated, and by increasing the variety of biological products to which such technologies can be applied. For example, today only plasma derivatives can be subjected to viral clearance procedures, but two novel technologies for pathogen inactivation in transfusable blood components are in clinical trials. Given the clinical need for safer blood products (as well as other biological products) it is only a matter of time before these efforts bear fruit.

The application of effective viral clearance methods to at least some human tissues is inevitable. Certainly the technical challenges are greatest for those products comprising or including living cells. It is difficult to envision an inactivation procedure that would not also inactivate a cellular product, nor can one readily imagine a method for removing viruses from a cellular product that would be effective against cellular viruses or proviral sequences. Nevertheless, there is a large number of devitalized tissues for which such difficulties do not exist. A method for inactivating pathogens in cortical bone by chemical treatment has recently been developed and is being applied.[16] Irradiation of cadaveric tissues by ionizing radiation is a fairly common technique to control bioburden, and is being refined to improve its effectiveness against viruses while retaining the structural and functional properties of the tissues.[17]

The potential for viral inactivation in the realm of human tissue-based products was discussed in the PHS recommendations made in 1994.[18]

> Thorough donor screening is considered the most effective method for preventing HIV transmission through transplantation; however, the use of chemical or physical inactivating or sterilizing agents to reduce further the already low risk of transmission has been considered. If such agents are to be useful, they must either inactivate or eliminate the virus while maintaining the functional integrity of the tissue or organ. No mechanism for inactivating virus in whole organs currently exists. However, several agents have been suggested as possible disinfectants for tissues such as bone fragments.
>
> ***Definitive recommendations cannot yet be made regarding inactivation of HIV in organs and tissues because of lack of information about potentially effective inactivation measures. Research should continue in this area.*** Efforts to evaluate the

---

15 See note 11.

16 C. Randal Mills, Regeneration Technologies, "BioCleanse Tissue Processing System: Biological Safety", presentation at the Biological Safety and Production Conference, Vienna, VA, April 2-5, 2001.

17 Hamer, A.J., Strachen, J.R., Black, M.M., Ibbotson, C.J., Stockley, I. And Elson, R.A. 1996. Biomechanical properties of cortical allograft bone using a new method of bone strength measurement. J. Bone Joint Surg. 78B: 363-368. Bright, R.W., Smarsh, J.D. and Gambill, V.V. Sterilization of Human Bone by Irradiation. In: Friedlaender, G.E., Mankin, H.J. and Sell, K.W. (eds.) Osteochondral Allografts. Little, Brown, Boston, pp223-232.

18 U.S. Public Health Service. 1994. Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs. MMWR 43(RR-8);1-17.

> effect of certain processing techniques on tissue sterility and quality should be expanded to include virologic studies for HIV.[19]

In earlier rulemaking, FDA was confronted directly with the question of viral inactivation of human cellular and tissue-based products:

> Two comments were made on alternative methods of preventing transmission of HIV-1, HIV-2, hepatitis B, and hepatitis C viruses. One comment asked that the rule provide for a waiver process based on alternative methods of viral inactivation....Presently, FDA is unaware of any alternative method of viral inactivation that FDA believes warrants omission of HIV and hepatitis testing. Therefore, FDA does not believe that such a change is warranted at this time. FDA is interested in public comment on this issue and will consider whether to include in future rulemaking a process for the agency to grant waivers from any regulation under part1270 (21 CFR part 1270).[20]

We do not advocate relaxing or abandoning any other safety measure established by the donor suitability or CGTP proposed rules. Rather, we believe that a multi-faceted approach is appropriate here, as it is for human blood products and plasma derivatives. Viral clearance procedures would then afford an additional layer of safety by addressing risks against which the other precautionary measures are ineffective. As the application of viral inactivation becomes feasible for human cellular and tissue-based products, it should certainly be required by the FDA.

It is clear from the Proposed Rule that the Agency has considered these issues, and anticipates the development of viral clearance technologies for human cellular and tissue-based products. First the definition of processing (manufacturing) includes sterilization processes and steps to inactivate and remove adventitious agents.[21] Second, any claims that a product is sterile or has been virally inactivated must be substantiated by validation studies.[22] Both provisions are entirely appropriate, but stop short of a definitive recommendation or requirement for sterilization or viral clearance.

The one provision of the Proposed Rule where pathogen inactivation is directly required relates to the risk of CJD associated with dura mater. Proposed Section 1271.230(c) would require that dura mater be processed using a validated procedure to reduce CJD infectivity, while preserving

---

19 Ibid.

20 U.S. Food and Drug Administration. Human Tissue Intended for Transplantation. Final Rule. 62 Federal Register 40429-40447, at 40433. July 29, 1997. Proposed §1271.155 of the CGTP Proposed Rule also provides for exemptions to the requirements of the rule if alternative procedures can provide at least as great an assurance of safety.

21 66 FR 1507 at 1516 (Processing is defined in proposed §1271.3(mm) as "any activity other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution performed on a human cellular or tissue-based product, including, but not limited to, preparation, ***sterilization, steps to inactivate and remove adventitious agents***, preservation for storage, and removal from storage." (emphasis added)).

22 66 FR 1507 at 1555 (Proposed §1271.230(b) reads: "Claims. Any process-related claim in labeling or promotional materials for a human cellular or tissue-based product, e.g., a claim for sterility or viral inactivation, shall be based on a validated process.").

the clinical utility of the product.[23] The example given of such a procedure is a sodium hydroxide (NaOH) treatment validated to reduce CJD infectivity (in an animal model) while preserving the tissue's clinical utility. Future methods that more effectively reduce CJD infectivity may be developed.

Once it is possible to manufacture a sterile or virally inactivated tissue product, to do otherwise would pose an unnecessary and unacceptable risk to the public health. FDA would be entirely justified in seeking to prevent the use of products that did not avail themselves of available safety measures and thereby posed unreasonable risks. The present wording of the Proposed Rule does not create a legally enforceable obligation in this respect. The dilemma is the impossibility of requiring a standard that cannot be met today regardless of how foreseeable implementation of that standard may be in the future. We believe that the addition of contingent wording to the Final Rule could establish a flexible standard that would not threaten the availability of products today, but would establish the explicit requirement that improved manufacturing methods be implemented as they become available.

The safety standards for human plasma derivatives and for natural products purified from animal sources are fairly well established. But the fact that measures such as viral clearance procedures during manufacturing have not been formally required by the Agency (except for monoclonal antibodies and products of biotechnology) creates some degree of uncertainty and perhaps sends an erroneous message that these standards are somehow of secondary importance. The present rulemaking is an opportunity for FDA to take a clear stand on product safety with respect to communicable diseases and the proactive measures a manufacturer ought to take in the preparation of these products. Establishing a contingent requirement would be entirely within FDA's jurisdiction under the PHS Act, and would be consistent with the well established but largely unwritten requirement for viral clearance in the manufacture of other products.

Background and Rationale—Pooling

The pooling of human-derived biological material may enhance the risk of transmitting infectious disease to recipients of a product made from that material. This is clearly illustrated by the past experience with dura mater processed in batches,[24] and by the experience with pooled human plasma and products derived from it.[25] However, more recent experience with human plasma derivatives suggests that the risk associated with these products, despite the fact that they are made from plasma derived from thousands of individual donors, is even less than that associated with transfusable components derived from single donors from which occasional (albeit extremely rare) transmissions of HIV and hepatitis B and C occur.[26] Thus, it is clear that

---

23 66 FR 1507 at 1517 and 1555 (Proposed §1271.230(c) reads: "Dura mater. Dura mater shall be processed using a validated procedure that reduces transmissible spongiform encephalopathy, while preserving the clinical utility of the product.").

24 Ibid at 1517.

25 For review see note 9. See also Lynch, T.J. and Fratantoni, J.C. 1999. Viral clearance methods applied to blood products. In: K.C. Anderson and P.M. Ness (eds.), Scientific Basis of Transfusion Medicine, 2nd ed., pp. 599-617, W.B. Saunders, Philadelphia.

26 See notes 8 and 9, and accompanying text.

safe products can be made from pooled human source material, provided that the processing of that material incorporates effective and robust viral clearance procedures.

Nevertheless, pooling human source material does entail at least a theoretical increase in the risk of transmitting disease, and is therefore unjustified unless some benefit to the patient is achieved by the pooling process (which cannot be achieved otherwise), and unless the increased risk is somehow mitigated (e.g., by viral clearance). Pooling, for example, would not be justified by considerations of convenience to the manufacturer or reduced cost of the product. But pooling may well be justified if the manufacture of a clinically beneficial product requires it, or if a broadly effective pathogen inactivation technique could not otherwise be incorporated into the manufacturing process.

The full array of human cellular and tissue-based products that may require pooling of source materials cannot be foreseen at this time. However some simple examples exist today. The use of demineralized bone matrix (DBM) is limited today because of a relatively high clinical failure rate among lots produced from individual donors. Current assays are of limited predictive value for selecting clinically efficacious lots, so pooling of raw materials has been suggested as a way of achieving a uniformly effective DBM product.[27] The processing of DBM entails conditions harsh enough to achieve significant levels of viral inactivation,[28] so the pooling process in this case could enhance product quality and effectiveness without increasing (and perhaps significantly decreasing) the risk of viral transmission.

Some viral inactivation procedures themselves may necessitate pooling in order to process sufficient materials to meet clinical demand. The processing of cortical bone by peroxide/solvent/detergent treatment is an example of such a procedure.[29]

Finally, it is unclear how an absolute "no-pooling" rule would affect combination products comprising a cellular or tissue-based product with another biologic (e.g. a growth factor, or a matrix material such as collagen or fibrin).[30]

The absolute prohibition on pooling in proposed Section 1271.220(c) is an unnecessarily strict and inflexible standard. While appropriate in most cases today, the absolute prohibition does not accommodate future technical advances and may discourage innovation that would ultimately benefit the public. The possibility of seeking an exemption or alternative under proposed Section 1271.155 does not entire solve these potential problems because of the greater uncertainty of obtaining such an exemption compared to compliance with a clearly articulated but flexible rule.

---

27 Maddox, E., Zhan, M., Mundy, G.R., Drohan, W.N. and Burgess, W.H. 2000. Optimizing human demineralized bone matrix for clinical application. Tissue Engineering 6: 441-448.

28 Zhang, M., Powers, R.M. Jr., Wolfenbarger, J.R. 1997. Effect(s) of the demineralization process on the osteoinductivity of demineralized bone matrix. J. Periodontol. 68: 1085. Scarborough, N.L., White, E.M., Hughes, J.V., Manrique, A.J., and Poser, J.W. 1995. Allograft safety: viral inactivation with bone demineralization. Cont. Orthop. 31: 257.

29 Ob. cit., note 16.

30 Lasa, C., Hollinger, J., Drohan, W.N. and MacPhee, M. 1995. Delivery of demineralized bone powder by fibrin sealant. Plast. Reconstr. Surg. 96:1409.

Specific Recommendations

1. Proposed Section 1271.180 should be modified to incorporate language requiring pathogen clearance (removal or inactivation) during manufacturing. The suggested language, underlined, follows:

> § 1271.180 Procedures.
>
> Each establishment shall establish and maintain procedures for all significant steps that it performs in the manufacture of human cellular and tissue-based products. These procedures shall be designed to prevent circumstances that increase the risk of the introduction, transmission, and spread of communicable disease through the use of human cellular and tissue-based products by ensuring that the products do not contain relevant communicable disease agents; that the products do not become contaminated during manufacturing; and that the function and integrity of the products are not impaired through improper manufacturing. Where ***[possible, feasible, practical]***, procedures to remove or inactivate viruses and other pathogens, including sterilization procedures, shall be incorporated into the manufacturing processes of human cellular and tissue-based products. Procedures shall be designed to ensure compliance with the requirements of this part. Prior to implementation, all procedures shall be reviewed and approved by a responsible person. At least once in a 12-month period, all procedures shall be reviewed and, if necessary, revised, and the review shall be documented. Procedures shall be readily available to the personnel in the area where the operations to which they relate are performed, unless this is impractical. Any deviation from a procedure shall be authorized in advance by a responsible person, recorded, and justified. An establishment may adopt current standard procedures, such as those in a technical manual prepared by another organization, provided the procedures are consistent with and at least as stringent as the requirements of this part and appropriate for the operations conducted at the establishment. Obsolete procedures shall be archived for at least 10 years.

The suggested language, above, includes three alternative words (bold italics) intended to make the requirement contingent on the actual ability of a manufacturer to incorporate such procedures into manufacturing. The term ***possible*** is not preferred since it may create too stringent a requirement: possibility in this case would likely turn on what is technically achievable without regard to cost or other practical considerations. Likewise, the term ***practical*** is also not preferred since it may create too loose a requirement: one might argue that any practical consideration, however trivial or marginal, would be sufficient to avoid an obligation to establish the requisite measures. Making a requirement to incorporate pathogen clearance procedures dependent on whether it is ***feasible*** to do so creates a flexible standard since feasibility may be determined on the basis of technical possibility and many other factors such as cost, product availability and so forth. Should FDA adopt this suggested language in the Final Rule, the meaning of whatever contingent term is used should be explained in the Preamble.

It is possible that the incorporation of more elaborate manufacturing methods may constitute more than minimal manipulation, and consequently affect the status of "361

products". It would be helpful to the industry if FDA would discuss this possibility in the publication of the Final Rule.

2. Proposed Section 1271.230(b) should be modified to delete the exemplary language referring to sterility or viral inactivation. Suggested language follows:

> (b) Claims. Any process-related claim in labeling or promotional materials for a human cellular or tissue-based product~~, e.g., a claim for sterility or viral inactivation,~~ shall be based on a validated process. Validation shall be documented, and the documentation shall be maintained at the establishment and made available for review on inspection.

3. A new Section 1271.230(c) should be added to specifically address the need for the validation of processes intended to achieve sterility or viral clearance. Suggested language follows:

> (b) Claims. Any process intended to produce a sterile human cellular or tissue-based product, or intended to remove or inactivate viruses or other pathogens that may contaminate a human cellular or tissue-based product, shall be validated. Validation shall establish the degree of sterility assurance or extent of pathogen inactivation or removal of which the process is capable, and shall establish that the process is adequately controlled to provide a high degree of assurance that the expected process capability is achieved during routine manufacturing. Validation shall be documented, and the documentation shall be maintained at the establishment and made available for review on inspection.

4. Current proposed Sections 1271.230(c), (d) and (e) should be redesignated (d), (e) and (f), respectively.

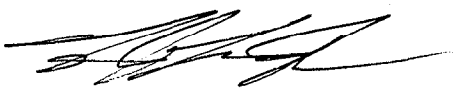
5. Proposed Section 1271.220(c) should be modified to remove the absolute prohibition against pooling. Suggested language follows:

> (c) Pooling. Human cells or tissue from two or more donors shall not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing, <u>unless the manufacturer documents that: (i) pooling is necessary to achieve the intended attributes of the product, and (ii) that the pooling process does not create an unreasonable risk of transmitting communicable disease to the recipients of the product.</u>

6. Any other revisions or amendments to the Proposed Rule, or to the companion registration and donor-suitability proposed rules, needed to conform other provisions to changes made in response to any comment offered here.

We appreciate the opportunity to comment on the Proposed Rule. Its formulation and the development of the entire regulatory framework for human cell and tissue products was an enormous undertaking of great importance and timeliness. We hope that the Agency will find our comments and suggestions useful and consider them in formulating the Final Rule for CGTPs.

Sincerely,



Thomas J. Lynch, J.D., Ph.D.
Senior Vice President
Regulatory and Quality