CryoLife®, Inc.
Biotechnologies for Medicine℠

May 7, 2001

Documents Management Branch (HFA – 305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comments to Docket No. 97N-484P; Proposed Current Good Tissue Practice .....

To Whom It May Concern:

CryoLife, Inc., which currently operates a licensed tissue bank located in Kennesaw, Georgia supplying various vascular and orthopedic tissues and as well as an FDA-registered medical device establishment supplying human heart valve devices, is appreciative of this opportunity to submit several comments regarding the proposed regulations establishing uniform Current Good Tissue Practice for manufacturers of human cellular and tissue-based products.

Our company has a well documented history in general support of such regulations for the tissue banking industry. We appreciate the philosophy the agency has adopted in promulgating regulations that seek to define objectives rather than define specific methodologies. We are pleased that the agency has addressed the issues emanating from the different regulatory schemes that are in place such as extending the donor screening requirements to tissues that are currently exempt by virtue of being regulated as devices or biologics. We believe that the decision placing global responsibility for the suitability of the tissue on the establishment that determines the tissue's adherence to specifications and makes it available for distribution is appropriate and one that CryoLife, in previous comments, has indicated willingness to accept and execute.

However, CryoLife, feels compelled to respectfully express concern with the specific terms "contamination, contaminated, and contaminant". Unless we have misinterpreted the agency's descriptive comments accompanying the proposed regulation, the terms focus primarily on microbial contamination. Later in 1271.220[a] the term "contaminated" is used without any qualifiers and in an absolute sense as requiring the tissue be "not contaminated". Taken together, the agency seems to be requiring that the tissue be "sterile" and that the processes of decontamination be validated to produce tissue that is not contaminated or is sterile. The agency well knows, or aught to know, that most human tissues and human heart valves are not distributed nor labeled as sterile and as viable tissue cannot be. If the agency insists that "no

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contamination" and "effectively disinfected" equate to processing that is validatable, using good scientific principles, to consistently provide tissue with no detectable microbial presence, then the agency seems to be requiring, *per se*, that all processed tissue be discarded as indicated in the discussion accompanying the regulation. The term disinfection, as used of necessity in the tissue banking industry, does not imply the more stringent criterium of total removal of microbial contamination. Using the terms "disinfection regimen" and "eradicating" together and focusing on fungal contamination to the exclusion of bacterial contamination in the discussion introduces bias into the discussion. It can be argued with equal scientific basis that the tissue disinfection regimens employed by all tissue banks fail, as a validatable process, to eradicate bacterial contamination as well. Any belief or claim to the contrary is based upon the common confusion that tissue banks provide sterile viable tissue. Clearly, if tissue banks could demonstrate eradication (sterility) it would behoove them to label their tissue as sterile as many bone processors currently do. Since they cannot, every tissue processor of which we are familiar, tests tissue after processing and discards tissue which demonstrates microbial growth. This not the same as eradicating contamination. It is reducing bioburden below limits detectable by routine testing.

CryoLife takes exception to the extrapolations of the number of deaths and infections related to heart valve contamination causing fungal endocarditis as discussed in the preamble to the proposed regulation. CryoLife believes it is well informed when it states that annual heart valve allograft distribution is likely ten-fold lower (5000-6000 annually) than the 61,000 annually referenced in the preamble. CryoLife further believes that with respect to such infections that fewer than 10 infections per year may be caused by contaminated valves. CryoLife grants the serious nature of such infections and given that the clinical data support the resistance of heart valve allografts to fungal infections compared to mechanical valves, CryoLife believes that direct reports to the company of such infections by implanting surgeons is a reasonably accurate estimation of the extent of the occurrence. The average of such reports is significantly lower than one per year. In any case, CryoLife does not automatically subscribe to the concept that discarding sometimes desperately needed tissue that has documented fungal contamination upon receipt significantly reduces clinical infection. Given that 50-70% of incoming tissue has documented microbial contamination of any given kind and the inherent limits of test methodology, the rate of false negatives for fungal contamination on receipt is equal to, if not higher, than that potential for false negatives after processing.

Given the difficulty of defining disinfection and the methodologies to demonstrate no microbial contamination of tissue, as well as the demonstrated ability of anti-fungals to significantly reduce fungal bioburden below normally detectable levels (that is disinfect), CryoLife believes that further attention to this issue is warranted. As written, we do not believe any facility currently engaged in processing viable tissue can comply with even a moderate interpretation of this section of the cGTP as elaborated upon in the preregulation discussion.

On a second issue, since CryoLife subscribes to the concept that the establishment that makes the tissue available is the overall responsible party, we are somewhat concerned with the requirements that appear to make every establishment in the chain of manufacturing bear an equal burden to ensure that each entity with which they contract adheres to the cGTP. It is suggested in the discussion accompanying the regulation that one method of accomplishing this end would be to audit all such entities. Given the intertwining matrix of such entities, were establishments to engage in this activity, it is not difficult to envision a constantly revolving inspection involving for CryoLife, for example, hosting 200-250 inspection audits per year and being required to conduct an estimated 300-350 audits of its own. This is particularly true if annual audits of the establishment's quality program were construed to include each contractor's and contractee's quality program. We believe that the responsibility of establishments that are not engaged in determining the tissues adherence to specifications and making the tissue available for distribution be directly limited to their own activities and that their responsibility toward contractors be limited to ensuring that the contractor is a registered tissue bank establishment and diligence to compliance not be expected to exceed an initial audit. As the agency might understand from their own resource constraints, requiring the responsible establishment to undertake annual auditing of tissue sources and distributors for compliance cannot be reasonably accomplished. CryoLife respectfully requests that the agency consider reasonable alternatives to such an intensive requirement. As a strategy the agency itself has adopted, perhaps requiring the responsible manufacturer to focus on establishments with greater compliance issues might be of greater benefit within the capabilities of such organizations.

Again CryoLife appreciates this opportunity and anticipates further dialogue on this and other continuing issues of interest to the tissue banking industry as a whole or CryoLife specifically. If there are questions, I may be reached at 278.290.4530 or vanderwyk.jim@cryolife.com.

Sincerely,

James C. Vander Wyk

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Vice-President, Regulatory Affairs and
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