CAMBREX

October 22, 2003

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

RE: Docket No. 2003D-0349

To Whom It May Concern,

On August 18, 2003 the Center for Biologics Evaluation and Research posted a notice in the Federal Register announcing the availability of the draft guidance document "Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs)" [Docket No. 2003D-0349], and requested comments on this document.

Cambrex Bio Science Walkersville is the leading supplier of endotoxin detection technology, including our FDA Licensed BioWhittaker™ Limulus Amebocyte Lysate (License # 709). Since our customers, and some reviewers are misinterpreting the testing requirements, FDA should correct the guidance document to reflect that the sponsors should not be required to show equivalence between these two methods.

Specifically, we wish to comment on the "Pyrogenicity/Endotoxin" section on page 17 of this document, specifically the statement:

> *Endotoxin testing using the Limulus Amebocyte Lysate (LAL) assay method is typically done as an alternative to pyrogenicity testing (see 21 CFR 610.13(b)) for early-phase trials. If the sponsor is using the LAL endotoxin method, you* [the reviewer] *should inform the sponsor that,* ***for licensure, the LAL endotoxin test must be shown, as explained in 21 CFR 610.9, to be equivalent to that of the pyrogenicity test described in 21 CFR 610.13(b)*** (emphasis added).

The Bacterial Endotoxins Test and the Rabbit Pyrogen Test (as specified in 21 CFR 610.13) are not equivalent for the following reasons:

- The Rabbit Pyrogen Test is a presence/absence test (pyrogenic/non-pyrogenic), while the LAL test can be quantitative.
- The Rabbit Pyrogen Test is highly variable, and may be affected by many issues, including environmental stresses on the rabbit.
- The LAL test is specific for bacterial endotoxin (lipopolysaccharide), while the Rabbit Pyrogen Test may detect other fever-inducing entities, such as TNF or other cytokines, and chemical pyrogens. These other fever-inducing agents generally represent less than 1% of pyrogens found in parenteral preparations.

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Additionally, page 10 of the 1987 "Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices" states:

> *A batch which fails a validated LAL release test should not be retested by the rabbit test and released if it passes. Due to the high variability and lack of reproducibility of the rabbit test as an endotoxin assay procedure, we do not consider it an appropriate retest procedure for LAL failures.*

Therefore, FDA in its own previous guidance acknowledges these differences. If these tests were truly equivalent, they would be interchangeable.

Toxicity testing is performed during pre-clinical evaluations of a given product to determine its potential toxicity. Rabbit pyrogen testing should be performed during this phase of product development to rule out the introduction of pyrogens other than bacterial endotoxin inherent to the production process of the product.

Once the production process has been evaluated for the absence of intrinsic non-bacterial pyrogens during the pre-clinical phase, the LAL Bacterial Endotoxins Test (BET) should replace the Rabbit Pyrogen Test as the product release test for Phase I, II, III, and marketed product. The LAL test has been approved by FDA since 1979 for final product testing to detect bacterial endotoxin, and the USP Bacterial Endotoxin Test <85> has been a compendial test since the twentieth edition of the United States Pharmacopoeia. The USP has been systematically changing to a BET test for injectable products since 1990, and phasing out the Rabbit Pyrogen Test.

We recommend that the language be changed to reflect these differences as follows:

> *Endotoxin testing using the Limulus Amebocyte Lysate (LAL) assay method is typically done to detect pyrogens (endotoxin) for products in early-phase clinical trials, and for marketed products. If the sponsor is using the LAL endotoxin method, you should inform the sponsor that, for licensure, the process for manufacture should be evaluated during pre-clinical phases for production of intrinsic pyrogenic substances other than endotoxin, using the pyrogenicity test described in 21 CFR 610.13(b). Once the process is shown to not contribute other intrinsic pyrogenic substances, the LAL test should be used to detect contaminating pyrogens.*

Thank you for the opportunity to comment on this important issue.

Sincerely,

S. Tosadori

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