NEXtran
AN AFFILIATE OF BAXTER HEALTHCARE CORPORATION

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May 7, 2001

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

Re: **Docket No. 00D-1662**; Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans

Dear Sir / Madam:

These comments are submitted by Nextran Inc., a wholly owned subsidiary of Baxter Healthcare Corporation, in response to the above referenced draft guidance published by the Food and Drug Administration (FDA) regarding the use of xenotransplantation products in humans. Nextran is the sponsor of an investigational new xenotransplantation biological product currently on file with the FDA.

Nextran respectfully submits these comments for the FDA's consideration during the finalization of the guidance document.

Sincerely yours,

John S. Logan, Ph.D.
Vice President,
Research & Development

00D-1662 C9

Comments

This draft guidance document is a comprehensive document and complements the PHS Guideline on Infectious Disease Issues in Xenotransplantation (January 19, 2001). We would like to address certain portions of the guidance.

SECTION III. D. 2.b. Health Screening, paragraph i.

The statement is made, "If infectious agents including normal flora that could potentially be infectious in an immunosuppressed recipient have been identified in source animals, the use of such animals should be avoided. However, the use of such animals may be warranted under certain circumstances." We refer you to Section 3.5.2 of the PHS Guidelines that state, "The use of source animals in which infectious agents, including latent viruses, have been identified should be avoided. However, the presence of an infectious agent in certain anatomic sites, for example the alimentary tract, should not preclude use of the source animal if the agent is documented to be absent in the xenotransplantation product." Clearly, the PHS guidelines recognize one such circumstance and we believe that each decision should be decided on a case by case review.

SECTION III. D. 4. a. Testing for infectious agents.

This section states, "When feasible, biopsy of the live animal cells, tissue or organ or other relevant tissue should be examined by histopathology and tested for infectious

agents by appropriate assays. ...All tests should be performed at a time as close as possible to the date of harvest of the live cells, tissues or organs, but which allows the results to be obtained prior to their use."

This section should include a discussion that a biopsy from a whole organ product **prior to harvest** may be contraindicated, and may in fact lead to a greater potential for contamination of a whole organ. Invasive procedures, such as biopsies, have the potential to introduce pathogens into the tissue. Alternative noninvasive measures employed prior to harvest should be discussed. Additionally, venipuncture performed at a time as close as possible to the date of whole organ harvest also represents a potential risk of sepsis even when performed under aseptic conditions.

Section III. G. Disposal of Animals and Use of Byproducts

The discussion in the first paragraph centers around "the ultimate disposition of source animals, including those animals in which the insertion of genetic information failed ("no-takes"), and sentinel animals bred for use in producing xenotransplantation products." It is stated that "Source animals should be disposed of in a manner consistent with the disposal of infectious medical waste in compliance with federal, state, and local requirements." Although these animals (transgenic or not) will not presently enter the food chain, we respectfully disagree that an animal that has been raised in a barrier facility, designated pathogen free, for the specific purpose of whole organ xenotransplantation, should be considered as infectious medical waste. These animals will be free from most of the organisms that are present in same species animals that are

used to produce human food. A nontransgenic source animal would be identical, except safer from a food safety perspective, to over 100 million pigs slaughtered per year for food today in the US. This requirement adds an additional unnecessary cost to the production of the whole organ xenotransplantation product.

SECTION IV. CHARACTERIZATION OF XENOTRANSPLANTATION PRODUCTS

This section describes in general the requirement that the final xenotransplantation product must be tested for safety, identity, purity, and potency. We agree that these are critical and must be established for the xenotransplantation product. We would like to reinforce the concept FDA has noted in the draft guidance that these assays will depend on the product itself. Conducting some of the standard accepted tests on a whole organ at harvest may not be feasible, practical, or safe. A variety of tests have been developed that are available from veterinary experts and from medical practice that may be more useful in establishing the safety, identity, purity, and potency in a source animal, and thus be applicable to the whole organ xenotransplant product.

SECTION V. C. 4. d. Assays Suitable for the Detection of Porcine Endogenous Retroviruses (PERV)

This section discusses conducting co-cultivation tests for PERV on a sample of the xenotransplantation product. It is unclear whether the intent is for the sponsor to conduct co-cultivation testing everytime an organ or cells for xenotransplantation are harvested or

only on a limited number of samples conducted during the general characterization of the actual product.

Nextran believes that co-cultivation testing for PERV is appropriate during the overall characterization, but is not necessary to be conducted on the product at each harvest, particularly with whole organs.

SECTION VII. D. 2. Secretion of Biologically Active Molecules by Xenotransplantation Products

We agree that it is important to consider relevant biologically active molecules produced by xenotransplanted organs or tissues, however, absent a deleterious physiological incompatibility we believe that it would be unwarranted to analyze every conceivable molecule produced by the organ throughout it's life for potential incompatibilities. Therefore, we suggest that the adequate physiological functioning of xenotransplanted organs be the guiding principle.

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