



MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: Pratibha Rana, HFM-380 & File of STN 125284

From: Philip Snoy DVM, HFM-22
Director, Division of Veterinary Services

Subject: Review of GTC's Biological License Application for recombinant Antithrombin III (rATIII) manufactured in the milk of transgenic goats

APPROVED

By Philip Snoy at 10:35 am, Nov 14, 2008

Sections Reviewed

I focused my review on Sections 3.2.A.1 (GTC Farm Operations) and 3.2.A.2 (Adventitious Agent Safety Evaluation). Additionally, I reviewed animal-related information from Sections 2.3.S.2 (Description of Manufacturing Process) and 3.2.S.2.3.3.1 (Qualification of Individual Production Goats/Milk).

Herd Health and Husbandry

I reviewed the following issues that were discussed in the submission and found them generally acceptable. In some instances, additional information is required for a final determination of acceptability. Those requests are made in the section below.

- 1) Milk collection and storage procedures at the GTC farm
- 2) Biosecurity, external and internal, for the production flock
- 3) Product-dedicated, source material (milk) collection equipment
- 4) Animal housing segregated by product
- 5) Protective clothing policy
- 6) Pest (potential adventitious agent vectors) management program
- 7) Sentinel animal program
- 8) Program minimizing the possibility of scrapie presence in the flock

- 9) Policy requiring goat feed to be free from ruminant-sourced proteins and ruminant-sourced fat since 1995
- 10) Health qualification of founder animals and of goats subsequently introduced before closing the flock in 2000
- 11) Closed flock status
- 12) Feed and water monitoring for quality, toxic contaminants, and, in the case of water, coliforms
- 13) Individual animal health records
- 14) Flock health maintenance and monitoring procedures
- 15) Established flock husbandry procedures to minimize exposure to and to assist in the control of adventitious agents
- 16) Traceability of milk (source material) from collection through the manufacturing process—procedures for animal identification and record keeping
- 17) Policy against use of live vaccines in the production flock
- 18) Established antibiotics withdrawal times
- 19) Multiple layers of safety from adventitious agents—physical and procedural barriers against introduction, production animal testing, source material testing, and viral removal/inactivation by the manufacturing process
- 20) Individual animal qualification criteria for entering production
- 21) Occupational health program to protect employees and the production flock
- 22) Established procedures for evaluating morbidity/mortality within production flock—diagnostic testing of sick animals and animal necropsy of unexpected deaths
- 23) Evaluation of farm location for previous use by agricultural animals and for proximity to potential sources of adventitious agents

Information Request

- 1) In Section 3.2.A.1.3.1.2, you describe “biannual” physicals for GTC Farm staff. Please define this term as either every 2 years or twice each year.

- 2) In Section 3.2.A.1.5.1, you allude to periodic physical examination of production animals by stating that “additional observations are performed with different frequencies for different subpopulations of goats within the overall herd.” Please provide information describing the details of periodic health evaluations to include: who performs the evaluation, how frequently regular exams are performed, what specific parameters are evaluated (i.e., cbc, chem screens, TPR, parasite screens, etc).
- 3) In Section 3.2.A.1.7 (page 22), you state that “necropsies are performed on all animals that die unexpectedly or for those animals that are euthanized for clinical reasons.” In addition to gross necropsy evaluation, are tissues collected for histologic evaluation? If so, what tissues are collected, who performs the microscopic evaluation, and is there a standard protocol for acquiring microbiologic samples from tissues to check for adventitious agents (if yes to this latter inquiry, please provide)?
- 4) In Section 3.2.A.1.7.1, you mention a Medical Review Board that reviews the issues surrounding a confirmed positive production animal found to have an adventitious agent. Who serves on this Board? Please provide a list of adventitious agents confirmed in the production herd in the last 5 years and give an example of one of the Board’s investigations into a confirmed positive production animal.
- 5) In Section 3.2.A.7.2 (page 24), you mention a “significant decrease in the relevant number of cases of clinical mastitis in all milking animals at the GTC Farm.” Please provide the data which provides the basis for this conclusion.
- 6) In Section 3.2.A.1.7.2.1, you mention that “morbidity and mortality data are reviewed quarterly by Veterinary Services and the GTC IACUC to look for significant trends in the clinical data.” Please provide this data for the last two years and any written review summary by the veterinarians or the IACUC.
- 7) In reference to Section 3.2A.1.8, please provide the SOP for prevention of treated/medicated animals from contributing to source material collection.
- 8) In Section 3.2.A.1.8.5, you state that “where possible, any provided supplements do not contain animal-derived by-products.” Please provide a list of supplements used at the GTC Farm that do contain animal-derived products.
- 9) In Appendix 1 (page 29), you state that “production parlor associated pens are cleaned approximately weekly.” Please give specific SOP requirements (or provide the specific SOP) for pen sanitation. Alternatively, define “approximately.”

- 10) In Section 3.2.A.2.6.1, you mention that “an assessment of risk of viral infection of the goatherd was performed.” Please provide this assessment and any updates to the first evaluation in 1999, especially to include the list of viral disease that was compiled for the initial assessment.

Action Item for GTC

- 1) Please add to your procedures, if it does not already exist, that you will notify the FDA immediately if you get a positive result when testing production goats or milk for adventitious agents of concern.