

FINDING OF NO SIGNIFICANT IMPACT

for

the Bc6 rDNA Construct in GTC 155-92 Goats

**Expressing Recombinant Human Antithrombin III
(rhAT or ATRYN)**

NADA 141-294

GTC Biotherapeutics, Inc.

**FOR PUBLIC DISPLAY
(HFA-305)**

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The Center for Veterinary Medicine has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment. Therefore, an environmental impact statement will not be prepared.

We have prepared the attached Environmental Assessment (EA) dated January 29, 2009, in support of a new animal drug application (NADA) by GTC Biotherapeutics, Inc. (GTC) for the Bc6 rDNA construct in the GTC 155-92 lineage of goats that have been genetically engineered (GE) to express recombinant human antithrombin III (rhAT; tradename ATryn[®] for use in humans or “ATRYN”)¹ in the milk of lactating does. ATRYN will be manufactured in the form of a sterile, lyophilized powder for use in making a solution for intravenous infusion. A formulation of this recombinant protein² is the subject of a biologics license application (BLA) that is currently under review by the Food and Drug Administration’s (FDA’s) Center for Biologics Evaluation and Research (CBER). This product is intended to treat patients with congenital antithrombin III (ATIII) deficiency to prevent life- threatening clot formation during high risk situations such as surgery and obstetrical procedures.

This EA focuses on the potential environmental effects of the GTC 155-92 GE goats and their waste products at, and around, the two sites where they are currently housed. The main site is the GTC farm in central Massachusetts where these goats are raised and a production herd of several hundred animals is used to produce ATRYN for use in humans. A secondary facility is located in central Pennsylvania where a small herd of a few dozen GTC 155-92 goats is held in reserve.

CBER will separately comply with its NEPA obligations arising from its review of the biologic license application submitted by GTC Biotherapeutics, Inc.

¹ The approved international nonproprietary name (INN) and United States Adopted Name (USAN) for this recombinant protein is antithrombin alfa. The FDA assigned proper name is antithrombin III (Recombinant).

² The product tradename for the formulated dosage form of this protein is ATryn[®] for Injection. Per CVM’s convention, all proprietary names of drugs are written in upper case letters. In this case ATRYN is equivalent to ATryn[®].

GTC has submitted extensive information to the FDA as part of its investigational new animal drug (INAD) file, new animal drug application (NADA), investigational drug application (IND), and BLA. In addition, members of FDA's staff inspected or site visited the GTC farm in Massachusetts on at least two occasions. Relevant information from all of these sources, as well as FDA's reviews of the data and information provided by GTC were used in the EA.

General risk questions addressed in the EA include the following:

- What are the risks associated with the GE goats while under confinement?
- What is the likelihood that the GE goats will escape from confinement?
- What are the likely consequences should the GE goats escape from confinement?

GTC Massachusetts Farm

As indicated in the EA, the hazards and risks associated with GE animals in confinement are highly dependent on the gene expression product and the ability of the inserted gene construct to mobilize and spread to other animals. In the case of the GTC 155-92 goat production herd at the GTC farm in Massachusetts, the following environmental risks were identified and considered for the goats while under confinement:

- *Risk of gene flow via mobilization of rDNA construct.*
- *Risk of direct toxicity resulting from increased environmental concentrations of rhAT.*
- *Risk of disease spread from confined housing of 155-92 goats.*
- *Risks that may be associated with the disposal of GE animal wastes or carcasses.*

CVM's review indicates that the Bc6 rDNA construct is not likely to mobilize and spread to other organisms, and the gene product (rhAT) does not pose an intrinsic hazard; therefore, the GTC 155-92 lineage of goats in confinement is not likely to present any significant risk to the environment.

At least five levels of containment are present at the GTC farm to prevent the escape of the GTC 155-92 goats. Containment includes physical barriers (two separate fences), 24-hour security, daily checks by the farm's veterinary staff, and video surveillance. In addition, all of the GTC 155-92 goats have redundant identification systems (ear tattoos, neck tags, and electronic transponders) that allow them to be identified easily and quickly. Taken as a whole, the containment and security systems insure that escape of any 155-92 GE goats from the GTC farm is highly improbable. In the unlikely event of an escape, the presence of redundant animal identification systems reduces the possibility that any of the goats will remain at large for an extended period of time.

As noted in the EA, assuming that one or more GTC 155-92 goats were able to escape the confines of the GTC farm, there is very little reason to believe that they would be able to survive, reproduce, or establish a population in the nearby environs, or that they would be able to migrate to another nearby habitat and do so. First, in order to establish a population, two or more animals would need to escape at approximately the same time, or interbreed with surrounding feral goats. Given the high value of these animals, and the intensive surveillance systems in place, escaped animals would likely be recaptured within a very short

period of time and returned to the farm. In the unlikely event that the escaped animals were not recovered, the likelihood of long-term survival, reproduction and establishment is extremely low. First, there are no known populations of feral goats in the northeastern United States. Second, the harsh winter climate of Massachusetts makes the likelihood of survival after escape low. Finally, the presence of potential predator species (e.g., dogs, coyotes) makes survival and establishment highly improbable. Further, reproduction in the wild is particularly unlikely because adult male and female rhAT goats are housed separately on the GTC farm, and thus unlikely to escape at the same time should any escapes actually occur. In addition, there is no evidence to indicate, and little reason to hypothesize, that the addition of the Bc6 rDNA construct to their genome has increased their fitness and made these goats any more likely to establish in the wild than normal domesticated goats.

As discussed in the EA, even if one or more 155-92 GE goats were able to escape and survive for an extended period of time outside the GTC farm, it is hard to postulate any significant adverse effects that they might have on the local environment. In addition, there is no reason to believe that the Bc6 rDNA construct would spread to other populations of feral goats as there is no information available to indicate any feral goat populations exist in Massachusetts or nearby states. Interactions with domesticated goats in the vicinity of the GTC farm are also not expected because the GTC 155-92 goats would be quickly recognized by their ear tattoos and neck tags, captured, and returned to the GTC farm. In addition, there are no known livestock farms in the area surrounding the GTC farm; therefore, interactions with other domestic goats are unlikely.

Because the Bc6 rDNA construct is not mobilizable, even if interactions were to occur with domesticated animals or wildlife species in the area, there is no realistic pathway for the gene to spread to these animals. Direct transfer to a related species, such as sheep, is not expected as the offspring of goat-sheep matings are generally stillborn or die as embryos, and goats do not interbreed with any other species. Thus, the probability for the Bc6 rDNA construct to spread to any animals other than goats is negligible.

Pennsylvania Goat Facility

In almost all respects, conditions that affect the risk analyses described for the GTC farm in Massachusetts are similar or identical to those for the Pennsylvania goat-holding facility. Major differences between the two are in the number of GE goats (several hundred in Massachusetts versus several dozen in Pennsylvania) and in the production of milk containing rhAT (none is produced in Pennsylvania). The GE goat facility in Pennsylvania has a similar level of physical containment to the GTC farm in Massachusetts and the GTC 155-92 goats there are never allowed outside of their barn. Procedures for animal husbandry and to insure biosecurity are also very similar to those for the Massachusetts farm and the animal identification systems are identical for both. Disposal procedures for goat wastes are similar to, and generally equivalent, to those followed in Massachusetts. One additional major difference between the two facilities is in the disposal of animal carcasses. They are incinerated off-site in Massachusetts as opposed to being buried 6 feet underground and treated with lime in Pennsylvania; however, both are USDA-acceptable means of destruction

and neither should present a risk to the environment because the gene construct does not pose an intrinsic hazard and is not likely to mobilize and spread.

An analysis of the available information indicates that the same conclusions should apply for the Pennsylvania facility as for the GTC Massachusetts farm with respect to the risks associated with confinement, the likelihood of escape, and likelihood of harm in the event that the 155-92 GE goats should in fact escape from confinement. The risks associated with confinement in Pennsylvania are minimal because the GE animals are identical and conditions of confinement are comparable to those at the farm in Massachusetts. Considering the high level of containment, the likelihood of escape at the Pennsylvania facility is also very low. As for the Massachusetts farm, in the unlikely event of an escape, the presence of redundant animal identification systems reduces the possibility that any of the goats will remain at large for an extended period of time. The environments surrounding both facilities are quite similar, largely wooded and semi-rural in nature. As in Massachusetts, coyotes are abundant in Pennsylvania and have caused significant losses in sheep/lamb flocks in the state. Therefore, should one or more of these animals escape, the likelihood for survival, reproduction and establishment of the 155-92 GE goats (or the probability they will cause adverse effects on the local environment) is very low and no greater in Pennsylvania than in Massachusetts.

Conclusion

There is adequate and substantial information available to conclude that GE goats in the GTC 155-92 lineage that contain Bc6 rDNA constructs are not expected to have a significant impact on the quality of the human environment when held under the current conditions of confinement at locations in Massachusetts and Pennsylvania.

Date

Steven D. Vaughn, D.V.M.
Director, Office of New Animal Drug Evaluation, HFV-100

Attachment:

Environmental Assessment for the Bc6 rDNA construct in GTC 155-92 Goats Expressing Recombinant Human Antithrombin III (rhAT or ATRYN); Dated January 29, 2009