



MEMORANDUM

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

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

From: Roman Drews, HFM-392
Chair of Review Committee & CMC reviewer

Through: Timothy Lee, HFM-392
Acting Chief, Laboratory of Hemostasis/DH/OBRR

Subject: Approval of Biologics License Application from GTC Biotherapeutics, Inc. for Antithrombin (Recombinant) (rAT) [ATryn®] manufactured from the milk of transgenic goats

This biologics license application (BLA) was reviewed by a committee that included the following CBER reviewers: Dr. Faith Barash (Epidemiology), Dr. Roman Drews (Chair and CMC/Product), Ms. Maryann Gallagher (Advertising and Labeling), Dr. Paul Hsieh (Biostatistics), Dr. Nisha Jain (Clinical), Dr. Iftekhar Mahmood (Clinical Pharmacology), Mr. Joseph Manik (Bioresearch monitoring), Pratibha Rana (Administrative/Regulatory), Dr. Philip Snoy (Veterinary Medicine), Dr. Evi Struble (Pharmacology/Toxicology), Dr. Chiang Syin (CMC/Facility).

The pre-licensure inspections were conducted at the following manufacturing facilities: GTC Biotherapeutics (GTC) production goat farm----b(4)-----, GTC ---b(4)----- facility (Framingham, MA), --b(4)-----, Inc. facility for the production of the rAT bulk drug substance ----b(4)----- facility for the production of final drug product (The Netherlands).

All outstanding issues resulting from the inspections were successfully resolved. Based on the information submitted by GTC, the review committee found the information regarding the safety, potency, and efficacy of ATryn to be acceptable and recommends the approval of this BLA.

Background

Recombinant Antithrombin (rAT) produced in the milk of transgenic goats is a single-chain glycoprotein composed of 432 amino acid. The molecule has six cysteine residues which form three disulfide bridges between Cys 8-128, 21-95, and 247-430, and four N-

linked glycosylation sites at asparagines 96, 135, 155, and 192. The amino-acid sequence, disulfide linkages, and glycosylation sites of rAT are identical to those of human plasma-derived AT. The carbohydrate composition and profile of rAT differ from those of human plasma-derived AT that result in an approximately 4-fold increase in heparin affinity as demonstrated in *in vitro* experiments. The structural scheme of the protein is provided below.

S ————— S					
HGSPVDICTA	KPRDIPMNPM	CIVRSPEKKA	TEDEGSEQKI	PEATNRKRVWE	50
————— S *					
LSKANSRFAT	TFYQHLADSK	NDNDNIFLSP	LSISTAFAMT	KLGAQNDILQ	100
S ————— *					
QLMEVFKFDI	ISEKTSQIH	FFFAKLNCR	YRKANKSSKL	VSANRLFGDK	150
* ————— *					
SLTFNETYQD	ISELVYGAKL	QPLDFKENAE	QSRAAINKWV	SNKTEGRITD	200
S —————					
VIPSEAINEL	TVLVLVNTIY	FKGLWKSKEF	PENTRKELFY	KADGESCSAS	250
MMYQEGKFRY	RRVAEGTQVL	ELPFKGDDIT	MVLILPKPEK	SLAKVEKELT	300
PEVLQEWLDE	LEEMMLVVHM	PRFRIEDGFS	LKEQLQDMGL	VDLFSPEKSK	350
LPGIVAEGRD	DLVVSDAFHK	AFLEVNEEGS	EAASSTAVVI	AGRSLNPNRV	400
S —————					
TFKANRPFLV	FIREVPLNTI	IFMGRVANPC	VK		432

* Glycosylation sites

rAT is a serine protease inhibitor that is the principal inhibitor of serine proteases in the blood coagulation system – thrombin, and Factor Xa, and to a lesser extent, factors IXa, XIa, XIIa, trypsin, plasmin, and kallikrein. AT inhibits the activity of these serine proteases by forming a 1:1 stoichiometric complex between the enzyme and inhibitor. This formation occurs at a relatively slow rate in the absence of heparin. When heparin is present, the protease binds to the lysyl residues on AT and dramatically accelerates the rate of complex formation (around 1000 times).

GTC's rAT is expressed in the milk of transgenic goats. The herd is maintained in a closed bio-secured system. The bio-security system addresses both external and internal control of diseases that may affect the herd. The health and welfare of the herd is under the supervision of GTC's full-time veterinary staff.

Milk (source material) is collected from qualified female animals and frozen until further processing. The frozen milk is stored by -----b(4)------. The manufacture of rAT bulk drug substance (BDS) is performed by -----b(4)------. rAT is recovered from pools of milk via a filtration system linked with an affinity chromatography (heparin resin) column, and two additional chromatography columns. Most of the analytical testing required for the manufacture and release of the final material is performed by staff at the GTC facility located in Framingham, MA. In terms of product safety, the animals and source material are tested for the presence of adventitious viruses. The manufacturing process has been validated for the

removal/inactivation of a panel of four model viruses that represent an acceptable range of physico-chemical and structural properties. In addition, the firm validated the ability of the manufacturing process to clear prion protein using animal infectivity assays.

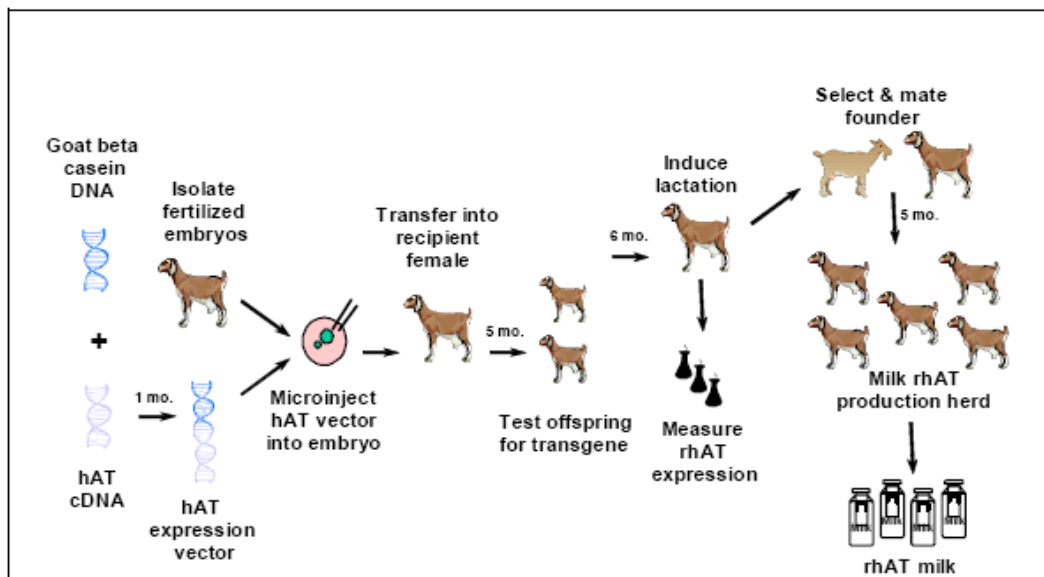
The rAT final drug product (FDP) is manufactured at -----b(4)----- facility located in the Netherlands. rAT FDP is a lyophilized product formulated with glycine, sodium chloride and sodium citrate with ---b(4)----- in each vial. The product is intended for intravenous infusion to patients with congenital AT deficiency prior to, during and following surgical or obstetrical procedures.

Bulk Drug Substance

Manufacturing Process – Development and Validation

Transgenic herd – general description

Female transgenic goats are the expression platform for the manufacturing of rAT. The genetic construct (transgene) that comprises of goat beta casein gene (regulatory elements directing expression to the mammary gland), and the human cDNA coding sequence for AT, was microinjected into goat embryos. The microinjected embryos were transferred to surrogate mothers. Goat progeny were born 5 months later and were analyzed for the presence of the AT transgene by -----b(4)----- . A male founder (155-92) was selected and mated with resulting transgenic female offspring being bred to lactate following parturition. The positive transgenic animals pass the transgene to subsequent generations in a Mendelian fashion. Genetic and milk tests are performed to assess the presence of rAT in the production animals. Transgenic offspring were further expanded using standard goat breeding techniques to create a herd of production animals. For details, please see the diagram attached below.



Transgene Construct

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In addition, the purification steps are controlled for the level of -----b(4)-----
----- . The maximum number of runs for chromatography resin and usage of filter
membranes have been established based on the data collected from the small and
commercial scales runs. So far, GTC has manufactured b(4) lots at the proposed
commercial manufacturing site using the manufacturing process described in this BLA.
Since the initiation of development of rAT,_{b(4)}lots of product have been manufactured _{b(4)}
at laboratory scale and b(4) at different scales). Lots of the final drug products that were
manufactured with the significant process changes have been used in non-clinical and
clinical studies.

Development and Validation

Development of rAT processing first occurred at [REDACTED] and included scaled down and commercial scale validation studies. The purification process was later transferred to [REDACTED] where rAT clinical batches were purified and used in hereditary deficiency studies. Transfer of the process to [REDACTED] included modifications involving closure of the [REDACTED]. The process has been re-validated in [REDACTED] facility. The process equipment, chromatography resins and analytical methods have not been changed. Furthermore, GTC introduced nano-filtration step (after heparin affinity column) to the transferred process. The introduction of nano-filtration required comparability studies that included biochemical tests, pre-clinical, and human pharmacokinetic study in normal volunteers (The results of these studies have been submitted to CBER review during the IND process and/or into this BLA).

Validation Studies

The validation studies for rAT purification process have been conducted at commercial and small scales. The scope and outcome of the validation studies are adequate. GTC submitted data deriving from the following studies:

- Commercial scale validation process performed at --b(4)-- facility
- Small scale developmental studies demonstrating robustness of the manufacturing steps and removal of goat milk proteins
- A side-by-side summary of the biochemical analyses for three batches manufactured at ----b(4)----- facilities

Three consecutive lots of rAT BDS (lots -----b(4)_) have been manufactured at -b(4)-- facility and met current release requirements for BDS. The manufacturing runs for these three lots were subjected to the additional testing for purity, yield, and impurities content. The testing was performed at the level of each unit operation. In addition, GTC performed extended characterization of milk pool and monitored rAT glycosylation throughout the process. The data characterizing manufacturing milk pools and composite samples are acceptable and have been already reviewed in the paragraph of this review concerning qualification of source material and production goats.

Process yield and purity of rAT BDS

The yield of rAT for three conformance lots ranged from -b(4)--- meeting specification for process yield of --b(4)--.

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Table 1. Comparison of hpAT to Antithrombin Alfa

Parameter	hpAT	Antithrombin Alfa
	Serine protease inhibitor (serpin)	Serine protease inhibitor (serpin)
Primary Structure	Single chain of 432 amino acids	Identical single chain of 432 amino acids
	Contains the reactive center Arg 393-Ser 394 which provides a cleavage site for proteinases such as thrombin	Contains the reactive center Arg 393-Ser 394 which provides a cleavage site for proteinases such as thrombin
	Low level of methionine oxidation (Thrombate & Kybermin P)	Level of methionine oxidation comparable to Thrombate & Kybermin P
Secondary Structure	6 cysteine residues forming 3 disulfide bonds (Cys 21-95, Cys 8-128, Cys 247-430)	Same 6 cysteine residues forming 3 disulfide bonds (Cys 21-95 Cys 8-28, Cys 247-430)
	Distinctive far and near UV CD profile	Same near and far CD profile
Glycosylation	4 N-linked glycosylation sites (Asn 96, 135, 155, 192)	4 N-linked glycosylation sites (Asn 96, 135, 155, 192)
	85% to 95% α isoform with four biantennary, mono and di-sialylated oligosaccharide chains	$\geq 80\%$ β -like isoform with biantennary, mono & di-sialylated oligosaccharide chains at three sites with hybrid & high mannose structures at Asn 155 and substitution of some N-acetyl neuraminic acid with N-glycolyl-neuraminic acid
	5% to 15% is the high heparin affinity β -isoform lacking glycosylation at	Also contains the β -isoform lacking glycosylation at Asn 135 (< 20%)

Parameter	hpAT	Antithrombin Alfa
	Asn 135	
	2-6 terminal sialic acid linkage	2-6 terminal sialic acid linkage
Purity	> 95% to 99% pure depending on manufacturer	> 99% pure
Inhibitor Activity	Inhibits thrombin and Factor Xa <i>in vitro</i> inhibition assay	Inhibits thrombin and Factor Xa <i>in vitro</i> inhibition assay
	Specific activity of US licensed Thrombate ~7 IU/mg	Specific activity of ATryn® ~ 7 IU/mg
Heparin Binding Affinity	Binds to heparin, which catalyzes a conformation change & an increase in activity	Binds to heparin, which catalyzes a conformation change & an increase in activity
	Contains 5% to 15% β -isoform with 3-fold to 10-fold higher heparin binding affinity	Contains mainly β -like heparin binding affinity (4-fold higher heparin binding than hpAT α -form) due to glycosylation differences
Antibody Reactivity	Recognized by polyclonal and monoclonal antibodies	Recognized by same polyclonal and monoclonal antibodies

Abbreviations: Asn = asparagine; Arg = arginine; CD = circular dichroism; Cys = cysteine; hpAT = human plasma-derived antithrombin; Ser = serine; US = United States; UV = ultraviolet.

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Control of rAT Bulk Drug Substance – Proposed Specifications

In general, the firm proposed the adequate array of analytical assays to assess the identity, purity, strength, potency, and quality attributes of rAT BDS. The analytical methods and proposed acceptance limits were based on the data obtained from the developmental studies and manufacturing experience of the firm. The acceptance limits were based on mean values and ± 3 Standard Deviation statistical calculation deriving from -b(4)- lots manufactured. The acceptance limits for process related impurities were mainly based on a limit of detection of the assay. The proposed specifications limits were confirmed by the non-clinical and clinical studies. The release data of the three conformance lots are attached below.

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However, based on the heightened biochemical characterization studies and testing performed to characterize three conformance batches of rAT BDS, I requested the

additional data to fully justify the final release specifications proposed by the firm. The details of the discussion with firm regarding BDS specifications are captured in the review of firm's response to CBER IR (Appendix 2). The final ATryn BDS release specifications proposed by GTC are captured in the table attached below and I found them acceptable.

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The validation of the manufacturing process for ATryn FDP and container closure issues are reviewed by Dr. Chiang Syin, Division of Manufacture and Product Quality. A flow diagram for the ATryn FDP manufacturing process is attached below.

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Proposed Final Release Specifications

The action limits for specification analyzes were established based on the data collected from b(4) lots of ATryn® FDP, of which 17 met the pre-set release specifications. These include three conformance lots (-----b(4)-----) manufactured consecutively. Date of manufacture has been on: -----b(4)-----, and ---b(4)-----, respectively. Conformance lot --b(4)----- did not meet release specification failed as a result of out-of-specification results for ----b(4)----- (due to the operator error) and to corresponding result for percent of ---b(4)--- rAT. However, it met the in-process control requirement and remaining final release limit. The tests performed during the release of the conformance batches are presented in the tables attached below.

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Over the course of product development, the additional analytical tests were performed for the release of rAT FDP lots. Lots deriving from the all stages of commercial product development were used in the non-clinical and clinical studies performed by the firm.

Table attached below illustrates the historical development of analytical tests used for release of ATryn® lots manufactured with different manufacturing changes.

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Table attached below lists specifications proposed for the ATryn FDP licensure. The acceptance limits, where applicable, are based on the following three criteria: mean value and plus/minus three standard deviations (data from-b(4)-lots manufactured at commercial scale), established values of the compendial tests, and limit of detection of the assay.

Based on the ATryn FDP characterization and developmental data, I found that initially proposed specification assays were not fully adequate to assess consistency of production and quality attributes of the product. Also, I requested additional data to justify the proposed acceptance limits. The details of discussion concerning the final release specification of ATryn FDP are captured in the review of the firm's response to CBER's IR (Appendix II). I found the modified release specification for ATryn FDP, summarized in the table attached below, as acceptable.

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Description and Composition of the Drug Product

Description and Composition of the Drug Product

ATryn® is a sterile lyophilized powder intended for intravenous infusion following reconstitution with Sterile Water for Injection (WFI). The product is filed into a --b(4)--- glass container and closed with a ----b(4)----- closure. Following lyophilization, the--b(4)-- closure is fully seated and the container is sealed with a -----b(4)----- with a ----b(4)----- cap. WFI recommended for reconstitution is not provided or packaged with the product.

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The details regarding product composition are provided in the table attached below. With the exception of rAT; there are no novel or human derived or animal derived materials added directly to the formulated drug product. The reconstituted product is stable when

stored at ambient room temperature for up to 12 hours, as demonstrated in Stability (3.2.P.8) part of the BLA.

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Stability Studies for ATryn FDP

GTC provided results of the ATryn FDP stability studies performed according to the proposed protocol. The data points, extent of testing, and proposed acceptance limits are acceptable. The studies were conducted at the intended storage temperature 2° – 8°C only i.e. does not fully follow recommendations of the pertinent ICH guidance documents with regards to test in accelerated and stressed conditions. Also, the submitted studies evaluate the stability of product reconstituted in the vial, and product reconstituted, diluted and stored in intravenous infusion syringes and bags. The table attached below illustrates in details a series of studies that were conducted by GTC to assess the stability of ATryn.

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[b(4)]

Primary (real time) stability studies

GTC summarized results of the three long-term stability studies (two ongoing and one completed) performed on ATryn lots that were manufactured by the current process performed at ----b(4)----- facilities.

The ongoing stability study, ---b(4)-----, started at 2005 and includes three conformance lots of FDP. These lots have been filled into the -b(4)- vials with -b(4)----- stoppers -----b(4)------. The submitted data demonstrated that FDP is stable up to 30 months (b(4) time points) at the intended storage temperature 2° – 8°C. The only trend is not significant but steady in the ---b(4)------. The tested values are well below limit of -b(4)- (the values varied from <0.1% to 0.2%) and the effect on quality attributes of ATryn (e.g. level of ---b(4)---) have not been observed. The proposed duration of the study is -b(4)- months.

The second ongoing stability study, --b(4)-----, includes one lot of ATryn (Lot #--b(4)--) that was manufactured from -----b(4)------. The study has been initiated in 2007. The lot was filled into the -b(4)--vials with -b(4)-- stoppers closure.

The unremarkable stability data are provided up to 18 months(b(4)time points)of storage at 2° – 8°C. The proposed duration of the study is 36 months.

The stability study --b(4)----- was completed after period of -b(4)-months of storage at 2° – 8°C. The study was initiated in 2003 and included three lots of ATryn filled into the --b(4)--vial with the --b(4)----- stopper closure. The following-b(4)-test time points were tested: Initial (release results), 3, 6, 9, 12, 18, 24, 30, 36, ---b(4)----- months. The ---b(4)- in ----b(4)----- in the ---b(4)----- (up to 0.5%) was the only notable trend in the submitted data staying within the acceptance limit -b(4)--. However, there are no noticeable effects on product's quality attributes including --b(4)----- of the rAT molecule.

The data submitted by GTC support requested shelf life of the ATryn final product, i.e., stored for 36 months at 2° – 8° C.

Proposed Stability Protocol

The initially proposed stability protocol was deficient in the following:

- Lack the accelerated and stressed conditions, as recommended by the pertinent ICH guidance documents
- Calculation for --b(4)-----
- Description of Appearance after the reconstitution of the product
- The 9 and 30 months testing time points into the stability study performed at 2° – 8°C.

GTC has corrected the aforementioned deficiencies and I found the modified stability protocols for the real time, accelerated, and stressed conditions (the scope of testing is attached in the tables below) acceptable. The acceptance limits for the real time stability study do not differ from those used at product release. GTC commits to place at --b(4)---- --- of ATryn on stability ---b(4)----- basis according to the proposed protocols and at least -b(4)-vials of the product will be tested on the given data point. The post-approval commitments concerning stability studies are attached in the separate paragraph of my review.

Long Term Stability Testing (2°-8°C)

The details of testing are provided in the table attached below.

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Accelerated Studies

The accelerated studies will be performed at --b(4)----- of relative humidity (RH) up to-b(4)-months. The table attached below specifies scope of testing and the proposed time-points. The specification acceptance limits do not differ from those that are used on product release. The accelerated stability studies are part of the stability protocol for ATryn® FDP and constitute post-marketing commitment.

Methods and Testing Schedule, --b(4)----RH

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Stressed-Temperature Excursion Study

GTC proposed to conduct the stressed studies to demonstrate robustness of product versus excursion of temperature. GTC proposed cycling conditions (-----b(4)-----
----- of relative humidity (RH).

The three lots of ATryn FDP (----b(4)----)----- will be placed on the temperature study according to the submitted protocol. The data will be submitted to CBER for review when studies will be finalized. The stressed stability studies that are part of the stability protocol and constitute post-marketing commitment will be performed up to 6 months at --b(4)---- of RH according to the table attached below. The specification limits do not differ from those used on product release.

Methods and Testing Schedule, --b(4)----RH

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Stability Studies for Reconstituted ATryn

Reconstituted ATryn in Plastic Infusion Bags (Stability Protocol SP115)

The study was performed to evaluate stability of ATryn in the proposed handling and dose administration conditions. Each of b(4) vials of ATryn were reconstituted with 10 mL of WFI and transferred to -b(4)- mL infusion bags held --b(4)----- at ambient temperature. The samples were collected at 0, 12, and -b(4)- hours for analyzes.

All samples met the current release specifications for ATryn and additional protocol criteria for visual inspection. Thus, the data support requested time for storage of reconstituted but undiluted drug product that is stored in the infusion bag up to -b(4)- hours at ambient temperature.

Reconstituted and Diluted ATryn in Syringes, Tubing and -b(4)- Infusion Bags (Stability Protocol --b(4)-----)

The purpose of this study was to evaluate the biochemical compatibility of the reconstituted ATryn when diluted with 0.9% sodium chloride to approximately 100 IU/mL and in contact with syringes, tubing and infusion bags. All these devices are made of ---b(4)----- The study samples were collected through an in-line 0.2 µm filter to evaluate the effect of filtration on product quality. Solutions of three different lots were tested during the b(4) hours of storage in the ambient temperature at 0, 8, 12, and b(4) hours. The samples were evaluated by appearance and product release assays. The physico-chemical properties of the product remained unchanged. However, the 5%-10% decrease in the potency (---b(4)----- assay) has been observed after 12 hours of

storage and overall --b(4)--- hours. Therefore, it is recommended that diluted product should be used within 8-12 hours when stored in the IV bags or syringes.

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Stability studies ATryn BDS

A series of real time and accelerated studies have been performed to evaluate stability of Atryn BDS. The formulated BDS is stored as an aseptically filtered -b(4)- solution in sterile -----b(4)----- shipping vessels at -b(4)-. prior fill and finish. The vessel contains -----b(4)-----. The following studies have been performed by GTC:

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The studies were conducted up to -b(4)- weeks at the temperature -b(4)-. In addition accelerated studies were performed at -b(4)- up to -b(4)- weeks. The testing includes analytical methods that are used for BDS release and adequately evaluated product potency and structural properties. -----b(4)-----

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I agree with the firm's conclusion that results of stability studies support storage of the ATryn formulated BDS for a period of-b(4)-days when BDS solution is stored at b(4) in -----b(4)----- to reduce potential for --b(4)--- of rAT molecule. I found proposed protocol for testing and time points, attached below, acceptable. The specification limits do not differ from those used at product release.

Methods and Testing Schedule

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Validation of the analytical assays

Product release assays

The analytical procedures used to evaluate ATryn purity, identity, ---b(4)-----, and safety have been successfully validated by GTC. The validation studies submitted by the firm demonstrate that analytical assays used for the routine release of ATryn BDS and ATryn FDP are suitable for their intended use, i.e. they are adequate to assess quality attributes of product and to confirm consistency of the released lots.

The ---b(4)----- assay (determination of ATryn potency) is a compendial method developed at -----b(4)------. This method was recently used for the qualification of the World Health Organization (WHO) International Potency Standard for AT. To demonstrate equivalency of the method performed at GTC laboratory, the firm validated -b(4)-- assay using standards and controls generated by -b(4)-. The validation of the ----b(4)----- assay included evaluation of repeatability, accuracy, intermediate precision, robustness, and specificity. The presented data satisfied the pre-set validation criteria and are acceptable. Interference from the -----b(4)----- spiked articles was tested. The largest interference with positive biased of 12% was observed by ---b(4)---. The ATryn purification process has been effective in removal of --b(4)---- and its level is controlled by the -b(4)- assay at the release of BDS. However, the discretion should be used when potency is tested on in-process, not fully purified, samples.

Most of the ATryn FDP specification release assays were transferred to the --b(4)---- manufacturing site in The Netherlands. The information concerning results of the transfer is limited but presented scope of the re-validation studies at --b(4)---- site is adequate.

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The ---b(4)----- assays

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Adventitious Agents Safety Evaluation

GTC applied a similar approach to the risk assessment for adventitious agent contamination that has been applied to the other products manufactured by the recombinant DNA technology, e.g. mammalian cell culture in the bioreactor. The following risk minimization factors for the rAT manufacturing process have been introduced:

1. General measures at GTC farm
2. Materials of non-animal origin used in rAT goats
3. Materials of biological origin
4. Viruses
5. Transmissible Spongiform Encephalopathy

The firm implemented a variety of general agent risk minimization measures for initial selection of farm site, sourcing of goats from US and New Zealand and maintenance of the biosecurity of the goat herd and their environment. The measures implemented by GTC to control safety of goat herd and its health were reviewed by Dr. Philip Snoy from CBER's Veterinary Services. This review concentrates on the control of adventitious agents in source material (milk) and measures mitigating risk of contamination of ATryn FDP.

There are several potential routes of non-animal adventitious agent introduction to the transgenic goats (feed materials, drinking water, semen, and medicinal agents). GTC implemented adequate measures to minimize the risk of these agents to the goats and their milk/source material for ATryn purification. Testing for levels of adventitious agents such herbicides, pesticides, and aflatoxin is performed on feedstuffs to ensure their compliance with US FDA recommendations for safe levels of these agents. Animals are maintained in semi-confined environment to minimize risk of uncontrolled digestion. Water is obtained from on-site wells that meet requirements of water for human consumption with regards to the presence of coliforms, heavy metals, pesticides, chemicals, and trace materials. If production goat is given antibiotics, then its source material must be tested to verify the absence of antibiotic residue before collection for use resumes.

Materials of biological origins used on farm or in the purification process (heparin) were selected and assessed for potential contamination by adventitious agents. The veterinary products used for goats care (vaccines, hormones, pharmaceuticals, etc) were selected to minimize use of animal-derived components.

The -b(4)- Heparin ----b(4)----- resin used for rAT purification contains Heparin -b(4)--- USP that originated from ---b(4)----- . The production process of heparin contains harsh steps that were validated for virus removal. In addition, GTC provided additional documentation regarding source and manufacture of heparin minimizing risk of additional, non-infectious, contaminants of heparin products.

Viruses

For the production of ATryn risk of viral contamination is mitigated at the level of the goat (reviewed by Dr. Philip Snoy), starting material (milk), and the clearance capacity of the purification process.

The milk pool before entering the purification process is screened for the presence of adventitious viruses using conventional in vitro cell line screening methodology. The current validated in vitro cell line viral screening protocol includes assessments for cythopatic effect, hemadsorption, and hemagglutination with various red cells and specific immunofluorescence assay for five presumably zoonotic viruses. The control cell lines are: MRC-5, Vero, BHK-21, and Goat Turbinate. The lines their detailed sensitivities with regards to known viruses are provided in the table attached below. The assays were validated for goat milk and rAT interference. The set of positive viral controls is adequate. Up to now, in all cases of the screened milk pools, adventitious agents were not detected.

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Validation of viral clearance by the manufacturing process

Virus inactivation/removal studies were performed on a scaled-down version of the rAT manufacturing steps. GTC followed recommendations of the pertinent ICH Q5A guidance document. The five steps examined for virus reduction included the three chromatographic purification steps, the initial 500 kDa pore size ---b(4)----- step, and dedicated to viral removal the nanofiltration step. The terminal dry heat treatment of ATryn FDP was also evaluated for viral inactivation. The chromatography steps include an affinity step (Heparin HyperD), an anion-exchange step (ANX-Sepharose), and -b(4)- hydrophobic interaction (Methyl-HyperD) chromatography. Additionally, the 500kDa membranes and chromatography columns were cycled at small scale to support the lifetime study.

The following viral validation reports were submitted by GTC for the review.

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The scaled down studies were performed with samples of starting material and intermediates obtained from the commercial scale process. The 500 kDa --b(4)---- step was performed in a ---b(4)----- matching the original purification process. The robustness of the scaled down nanofiltration step was verified by changes in the -b(4)----- and ----b(4)----- . The scaled-down chromatography columns maintained the same -----b(4)-----, and the same -----b(4)----- as are used at the commercial scale.

All process load solutions and elution buffers were tested for ----b(4)--- on each of the --b(4)-- used in the viral infectivity assays. The viral titer calculated based on the results of infectivity assays and log reduction achieved for each process step was calculated according to the requirements of the guidance documents. The final step in ATryn manufacturing process is dry heat treatment of the lyophilized product at -b(4)----- for -b(4)- hours in a --b(4)----. GTC presented data that include ---b(4)-----, ----b(4)----- . The results captured in the table attached include the worst case scenario for the terminal heat treatment studies.

[b(4)]

As indicated in the attached table, GTC performed only one study (one experimental run) for Polio Virus and Mouse Adenovirus. Furthermore, VirA/Gard 500-kDa and -b(4)-reduction steps are based on the same mechanism of viral removal and cannot be considered as an orthogonal step. Thus, the referenced clearance values cannot be claimed by GTC on the product circular. Please note, that the final viral clearance include one more step that that is dedicated to the inactivation of viruses, i.e. heat treatment for -b(4)- for-b(4)-hours. The table that summarizes capacity of the ATryn manufacturing process to clear viruses is attached below. (As already indicated above, GTC can claim only one filtration step and values for Polio Virus and Mouse Adenovirus cannot be used in the ATryn circular).

Table 1. Cumulative Log₁₀ Reduction of Viruses by the ATryn Process

Process Step	Pseudorabies Virus	Xenotropic Murine Retrovirus	Human Adeno-virus	Porcine Parvo-virus	Polio Virus	Mouse Adeno-virus
VirA/Gard 500-kD	≥ 5.1	≥ 3.7	≥ 5.3	1.7	4.1	3.5
Heparin HyperD	1.6	1.2	N/A	1.4	4.0	2.3
Nanofiltration	≥ 2.9	≥ 3.8	≥ 6.3	3.7	ND	ND
ANX-Sepharose	3.6	1.0	≥ 7.1	N/A	2.4	N/A
Methyl HyperD	≥ 5.6	≥ 4.4	≥ 4.8	≥ 5.7	≥ 5.0	≥ 2.7
Heat Treatment	2.8	≥ 5.0	1.8	2.4	≥ 1.9	ND
Total Reduction	≥ 21.6	≥ 19.1	≥ 25.3	≥ 14.9	≥ 17.4	≥ 8.5

ND = Not Determined

N/A = not applicable since the reduction was below 1 log₁₀

-----b(4)-----
 -----.

[b(4)]

Lifetime studies on the filtration membranes and purification columns

The attached below table shows number of cycles completed by the tested purification steps and proposed number of cycles to replacement of the membrane/resin during the manufacture of ATryn. A comparison of the new and used media demonstrated that

recovery, purity and chromatograms shape were comparable. The recycled materials were also evaluated for their ability to remove spiked viruses. The proposed numbers of production runs (cycles) are acceptable, i.e. GTC will replace the membranes and resins prior to the number of cycles successfully completed at small scale studies and are supported by the viral validation data.

[b(4)]

Model Virus choices

The selection of viral panel used in the validation study is acceptable. The selection included enveloped and non-enveloped, large and small, inactivation sensitive and resistant, and DNA and RNA viruses. This assures robustness of the viral clearance demonstrated for ATryn purification process. For example, pseudorabies virus is a relevant virus and also model virus for caprine herpes virus.

[b(4)]

[b(4)]

Conclusion

Using the formula provided by the ICH Q5A guidance document, GTC provided hypothetical estimate of viral particles per ATryn dose. The CAEV retrovirus is the most prevalent virus known to be transmitted by goat's milk. Estimating CAEV titer in the milk, capacity to remove retroviruses by the purification process, and ATryn daily dose, less than 1 particle per billion doses would be expected.

Considering veterinary control of the goat herd, monitoring of milk donations and purification pools for the absence of viruses, and validated viral removal rates by the manufacturing process, it can be concluded that GTC implemented adequate measures to mitigate risk of potential contamination of ATryn FDP with the adventitious viral agents.

Transmissible Spongiform Encephalopathy (TSE)

The TSE of goats and sheep is scrapie and causative agent is referred as prion. GTC has implemented a comprehensive risk assessment that includes: monitoring goat health, selection of "ruminant free" farm location, controlled feed, and importing animals from New Zealand to form USDA certified scrapie-free goat herd. (The risk mitigation program regarding scrapie infection at goat/farm level has been reviewed by Dr. Philip Snoy). In addition, milk is evaluated as safe with respect to TSE transmission (Category IV – no detectable infectivity) (*Report of a WHO Consultation on Medicinal and other Products in Relation to Human and Animal Transmissible Spongiform Encephalopathies*). The most recent literature indicates that there is a theoretical risk of the transmission of scrapie from ewe to lamb via milk or colostrum in the experimental setting using sheep model that is susceptible to prion protein. However, the prion agent has not been found in milk and the practical/clinical relevance of this finding has not yet been established. The prevalence of scrapie infection in national flocks is close to zero at present.

Furthermore, GTC submitted data demonstrating removal of scrapie agent by ATryn purification process. The four purification steps have been validated for prion removal- 500kDa filtration/--b(4)----- membrane, heparin affinity column, anion exchange chromatography, and hydrophobic interaction chromatography. The final log reduction values are submitted in the table attached below. Although the nanofilter has not been validated, the ≥ 2.8 log of prion removal has been reported in the literature for this type of filtration. Although GTC claims in materials submitted into BLA the cumulative reduction factor for scrapie agent this value, following the current FDA thinking, will not be claimed on the product circular.

Table 23. Scrapie Reduction by the Antithrombin Alfa Purification Process

Step	Unit Operation	Log ₁₀ Reduction
1	Tangential flow filtration	2.0
2	Affinity chromatography	2.2
4	Anion exchange chromatography	≥ 3.3
5	Hydrophobic interaction chromatography	≥ 3.8
	Cumulative Reduction	≥ 11.3

The model TSE chosen for GTC study was a -b(4)-adapted scrapie agent strain -b(4)- which was originally isolated from natural infection in --b(4)----- . Since goat scrapie infections in the US are extremely rare and in all cases are likely due to infection with the -b(4)- scrapie agent, this experimental approach is acceptable. The control experiments demonstrated lack of effect of rAT and buffers on the outcome of the infectivity assay. Scrapied -b(4)- brain homogenates (10% w/v) were prepared and diluted with process samples --b(4)----- For chromatography columns and 500 kDa tangential flow filtration the pool volumes (mass distribution) was estimated by the measurement of scrapie titers. The critical operational parameters for the tested operation units at small-scale were comparable to these on commercial scale.

Inoculation of the diluted controls or process samples was by intracerebral injection of 30 µl into ----b(4)-----, which were then monitored for clinical changes. At 9 to 10 months, initial mortality results were obtained and at 14 to 16 months, surviving animals were killed and their brains histopathologically analyzed for signs of scrapie lesions. Scrapie titers were determined using an -b(4)- calculation by the method of --b(4)----. The studies were performed by -----b(4)----- . The submitted data are acceptable.

In addition, GTC calculated the theoretical particles of scrapie per ATryn dose following recommendation of the ICH Q5A guidance (worst case scenario). Considering presence of scrapie agent in the milk at the level of -b(4)-of infectious units,-b(4)-log clearance factor, and-b(4)-/day dose of ATryn, it would be less than one scrapie agent per ~ 500,000 doses.

Conclusion

The risk of transmission of any zoonotic disease through the medicinal products derived from animal sources is a legitimate concern. But, considering the aforementioned preventive measures implemented by GTC and our current knowledge about risk associated with the use of goat milk as starting material for ATryn purification, I agree with the firm's statement that ATryn has extremely low risk of transmitting any TSE agent.

Recommendation

The review committee found the information submitted to this BLA supports the safety, potency, and efficacy of ATryn® and recommends the approval of this BLA, with the following post-marketing commitments.

Post-Marketing Commitments

1. -----b(4)-----

-----.

2. -----b(4)-----

-----.

-----b(4)-----: --b(4)--

3. -----b(4)-----

-----.

4. -----b(4)-----
-----.

-----b(4)-----: ---b(4)---.

5. -----b(4)-----
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-----b(4)-----: --b(4)--

-----b(4)-----: --b(4)---.

Appendix I

Information Request (IR) and review of GTC's responses regarding control of herd of transgenic goats and starting material (goat milk)

1. Regarding --b(4)-- stability, please provide:

- a. Information about -----b(4)----- expression of the rAT transgene in the transgenic goats.

Firm's response:

No direct studies have been performed on -----b(4)----- expression of the rAT transgene in the transgenic goats. But the firm provided results of the developmental studies that included expression pattern in goats of the ----b(4)-----

-----.

There is no evidence that health of transgenic goats producing rAT is compromised by the expression of rAT. In addition to the aforementioned developmental studies, GTC submitted measurements of the rAT level in the blood stream of the production goats. Two experimental techniques were used - -----b(4)-----

-----.

I found GTC's response acceptable.

- b. Information confirming that DNA sequencing of the rAT transgene coding region was performed for ----b(4)----- of goats qualified for the production sub-group. If the sequencing has not been performed, please provide DNA sequence representative of the last generation of goats that are currently used in the manufacture of rAT.

Firm's response:

The firm pointed out that in order to qualify to the production herd goats have to pass stringent criteria that include assessment of -b(4)- stability. Testing include transgene

-----b(4)-----.

Furthermore, the milk pools entering purification process are tested for the levels of rAT and release specification of the Atryn BDS that include -b(4)- assessing ---b(4)-----.

Thus the -b(4)- stability (---b(4)-----) of the goats deriving from the growing number of generations is directly and indirectly controlled by the manufacturing process. There were no goat, milk, or product batch rejected because of the failure of the testing related to the --b(4)-- stability of transgene. Up to now, milk deriving from the -b(4)- generations of goats has been used in the manufacture of ATryn. The contribution of the-b(4)-generation of goats is limited to 2007 and ---b(4)----- of the milk production pool. The firm submitted acceptable transgene sequencing data through the -b(4)- generation of the production goats. The samples from the -b(4)- generation and additional animals of -b(4)- generation are currently being sequenced by the firm (the final data are not yet available for review). This issue has been discussed with the company during telecon held on December 5th, 2008. GTC representatives agreed with the reviewer recommendations that the rAT -b(4)- stability program should include periodical confirmation of DNA sequence that should be specified in the pertinent SOP. On December 16th, 2008 the firm committed that DNA from at least-b(4)-production animals of -b(4)- generation will sequence to confirm fidelity of rAT DNA sequence. The -b(4)--- Stability protocol and SOP defining sequencing methodology will be available during the first bi-annual cGMP inspection of the GTC facility.

I found response provided by GTC adequate.

2. Regarding qualification of production goats and milk pools,

- a. Please establish in-process limits specifying the maximum duration of lactation and number of lactations per animal that is allowed in the manufacture of rAT. Alternatively, please submit data to demonstrate that your source material, milk, is suitable for the manufacture of rAT regardless of the duration of lactation and number of lactations for each production animal.

Firm's response:

GTC accumulated data from over -b(4)-lactations of rAT goats which is supportive of the company's conclusion that source material/milk is suitable for use in manufacture regardless of the duration of lactation or number of lactation. The highest number of lactations from one animal whose milk is used in ATryn production is -b(4)-. The ---b(4)-----rAT has been monitored and an array of milk proteins has been monitored across both the duration of lactation and a number of lactation for numerous animals. A ----b(4)----- method for quantitating goat milk proteins was used to

additional data demonstrating that level of rAT remains constant throughout many tested lactations. In addition, milk pools are controlled for rAT levels and have to meet the acceptance criteria before entering purification process.

3. Regarding specification limits for composite milk pools:

- a. Please provide justifications for the specification limit of -b(4)- for --b(4)---- while the highest observed level of --b(4)----- in the composite milk pools was -b(4)-.

Firm's response:

GTC stated that the justification for the specification limit of -b(4)- for --b(4)----- is based on the -b(4)- of the manufacturing history for ATryn program, which used -b(4)---- ----- pooling strategies and testing/sampling paradigms. Using the current milk pooling paradigm, the highest observed concentration of --b(4)----- in relation to the other tested proteins. The manufacturing experience and process validation data demonstrate that up to ---b(4)----- is sufficiently removed by the purification process. Following the discussion between this reviewer and GTC representatives hold on December 5th, 2008 the firm proposed a new limit for --b(4)----- that is based on values of -b(4)- milk pools and truly represents the current pooling strategy. The revised limit provided by GTC is acceptable.

- b. Please revise the specification for---b(4)----- based on your manufacturing experience. In addition, please provide the following:

Firm's response:

GTC responded that goat herd is primarily composed from --b(4)-----, and --b(4)--- cross-breeds. Due to the allelic variation of the--b(4)--- gene a significant variation in--b(4)--protein concentration is observed in the milk. There are -b(4)- allelic variations giving rise to -b(4)- classes of--b(4)--expression levels (varying on average from --b(4)-- grams per litter). The study of--b(4)---expression in the collected milk supported by the genetic characterization of the goats demonstrated that the GTC herd is mainly composed of animals that are of the -b(4)---- that secrete very low levels of --b(4)---or do not secrete it at all. However, in the history of ATryn manufacture, few animals expressed up to ---b(4)----- . According to the firm, the acceptance limit of -b(4)--- reflects on true manufacturing history of ATryn but was introduced before implementation of the current milk pooling paradigm (presented in the BLA). Subsequently, following the telecon held with GTC representatives on December 05, 2008, the company re-analyzed data collected from the milk pools composed only by the current paradigm. The revision of the data indicates that no--b(4)-----was detected. Thus, to better represent the current manufacturing process, GTC proposed a new acceptance limit for--b(4)---content: ----b(4)----- I agree with the proposed revision.

- Data demonstrating that rAT batches used in the clinical studies were manufactured using composite milk pools containing---b(4)--

Firm's response:

Measurement of--b(4)----content in the milk of individual goat or pools has been introduced in the late clinical development, in the time of implementation of pooling and testing paradigm. However, most of the animals do not secrete or secrete very little of -b(4)----- . Thus it is rightly presumed by GTC that no or trace amount of--b(4)----- would be detected in the milk pools entering purification stream.

- Data demonstrating clearance of--b(4)--- by the purification process of rAT

Firm's response:

GTC stated that ---b(4)----- goat (dominant in ATryn herd) produced the “dirtiest” quality milk, i.e. rich in cell debris resulting from atypical apocrine secretion. Thus the ATryn purification process has been designed and validated based on the worst case scenario with regards to milk impurities. The data on the clearance of--b(4)----by the rAT purification process was inadvertently omitted from the original BLA submission. The data provided by GTC in response to IR demonstrate that clearance of -b(4)-- by the ATryn purification process has been effectively validated. Utilizing --b(4)----- antibodies against -----b(4)----- protein -b(4)-- log of clearance has been demonstrated by --b(4)-- technique.

- Data showing that the assay for ---b(4)----- proteins in rAT drug substance is validated for the detection of--b(4)--

Firm's response:

The firm responded that the individual constituents of the -----b(4)----- (CGMP) antigen used to produce the --b(4)----- antibodies used in CGMP -b(4)--- were verified by ---b(4)----- . The results confirmed presence of--b(4)----- among the tested antigens. Also the -b(4)-- blot performed with the individually purified goat milk proteins detected by the CGMP assay antibodies confirmed that--b(4)---- antigen is captured by the assay. The identity of individual goat milk proteins were also confirmed by ----b(4)----- acid sequence. The response provided by GTC is satisfactory.

Appendix II

Information Request (IR) and GTC responses

1. Regarding the Proposed Specification for the Bulk Drug Substance (BDS):

a. Please retain your established acceptance limits for the following parameters

i) ---b(4)-----

Firm's response:

GTC provided additional validation data demonstrating removal of ---b(4)--- up to-b(4)-logs by the current purification process. The data were obtained from the studies of-b(4)-lots of ATryn BDS manufactured at commercial scale. The levels of-b(4)--content in BDS did not ----b(4)----- that is equivalent of --b(4)--per dose (i.e. significantly below the current recommendation of guidance documents). Thus I agree with the firm rationale to discontinue the routine release measurements of the -b(4)-content in ATryn BDS. The firm will have to re-validate -b(4)- clearance if any major change will be introduced to the ATryn purification steps.

ii) -----b(4)----- Composition

Firm's response:

The firm provided additional data demonstrating that the ---b(4)----- assay is variable and does not provide an accurate measurement of --b(4)-- content of the tested -b(4)--. The firm pointed out that -----b(4)----- map, assay routinely used for ATryn release, is a much better indicator of the consistency of ---b(4)----- . In addition, two other BDS release assays, -----b(4)----- Content and --b(4)-----, are sensitive indicators of the potential variation in the -b(4)- content and its implication on ATryn *in vivo* efficacy and safety profile. During the teleconference with GTC held on December 5th, 2008, this reviewer agreed with the firm that ---b(4)----- composition release test will not add value to the assessment of ATryn manufacturing consistency. However, it was agreed that the -----b(4)----- test will be performed to release ATryn final drug product. This will additionally ensure its structural consistency.

b. In addition to -----b(4)----- content, please also establish acceptance limits for the two detected species of -----b(4)-----.

Firm's response:

Following the FDA request, the firm agreed to add acceptance limits for the two detected species of -----b(4)----- . The firm provided additional data to justify the proposed acceptance limits: -----b(4)----- . The specification limit for -b(4)- will be -b(4)-

Since the -b(4)- type of ---b(4)----- is not naturally synthesized by humans, GTC provided additionally requested data demonstrating that ATryn with as much as 56% of -b(4)- has been successfully used in the clinical trials.

The response provided by GTC is acceptable.

- c. Please retain your specification for the content of the --b(4)--- form of rAT expressed as ---b(4)----- measured by the --b(4)-- assay.

Firm's response:

The firm responded that the --b(4)--- assay was originally intended to provide a measure of rAT -b(4)- be determining the --b(4)----- of rAT -----b(4)----- compared to -----b(4)----- . The assay output was later adapted to analyze the -b(4)----- form. It seems that the level of --b(4)--- of rAT does not affect its *in vitro* potency. The firm pointed out that value of limit for the ---b(4)----- form reflects a simple arithmetic calculation - if sample meets criteria for --b(4)---, and for -b(4)- for -b(4)- form, the --b(4)----- form equals -b(4)-. Thus, I agree with the firm's statement that a percent of --b(4)----- specification limit would be removal of simply repetitive and of no clear scientific value.

- d. Please establish an acceptance limit for --b(4)----, based on the ratio of the Potency and Strength of rAT.

Firm's response:

The firm set the specification limit for -----b(4)----- based on the calculated data from-b(4)-lots of drug substance. The specification limits have been based on the mean -b(4)- standard deviations.
The response is acceptable.

- e. Please establish a criterion for visual inspection of the BDS solution that includes assessment of color and clarity.

Firm's response:

The firm proposed specification for color and appearance, i.e. lots of ATryn BDS must conform to the specification of: clear or slightly turbid colorless solution. This is acceptable.

2. Regarding the Proposed Specification for the Final Drug Product (FDP):

- a. Please retain your specification for the content of the --b(4)-- form of rAT expressed as ---b(4)----- Purity measured by the -b(4)- assay.

Firm's response:

The firm's response regarding assessing -b(4)- of ATryn BDS is applicable here. For details please see above.

- b. Please retain your established acceptance criteria assessing the heterogeneity of rAT by ----b(4)-----.

Firm's response:

The firm will retain the ----b(4)----- assay for the routine release for ATryn FDP. The acceptance limits, i.e. -----b(4)-----
-----b(4)-----, The submitted data support the proposed specification ensuring product consistency.

- c. Please establish an acceptance limit for ----b(4)-----, based on the ratio of ----b(4)--- and ---b(4)---- of rAT.

Firm's response:

The firm proposed acceptance limit that have been used for the release of conformance lots of ATryn FDP, i.e. --b(4)----- . Since the limits are based on the current manufacturing experience, I found them acceptable.

- d. Please establish a criterion for the visual inspection of the FDP solution after reconstitution that includes assessment of its color and clarity.

Firm's response:

The firm proposed acceptable criterion descriptive of color and appearance for final release of the rAT FDP, i.e. product post reconstitution must conform to the specification of: clear or slightly turbid colorless solution.

- e. Please establish the ---b(4)----- specification with respect to ATryn® potency.

Firm's response:

GTC provided additional validation data for ---b(4)----- testing that are based on the measurements of ----b(4)----- of ATryn vials. The additional data alleviated my initial concerns regarding insufficient information regarding --b(4)---- of the filled vials and necessity for its routine testing at ATryn release. As, pointed out during the discussion with the firm on December 5th, 2008, this matter will be further evaluated by the FDA during the first cGMP inspection.

3. Regarding the chromatogram from the ---b(4)---- assay, please identify the proteins eluted in the -----b(4)----- peak.

Firm's response:

The response to this question is acceptable, i.e. the eluted proteins are rAT --b(4)---, as demonstrated by the results of additional experiments submitted by GTC. The levels of -----b(4)----- is captured by the FDP release specifications.

4. Please follow the CBER convention for non-proprietary names of blood products. For example, the non-proprietary name for plasma-derived Antithrombin III product is *Antithrombin III (Human)*. Therefore, please use *Antithrombin III (Recombinant)* as the non-proprietary name for your product.

Firm's response:

During discussion with the firm on December 5th, 2008, and considering nomenclature currently proposed by Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis, CBER proposed that the non-proprietary name for ATryn in the United States will be: Antithrombin (Recombinant), without the roman numeral III. The firm agreed.