SUMMARY FOR BASIS OF APPROVAL

PLA # 95-0041
Applicant: CYTOGEN
600 College Road East
Princeton, NJ 08540
Manufacturer: CYTOGEN
600 College Road East
Princeton, NJ 08540

USAN name: Capromab Pendetide
Trade name: ProstaScint

Common Name: 7E11-C5, CYT-356

I. HISTORY AND PROPERTIES OF THE PRODUCT

In 1987, Horoszewicz *et al* developed a murine $IgG_{1\kappa}$ monoclonal antibody, designated 7E11-C5. This antibody is secreted by a hybridoma cell line produced by fusing P3x63Ag8.653 myeloma cells with spleen cells from BALB/c mice immunized with whole cells and membrane extracts of the human prostate adenocarcinoma cell line LNCaP. 7E11-C5 reacts with a tumor-associated protein, known as prostate-specific membrane antigen (PSMA), which is specific for normal and neoplastic prostate cells. PSMA is a membrane glycoprotein of a molecular weight of 100,000 Daltons. Part of the PSMA antigen has a 54% homology with the transferrin receptor. Recently, more important structural and functional homology has been found with a N-acetylated α-linked acidic dipeptidase involved in the activity of glutamatergic neurons. The antigenic epitope recognized by CYT-351 is located in the cytoplasmic domain of PSMA. Immunoelectron microscopy localized the antigenic epitope to both the internal region of the plasma membrane and certain cytoplasmic organelles. Recent data suggest that hormone ablation therapy either has no effect or upregulates PSMA expression.

7E11-C5 was renamed CYT-351 by CYTOGEN. An immunoconjugate was prepared by site specific modification of the carbohydrate groups of CYT-351 and covalent binding to the tripeptide linker chelator glycyl-tyrosyl-(N-ε-diethylenetriaminopentaacetic acid)-lysine hydrochloride (GYK-DTPA-HCl. CYT-063). The resultant immunoconjugate was designated CYT-356. The USAN name for CYT-356 is Capromab Pendetide. CYT-356 has been given the trade name ProstaScint™. This nomenclature is summarized below:

Basic Nomenclature

Designation	Description
7E11-C5	Original Name of MoAb Developed by Horoszewicz *et al*
CYT-351	CYTOGEN's Designated Name for 7E11-C5
CYT-063	Tripeptide Linker-Chelator (GYK-DTPA·HCl)
CYT-356	Immunoconjugate of CYT-351 & CYT-063
Capromab Pendetide	USAN Name for CYT-356
ProstaScint™	Trade Name for Capromab Pendetide (CYT-356)

In *in vitro* preclinical studies, CYT-351 demonstrated reactivity with 90-100% of primary and metastatic prostatic carcinoma cell lines tested. The antibody did not show reactivity with the following cell lines: breast, colon, lung, kidney, or bladder carcinomas, lymphoma, melanoma, or sarcoma. Some cross-reactivity with normal skeletal muscle, heart muscle, kidney proximal tubule, and skin was observed. However, the reactivity of both CYT-351 and CYT-356 was greatest with prostatic malignancy, followed by benign prostatic hypertrophy, and then normal prostate.

In vivo preclinical studies demonstrated localization of In-111-labeled-CYT-356 to LNCaP prostatic carcinoma xenografts in nude mice. The optimal tumor images were observed between 2-7 days post-injection. The uptake of In-111-CYT-356 was tumor specific. Approximately 6-10% of the administered dose was taken up by the liver. In studies in non-tumor bearing mice, In-111-CYT-356 distributed uniformly to lung, liver, spleen, and kidney, accumulating to a lesser degree in the testes and skeletal muscle. In PK studies in *Cynomolgus* monkeys, the mean half-life of In-111-CYT-356 was 44½ hours (range 32-47 hours), with a volume of distribution of 57-83 ml/kg. Administration of In-111-CYT-356 did not appear to have any adverse effects on any of the animals.

A limited series of toxicity studies were conducted to investigate the safety of CYT-356. Using the intravenous route of injection, single and repeat dose toxicity studies were performed using the rat and rabbit. No clinically relevant toxicities were observed.

II. Indications and Usage

Capromab Pendetide-In is a diagnostic imaging agent indicated for use in high-risk patients with biopsy-proven prostate cancer in whom there is a high clinical suspicion of occult metastatic disease and a negative or equivocal standard staging evaluation. Capromab Pendetide is not indicated in patients who are not at high risk for recurrent and/or metastatic prostate cancer. The information provided by Capromab Pendetide-In scanning should be considered in conjunction with other diagnostic information. Therapeutic decisions should not be based on the Capromab Pendetide-In scan without histological confirmation. Bone scans are more sensitive than Capromab Pendetide for the detections of metastasis to bone, and Capromab Pendetide-In should not replace bone scan for the evaluation of skeletal metastases. Capromab Pendetide may be safely re-administered (e.g., following infiltration of the infusion or a technically inadequate scan); however it is not indicated for repeat administration for the purpose of comparison of the Capromab Pendetide images.

Capromab Pendetide-In should not be used in patients who are hypersensitive to this or any other product of murine origin or to In-111 chloride.

III. Dosage Form, Route of Administration an Recommended Usage

Each Capromab Pendetide kit contains, in two vials, all of the non-radioactive ingredients necessary to produce a single unit dose of Capromab Pendetide-In, an immunoscintigraphic agent for administration only by intravenous injection. A single-dose vial of Capromab Pendetide, contains 0.5 mg of Capromab Pendetide in 1 ml of sodium phosphate buffered saline solution adjusted to pH 6. Capromab Pendetide is sterile, pyrogen-free, clear, colorless and may contain some translucent particles. A vial of sodium acetate buffer contains 82 mg of sodium acetate in

2 ml of water for Injection adjusted to pH 5-7 with glacial acetic acid; it is sterile, pyrogen-free, clear, and colorless. Neither solution contains a preservative.

In accordance with the directions provided, the sodium acetate solution must be added to the In-111 chloride solution to buffer it prior to radiolabeling Capromab Pendetide. After radiolabeling with In-111, the immunoscintigraphic agent In-111-Capromab Pendetide is formed.

Each kit also includes one sterile 0.22 µm Millex® GV filter, prescribing information, and two identification labels.

The recommended dose of Capromab Pendetide is 0.5 mg radiolabeled with 5 mCi of In-111 chloride. Each dose is administered intravenously over 5 minutes and should not be mixed with any other medication during its administration. The patient dose of the radiolabel should be measured in a dose calibrator prior to administration.

Each Capromab Pendetide kit is a unit dose package. After radiolabeling with In-111, the entire Capromab Pendetide-In dose should be administered to the patient. Reducing the dose of either component may adversely impact imaging results and is, therefore, not recommended.

The maximum amount of Capromab Pendetide that can be safely administered has not been determined. In clinical studies, single doses of 10 mg of Capromab Pendetide-In were administered to 20 patients with prostate cancer; the type and frequency of adverse reactions at this dose were similar to those observed with lower doses.

IV. MANUFACTURING AND CONTROLS

IV.A. Manufacturing of CYT-351.

IV.A.1. Cell Banks.

Master and Manufacturer's Working Cell Banks (MCB &MWCB) were established following the "Points to Consider in the Characterization of Cell Lines Used for the Production of Biologicals." Cell banks are free from microbial, fungal and adventitious viral contamination.

IV.A.2. Clonal Identity of the Serum-Free Cell Banks.

To demonstrate clonal identity of the serum-free cell banks, CYT-351 cells from the serum-free MWCB and from a Post-Production cell bank prepared from a full scale CYT-351 manufacturing run were cloned at strict limiting dilution and assayed for IgG production and production of immunoreactive CYT-351. Seventy per cent of the clones obtained from the MWCB produced immunoreactive CYT-351 antibody. Clones producing nonspecific antibodies were not detected. Seventy-three per cent of the clones obtained from the Post Production cell bank produced immunoreactive CYT-351. One clone (0.3%) producing a nonspecific antibody was detected. These results demonstrate the clonal identity of the serum-free CYT-351 cell banks and validate the stability of the MWCB.

IV.B. Production of CYT-351.

The monoclonal antibody CYT-351 was originally manufactured by [redacted]. Subsequently, Cytogen manufactured the antibody using two different protocols (called B and C). Process C is used commercially. The three processes that have been used for the manufacturing of this antibody are detailed below:

[redacted]

IV.B.2 Cytogen Process B

Three lots were produced by using the [redacted] bioreactor system fitted with [redacted] bioreactor cores. Cells from the Cytogen serum adapted MWCB were thawed and expanded in DMEM/NCTC medium supplemented with calf serum and weaned into serum-free DMEM/NCTC/Biotin production medium. Note that the serum-free MCB was not derived from cloning of serum-free adapted cells. Purification of the antibody involved sequential chromatography in Protein A, DEAE-Sepharose, and S-Sepharose columns.

IV.B.3. Cytogen Process C (Commercial Process).

In this process, Cytogen uses an [redacted] bioreactor, fitted with six hollow fiber bioreactor cartridges. This process used cells from a serum-free MCB generated by Cytogen. Serum-free CMM-1 (Cytogen) was used as production medium. Two sequential harvests were collected from this run and the antibody was purified separately, to prove harvest to harvest consistency. The antibody was purified by using a four-step chromatography process that involved chromatography on Sephadex G-25, Protein A, DEAE-Sepharose, and S-Sepharose column.

IV.B.4. Equivalence of CYT-351 produced at Cytogen [redacted]

Six lots of Cytogen 351 and [redacted] CYT-351 were produced. The tests used to demonstrate equivalence of the purified antibodies included: Electrophoretic Mobility, Isoelectric Focusing, Immunoreactivity, Binding Affinity, Monosaccharide analysis, Oligosaccharide analysis, Isotype, Monomer content, Appearance, Protein concentration and pH. The results of these tests demonstrated the equivalence of the antibodies produced by the three processes, despite the production medium or the bioreactor technology used. Pharmacokinetics based comparisons in humans of CYT-356 from different manufacturing processes did not reveal any significant differences.

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IV.B.5. CYT-351 Production.

Cells are grown in a serum free medium formulated
CYT-351 is produced by expanding a vial of the MWCB to create the inoculum for the bioreactor. Cells are maintained in stable culture conditions of temperature, oxygen, pH, medium fed and harvest. Harvested medium is clarified by filtration and stored at 2-8ºC. CYT-351 production runs are in the bioreactor typically for 60 days. Harvests are periodically checked for antibody titer, endotoxin, bioburden, and immunoreactivity. Prior to purification, pooled harvest samples are tested for antibody concentration, mycoplasma, sterility, and virus by reverse transcriptase, XC plaque, and S+L- Focus and other *in vitro* viral testing.

IV.B.6. CYT-351 Purification.

CYT-351 is purified in a multi step column chromatography carried out in a closed chromatography system at room temperature. pH, conductivity and protein concentration are monitored through the purification process.

The purification is performed in six steps:

Step 1: Filtration, clarification and concentration of pooled harvests.

Step 2: Gel filtration chromatography in Sephadex G-25.

Step 3: Affinity chromatography on Protein A.

Step 4: Anion Exchange chromatography on DEAE-Sepharose.

Step 5: Cation Exchange chromatography on S-Sepharose.

Step 6: Filtration though a .22 µM filter.

After this step the antibody is sampled and stored at 2-8ºC until release.

A CYT-351 Standard was established from CYT-351 batch C2K0537AP. The evaluation with the following tests determined the acceptability as standard: immunoreactivity, electrophoretic mobility, isoelectric focusing, monomer content, N-terminal amino sequence, isotype and appearance. CYT-351 is characterized for potency, purity and freedom from process contaminants and adventitious agents by different assays, including: S+L- Focus assay, XC plaque assay (ecotropic viruses), reverse transcriptase in the presence of Mn^{++} and Mg^{++}, sterility, Mycoplasma, pH, Electrophoretic Mobility, Isoelectric Focusing, Monomer content, Isotype, Protein A, Immunoreactivity, Appearance, Transferrin, Bovine Serum Albumin, DNA, Insulin-like Growth Factor, Sterility, and Bacterial Endotoxin.

IV.B.7. Validation of the CYT-351 purification process.

A study was designed to validate the purification process of the monoclonal antibody CYT-351. The study demonstrated, by a variety of techniques, that the purification process diminishes the

presence of contaminants present in the culture medium and it can produce three consistent lots of purified product (C3C0816, C3J0821, and C3J0825).
The following test methods were used in performing this study:

Assay	Method
pH	Probe
Conductivity	Probe
Protein concentration	Ultraviolet Spectroscopy
Murine IgG Concentration	Abx HPLC
Immunoreactivity	ELISA
DNA concentration >100 ng/ml	Fluorometer
DNA concentration < 100 ng/ml	^{32}P Probe Hybridization
BSA Concentration	ELISA
Long R3 IGF-1 concentration	RIA
Bovine Transferrin Concentration	ELISA
Protein A Concentration	ELISA
Cortisol Concentration	RIA
Testosterone Concentration	RIA
SDS-PAGE	Polyacrylamide gel
Isoelectric Focusing	Polyacrylamide gel
Monomeric IgG	Size exclusion HPLC
Bioburden	Bacterial plate count
Bacterial Endotoxin	LAL gel-clot
Isotype	gel-immunodiffusion

Eight lots of antibody CYT-351 have been found indistinguishable by these assays. Immunoconjugate CYT-356 from all the lots met all specifications. No differences in clinical effectiveness have been observed among the different lots. The lot release specifications of monoclonal antibody CYT-351 are listed in the following table.

Lot Release Specifications of Monoclonal Antibody CYT-351

Assay/Method	Specification
Protein concentration (TP1015)	5-11 mg/ml
Immunoreactivity (TP1093)	Slope ratio 65-120%
Isotype (TP1087)	IgG1 κ
Isoform profile (TP1046)	Pattern comparable to reference standard
Electrophoretic Mobility (TP1045)	Pattern comparable to reference standard
Monomeric IgG (TP1035)	Area ≥ 95%
Appearance (TP1053)	Colorless solution. It may contain translucent particles
pH (TP1025)	5.7-6.3
Bacterial Endotoxin (TP1037)	<1.0 EU/mg
Sterility (21CFR 610.12f)	No growth
DNA (probe hybridization)	<20 pg/mg
IGF1 (TP1170)	<5.0 ppm
Bovine Transferrin Concentration (TP1181)	< 25 ppm
BSA Concentration (TP1175)	< 25 ppm
Protein A Concentration (TP1107)	< 25 ppm

IV.C. Viral Removal/Inactivation Studies

The viral content of the starting crude CYT-351 bulk was determined by means of two assays. Quantitative Transmission Electron Microscopy showed that the conditioned media contained a maximum range of 11.5-12.5 logs of viral particles. Infectivity assays included mycoplasma, *in vitro* viral testing, reverse transcriptase, extended XC plaque and extended xenotropic retrovirus (S+L-) assays. All five lots of conditioned media were negative in these tests. Cell bank assays were also negative except the S+L- assay on C3C0816 post-production cells. Thus a xenotropic retrovirus (X-MuLV) was included in the virus removal/inactivation studies.

The results of the viral removal/inactivation studies showed a total of >9.2 logs of virus removal for E-MuLV; a total of > 16.3 logs of virus removal for X-MuLV, the only type of virus detected to be associated with the cells; a total of > 14.2 logs of removal for SV40; a total of 18.9 logs of removal for HSV-1; and a total of 4.4 logs of removal for the polio virus. These results meet the requirement of > 3 logs in excess of the initial virus burden to be removed/inactivated. Furthermore, by infectivity assays, no X-MuLV or other viruses were present in any of the conditioned media from the production runs.

IV.D. Description of Specifications and tests methods for other components and materials of the Capromab Pendetide Kits.

Other components used by CYTOGEN in the manufacture of Capromab Pendetide kits are as follows:

- Linker-chelator CYT-063, Glycyl-Tyrosyl-(N-ε-diethylenetriaminopentaacetic Acid)-Lysine Hydrochloride (GYK-DTPA.HCL).
- Phosphate Buffered Saline Solution
- Sodium Acetate Solution

IV.D.1 Linker-chelator CYT-063, Glycyl-Tyrosyl-(N-ε-diethylenetriaminopentaacetic Acid)-Lysine Hydrochloride (GYK-DTPA.HCL).

Linker-chelator CYT-063 [Glycyl-Tyrosyl-(N-ε-diethylenetriaminopentaacetic acid)-lysine hydrochloride] (GYK-DTPA.HCL), used in the conjugation can be either newly synthesized or recovered from a previous conjugation.

CYT-063 is synthesized under contract for CYTOGEN
Upon receipt, CYT-063 is tested according to several criteria and specifications, including: appearance, identity by ^{13}C-NMR, residual solvent determination by ^{1}H-NMR, moisture content, chloride content, and purity by HPLC.

Stability data for CYT-063 after storage at 2-8ºC for 4 years have been obtained. The product has been found to be stable under these conditions, as assessed by determination of the parameters mentioned above. The product is assayed according to the following methods:

Parameter	Method	Specification
Appearance	Visual Inspection	White to off-white powder
Residual Solvents	^{1}H-NMR	
a. acetic acid		≤ 0.5%
b. dimethylformamide		≤ 0.5%
c. methanol		≤ 0.5%
d. diisopropyl amine		≤ 0.5%
e. % total of the residual solvents a-d		≤ 1.0%
Moisture	Karl Fisher	≤ 7.0%
Chloride Content	PIXE	≤ 5.0%
Purity	HPLC	≥ 95.0%
Related impurities	HPLC	≤ 5.0%
Identity standard	^{13}C-NMR	Spectrum comparable to reference

IV.D.2. Phosphate Buffered Saline

PBS (10 mM sodium phosphate, 0.15 M sodium chloride, pH 6)solution is prepared by for CYTOGEN PBS is assayed according to the following methods:

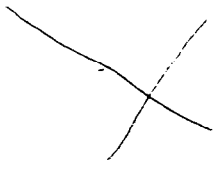
Parameter	Method	Specification
pH	pH meter	5.9-6.1
Sterility	USP <71>	Passes
Elemental Analysis	PIXE	full spectrum
P content		260-330 ppm
chlorine		< 1%
Osmolarity	Osmometer	280-320 mOsm
Particulate matter	Visual inspection	None visible
Appearance	Visual Inspection	Clear, colorless liquid

CYTOGEN Test Acceptance Criteria		
Test for chloride ion	USP <191>	Test Positive
Test for phosphate ion	USP <191>	Test positive
Conductivity	Conductivity meter	16 ±2 mmho/cm
Bacterial endotoxin	USP <85>	0.25 EU/ml

IV.D.3. Sodium Acetate Solution 0.5 Molar

Sodium acetate solution, 0.5 molar, is manufactured by CYTOGEN and supplied in glass vials containing 2 ml as part of the Capromab Pentedetide kit. The solution is used to buffer the In-111 solution prior to labeling of the antibody.

The quantitative formulation of a vial of sodium acetate solution is as follows:



The vials of sodium acetate buffer solution are assayed according to the following methods

Parameter	Method	Specification
Appearance	TP1145 and 1146	Colorless, appearance of water
Concentration	USP: Monograph sodium acetate solution assay	0.45 -0.55 M
pH	pH meter	5.7-6.2
Volume in container	USP <1>	2.0-2.5 ml
Bacterial endotoxin	USP <85>	2 EU/ml
Sterility	USP <71>	passes test

IV.D.4. Millex GV Filters

This filter is included with the Capromab Pentedetide kit and is an approved medical device.

IV.E. Manufacturing process for the immunoconjugate CYT-356.

The manufacture of bulk CYT-356 consists of oxidation of the carbohydrate moieties of purified CYT-351 to aldehydes with sodium metaperiodate. The excess periodate is removed by Sephadex G25 gel filtration chromatography, and the oxidized protein is allowed to react with the linker chelator CYT-063. The mixture is concentrated and purified by chromatography on Superose 12. The product is collected, diluted with PBS to a concentration of 0.55-0.60 mg/ml, and filtered through a 0.22 µM filter into a sterile polystyrene container. Environmental monitoring is carried out before, during and after the manufacturing process. The immunoconjugate is subjected to in-process and final testings, including determination of monomer content, protein concentration, cyanide content, and excess GYK-DPTA. The quantitative formulation of a vial of CYT-356 is as follows:

The parameters and specifications for bulk product release and final container release of CYT-356 are included in the following tables:

Bulk Product Release CYT-356 Bulk Solution

Parameter	Specification
Monomer	≥ 95%
Non conjugated CYT-063	In-111 CYT-063 ≤ 10%
In-111 labeling	≥ 90%
Appearance	Clear and colorless solution. May content translucid particles.
pH	5.7-6.3
Protein Concentration	0.55-0.60 mg/ml
Cyanide Content	< 1.0 µg/ml
Sterility Bulk	Meets requirements
Bacterial endotoxin	< 20 EU/ml

Final Container Release CYT-356

Parameter	Specification
Appearance	Clear and colorless solution. May content translucid particles.
Electrophoretic Mobility	SDS-PAGE equivalent to CYT-356 Standard a. Non-reduced b. Reduced
In-111 Labeling	In-111 labeled CYT-356 ≥ 90.0%
Immunoreactivity	≥ 70%
Affinity	0.5-5.0 μM^{-1}
Protein Content	0.50-0.63 mg/vial
pH	5.7-6.3
Rabbit Pyrogen	Non-pyrogenic Dose: 3.0 mg/kg rabbit
Sterility	Meets Requirements
General Safety	Meets Requirements
Chelator ratio	≤ 3.0 (CYT-063/CYT-356)
Bacterial endotoxin	For information only

Tabulation of Bulk Test Results for CYT-356

Parameter	Specification	Test Results (n=1)		
		Y4D0843	Y4H0856	Y4K0858
Electrophoretic Mobility	SDS-PAGE pattern equivalent to a CYT-356 Standard. a. non-reduced. b. reduced	a. meets b. meets	a. meets b. meets	a. meets b. meets
Monomer CYT-356	Area % IgG response ≥ 95%	99.6, 99.7 Avg = 99.7	99.6, 99.7 Avg=99.7	99.6, 99.5 Avg=99.6
Non conjugated CYT-063	In-111 labeled CYT-063 ≤ 10%	2.0, 2.0 Avg=2.0	2.6, 2.7 Avg=2.7	2.2, 2.2 Avg=2.2
In-111 Labeling	In-111 labeled CYT-356 ≥ 90%	97.4, 97.5 Avg= 97.5	95.5, 95.5 Avg=95.5	97.4, 97.1 Avg=97.3
Immunoreactivity	Slope ratio 65%-120%	80, 87 Avg=84	87	76
Appearance	Clear, colorless solution. May contain translucid particles	meets	meets	meets
pH	5.7-6.3	6.0	6.0	6.0
Protein Concentration	0.55-0.60 mg/ml	0.59, 0.59 Avg=0.59	0.57, 0.57 Avg=0.57	0.55, 0.55 Avg=0.55
Cyanide content	< 1.0 µg/ml	0.05	0.14	0.06
Sterility	Meets requirements	meets	meets	meets
Bacterial endotoxin	< 20 EU/ml	< 20	< 20	< 20
Sterility	No growth	Meets	Meets	Meets
Pyrogen	Non Pyrogenic 3.0 ml/kg	Meets	Meets	Meets
Safety	Meets requirements	Meets	Meets	Meets

IV.F. Validation of the immunoconjugation process

A study was designed to validate the ranges for key reaction parameters allowed in the manufacturing process for CYT-356 immunoconjugate. Additionally, the ratios of reactants to antibody were varied by 50%. The results of this study validated the conjugation process of monoclonal antibody CYT-351 with chelator CYT-063. The study demonstrated that, in the conditions of pH temperature and time used, conjugation occurs in a reproducible manner. In addition, the concentrations of reactants can vary as much as ± 50% with the final product still meeting specifications.

V. CAPROMAB PENDETIDE STABILITY AND EXPIRATION DATING

V.A. Stability of Cyt-351

Stability data for CYT-351 after storage of two lots at 2-8ºC for 36 months have been obtained. No change was observed in immunoreactivity, electrophoretic mobility, isoelectric focusing, monomer content, protein concentration, pH, and appearance. Stability data after storage at -70ºC have also been obtained for one lot. The lot is stable.

V.B. Stability of CYT-356 Final Product Vials

Stability data for the immunoconjugate CYT-356 have been accumulated on nine lots of the same formulation of finished product vials. As of December 1994, three lots manufactured have shown satisfactory stability for two years.

The stability of the CYT-356 final product vials is assessed by using the criteria included in the following table:

Parameter	Assay	Specification
Potency and Identity	Immunoreactivity	≥ 75%
	Affinity	Compares to Standard
	Protein content	0.50 - 0.63 mg/ml
Purity	Electrophoretic mobility	Equivalent to reference standard
	Monomer content	≥ 95%
	In-111 labeling	≥ 90%
	Non-conjugated In-111	≤ 10%
	Appearance	Colorless Solution, may contain translucent particles
pH		5.7 - 6.3

V.B.1. Chelation Stability of In-111 CYT-356.

The radiochemical purity of the conjugate was measured after 24 hours of labeling and found to be ≥ 95%. The expiration timing for the radiolabeled conjugate is of 8 hours. Stability is demonstrated for three times the dating period.

V.B.2. Stability of the CYT-356 Bulk solution

Stability of the Bulk CYT-356 solution stored in a 4L sterile polystyrene container has been demonstrated for 6 months.

V.C. Stability of linker-chelator CYT-063

Data previously submitted by Cytogen support a four year expiry for CYT-063.

V.D. Stability of Sodium Acetate Solution 0.5 M

Five lots have been followed for stability. As of December 1994, each of these lots has been shown to be stable for at least 24 months, and one up to 60 months. No changes have been observed in appearance, pH and acetate concentration at any time point.

V.E. Integrity of the container-closure system

Vials in upright and inverted position were stored for 17 months. Vials stored at 2-8ºC for 42 months have also been used for this study. No contaminated vials were found. These data demonstrate that the container-closure system will maintain the sterility of the product for the proposed dating period.

V.F. Stability under inverted Storage Conditions

CYT-356 vials stored inverted at 2-8ºC were tested after 3 months' storage. The product remained within specifications when tested for appearance, immunoreactivity, protein content, pH, electrophoretic mobility, monomer, non conjugated CYT-063, radioisotope labeling, and bacterial endotoxin.

V.G. Summary of proposed expiration dating periods

According to the stability data obtained, these are the expiration dating periods proposed:

Kit Component	Proposing Dating Period
Capromab Pendetide (CYT-356)	2 years
Sodium Acetate Solution	4 years

Components used to manufacture CYT-356	Proposing Dating Period
Monoclonal Antibody CYT-351	3 years
Linker-chelator CYT 063	4 years

The expiration date for the vials of CYT-356 and sodium acetate solution will be imprinted on the final container label at the time the vials are labeled.

V.H. Stability Protocol for Marketed Capromab Pendetide Kits

A stability program for Capromab Pendetide kits have been designed in which the first three marketed lots of CYT-356 and sodium acetate solution will be tested. For subsequent lots, samples will be retained for stability evaluation from one production lot of CYT-356 at 6-month intervals. For sodium acetate solution, samples will be retained for evaluation at yearly intervals. Parameters to check include: potency, identity, immunoreactivity, protein content, purity, monomer content, non conjugated CYT-063, radioisotope labeling, appearance, pH, bacterial endotoxin, and sterility.

VI. ESTABLISHMENT INSPECTION

And inspection of Cytogen Corporation facilities was performed from July 31 to August 3, 1995. The following production activities were observed: cell culture, purification, conjugation, and labeling. Facilities and procedures were found to be in compliance with current good manufacturing practices. Responses to form FDA 483 observations were submitted by Cytogen on November 9, 1995.

VII. ENVIRONMENTAL IMPACT

An Environmental Impact Analysis Report was submitted by Cytogen As part of the establishment and product license applications. The establishment complies with national and local environmental regulations. No negative impact in the environment is expected from the production of the CYT-356 immunoconjugate.

VIII. PRECLINICAL STUDIES

VIII.A. Immunohistology

A number of studies have been performed to assess the reactivity of CYT-351 and CYT-356 with normal tissues and benign and malignant tumors. These studies generally used acetone fixed frozen tissues in conjunction with peroxidase-based immunocytochemical techniques.
These studies have demonstrated that:

1. CYT-356 reacts with normal prostatic tissue but more intensely with most prostate tumors. Metastases have stronger reactivity than primary tumors.
2. CYT-356 does not react with other human tumors.
3. In addition to normal prostatic tissue. Weak staining can be observed in the proximal tubules of the kidney, small intestine, and the sweat glands of the skin. A strong reactivity was observed with striated skeletal muscle, but this reactivity is of cytoplasmic origin and does not interfere with the targeting of the antibody to prostate tumors intended *in vivo*.
4. Tissue reactivities of CYT-351 and CYT-356 are indistinguishable from each other.

VIII.B. Animal Models and Study Methodology

VIII.B.1. Studies on Mice

Studies in tumor-bearing and normal athymic mice were conducted to determine the biodistributive behavior *in vivo* of In-111 CYT-356 administered by the intravenous route. These studies also intended the evaluation of the localization and imaging qualities of this radiolabeled immunoconjugate in human prostate tumor xenografts grown subcutaneously in nude mice. The data collected in these studies consistently indicated that for In-111 Capromab pentedetide:

1.- The intravenous route was an effective means of administration
2.- Discernible tumor images were obtained in PMSA positive tumor xenografts in mice.
3.- Localization to prostate tumor xenografts is antigen specific.
4.- No abnormal biodistribution to uninvolved, normal organs or tissues was observed in either tumor-bearing or normal nude mice.

5.- No adverse effects were observed due to administration of In-111 CYT-356.

VIII.B.2. Exploratory studies in Cynomolgus Monkeys

Studies were conducted in Cynomolgus monkeys to assess the clinical effects of administration of CYT-356 of In-111 CYT-356 and its localization in monkey skeletal muscle. Furthermore, blood pharmacokinetics of In-111 CYT-356 was assessed in this non-human primate model.

These studies showed that.

1. A single injection of 2.7 mg/kg of CYT-356 no mortality or adverse clinical effects were observed over the course of a 3-day post injection period.
2. In-111 CYT-356 was not taken up by skeletal muscle. Thus, the immunohistological activity of CYT-356 observed in vitro does not have demonstrable sequelae in monkeys *in vivo*.

IX. CLINICAL DEVELOPMENT PROGRAM.

The clinical program conducted under BB-IND 3311 consisted of six studies:

- ☒ One phase I dose-ranging study (356In10);
- ☒ One repeat-dosing study (356In11);
- ☒ A phase II study (356In12) and a pivotal trial (356In15) which studied the visualization of pelvic lymph node metastases prior to staging lymphadenectomy; and
- ☒ A phase II study (356In14) and a pivotal trial (356In16) which studied the visualization of possible locoregional recurrence after initial curative therapy.

Pharmacokinetic evaluations were included in all studies except for study 356In12.
These studies are summarized in the following table:

Study Nº	Type of Study	Nº of Pts	Patient Population
356In10	Dose Ranging	80	Pre-Lymphadenectomy (32 Pts) & Known Metastatic Ca (48 Pts)
356In11	Repeat Dosing	61	Residual/Recurrent Prostate Ca
356In12	Phase II: Imaging	76	Clinically Localized Prostate Ca Pre-Staging Lymphadenectomy
356In14	Phase II: Imaging	87	Elevated PSA—R/O Locoregional Recurrence of Prostatic Ca
356In15	Pivotal: Initial Staging	160	Clinically Localized Prostate Ca Pre-Staging Lymphadenectomy
356In16	Pivotal: Occult Disease	183	Elevated PSA—R/O Locoregional Recurrence of Prostatic Ca

Since submission of the PLA, several other studies have been initiated: Study 356In17, studying patients with recurrent disease undergoing treatment; study 356In19, a "compassionate use" protocol for patients with suspected recurrence; and study 356In21, which studies a teaching program for Capromab Pendetide imaging.

Biopsy-confirmation of scan results was required in the phase II and pivotal trials. Since the eligibility criteria of these trials dictated a negative metastatic work-up, few patients with extrapelvic disease were accrued to the major studies. Thus, with a few exceptions, biopsy confirmation is not available for areas of Capromab Pendetide-In uptake outside of the pelvis. The areas of Capromab Pendetide-In uptake outside the pelvis were to be evaluated with other imaging studies. However, the protocols were not designed to prospectively follow these extrapelvic areas of uptake to confirm they represented metastatic disease. Therefore, data for evaluation of extrapelvic uptake of Capromab Pendetide-In are limited.

IX.A. Imaging Performance

A total of 405 patients in the four trials had an interpretable Capromab Pendetide-In scan with biopsy confirmation. There was a considerable variation in outcome between the four studies. The outcome data from the four major trials are summarized below:

Results of the Four Major Studies

Tissue Biopsy Results	Capromab Pendetide-In Scan Results							
	Positive Scan				Negative Scan			
	Study356 In12 N=12	Study 356 In14 N=31	Study 356 In15 N=65	Study 356 In16 N=58	Study 356 In12 N=52	Study 356 In14 N=12	Study 356 In15 N=76	Study356 In16 N=100
Positive	11 (92%)	21 (68%)	40 (62%)	29 (50%)	10 (19%)	7 (58%)	24 (32%)	30 (30%)
Negative	1 (8%)	10 (32%)	25 (38%)	29 (50%)	42 (81%)	5 (42%)	51 (68%)	70 (70%)

Thus, the percent of positive scans that were false positives ranged from 8% (study 356In12) to 50% (study 356In16) and the percent of negative scans that were false negatives ranged from 19% (study 356In12) to 58% (study 356In14). The pivotal trials were somewhat more consistent. The percent of positive scans that were false positives was 38% (study 356In15) and 50% (study 356In16), while the percent of negative scans that were false negatives was 30% (study 356In16) and 32% (study 356In15).

The sensitivities, specificities, accuracies, and positive and negative predictive values, with the 95% Confidence Intervals (CI), as calculated for the four major studies are tabulated below:

Imaging Parameters in the Four Major Studies

Imaging Parameter (*95% CI*)	Study Nº			
	356In12 (N=64)	356In14 (N=43)	356In15 (n=140)	356In16 (N=158)
Sensitivity	52% (*30%-74%*)	75% (*55%-89%*)	62% (*50%-74%*)	49% (*36%-63%*)
Specificity	98% (*88%-100%*)	33% (*12%-62%*)	67% (*55%-77%*)	71% (*61%-79%*)
Accuracy	83% (*71%-91%*)	60% (*44%-75%*)	65% (*56%-73%*)	62% (*55%-78%*)
Positive Predictive Value	92% (*62%-100%*)	68% (*49%-83%*)	62% (*49%-73%*)	50% (*37%-63%*)
Negative Predictive Value	81% (*67%-90%*)	42% (*15%-72%*)	68% (*56%-78%*)	70% (*60%-79%*)

As reflected on the table, there was considerable variation in the results. The sensitivities ranged from 49% (study 356In16) to 75% (study 356In14). The specificities ranged from 33% (study 356In14) to 98% (study 356In12). The accuracy ranged from 60% (study 356In14) to 83% (study 356In12). The positive predictive value (PPV) ranged from 50% (study 356In16) to 92% (study 356In12). The negative predictive value (NPV) ranged from 42% (study 356In14) to 81% (study 356In12). The 95% CIs were broad.

In most instances, data from the two phase II trials (studies 356In12 and 356In14) represented the upper and lower boundaries of the range. However, the data obtained from the two pivotal trials (356In15 and 356In16) were more consistent. In the two pivotal trials, the sensitivities were 49% (study 356In16) and 62% (study 356In15); the specificities were 67% (study 356In15) and 71% (study 356In16); and the accuracies were 62% (study 356In16) and 65% (study 356In15).

It should be recalled that the PPV, NPV, and accuracy are influenced by the prevalence of the condition of interest in the population being studied, and the populations chosen for study were at a high risk for lymph node metastases (studies 356In12 and 356In15) or locoregional recurrence (studies 356In14 and 356In16). Using the sample prevalence rate from each of the four major studies the PPV, NPV, and accuracy can be projected for different prevalence rates. This analysis is given in the table below:

PPV, NPV, & Accuracy at Differing Prevalence Rates[1]

Parameter	Study Nº	Prevalence in the Population						
		"Low Risk"	"Medium Risk"		"High Risk"		"Very-High Risk"	
		10%	20%	30%	40%	50%	60%	70%
Positive Predictive Value	356In12	71%	85%	91%	94%	96%	97%	98%
	356In14	11%	22%	33%	43%	53%	63%	72%
	356In15	17%	32%	45%	56%	66%	74%	82%
	356In16	16%	30%	42%	53%	63%	72%	80%
Negative Predictive Value	356In12	95%	89%	83%	75%	67%	58%	47%
	356In14	92%	84%	76%	67%	57%	47%	36%
	356In15	94%	87%	81%	73%	64%	54%	43%
	356In16	93%	85%	76%	68%	58%	48%	37%
Accuracy	356In12	93%	89%	84%	80%	75%	70%	66%
	356In14	38%	42%	46%	50%	54%	58%	63%
	356In15	67%	66%	66%	65%	65%	64%	64%
	356In16	69%	66%	64%	62%	60%	58%	56%

The PPV, NPV, and accuracy of the two pivotal trials (356In15 and 356In16) are reasonable consistent over the range of prevalence rates and, again, the two phase II studies (356In12 and 356In14) would appear to be outliers—especially 356In12. These data illustrate the major impact of the prevalence rate on the PPV. In patients who are at a low risk for nodal metastases or locoregional recurrence, the PPV of a Capromab Pendetide-In scan will be <20%—or four out of five positive scans will be a false positive. In patients who are at a very high risk for lymph node metastases or locoregional recurrence, the PPV of a Capromab Pendetide-In scan will be ~75%—or one out of four positive scans will be a false positive. The NPV in the low-risk population was almost 95%, and in the very high-risk population it was ~40-50%. However, the evaluation of the PPV should take into account an "intrinsic" PPV that is equal to the prevalence, while the evaluation of the NPV should take into account an intrinsic NPV that is equal to one minus the prevalence.[2]

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[1] The classification of low, medium, high, and very-high risk are arbitrary; however, the "high risk" grouping does encompass the prevalence rate of the overall study population.

[2] If an agent which generates only positive images (*i.e.*, an active control) is administered to patients in a population with a tumor prevalence of X, it would result in X true positives and $1\text{-}X$ false positives when biopsied. The PPV of this agent would be $X \div X + 1\text{-}X = X$. An agent which does not image (*i.e.*, an inactive control) given to patients in a population with a tumor prevalence of X would result in X false negatives and $1-X$ true negatives when biopsied. The

If the "intrinsic value" is subtracted from the projected value, the "net" value can be used to estimate the magnitude of any added value provided by the scan. The accuracy of the scan was quite consistent over the range of prevalences, especially in study 356In15 (which ought to provide the most reliable picture of the imaging performance of Capromab Pendetide-In). Overall, it would appear that the accuracy of the Capromab Pendetide-In scan was 55-70%, meaning about one-third of the Capromab Pendetide-In scans will be in error, regardless of the prevalence in the population.

IX.B. Safety

A total of 647 patients received at least one dose of Capromab Pendetide-In. The adverse reactions reported in more than one patient that were attributed to Capromab Pendetide-In are tabulated below:

Pooled Safety Data for Capromab Pendetide-In

Adverse Reaction	Study Nº					
	356In10 N=80	356In11 N=61	356In12 N=76	356In14 N=87	356In15 N=160	356In16 N=183
Hyperbilirubinemia	—	2	—	1	1	2
Decrease in BP	—	1	2	—	—	3
Increase in BP	1	2	—	1	1	1
Elevated Liver Enzyme	—	2	—	3	—	—
Infusion Site Symptoms	1	—	—	1	1	1
Post-Infusion Pruritus	—	—	1	—	1	—
Rash	—	—	—	—	1	1

One case of hyperbilirubinemia was judged severe (bilirubin 2.4 mg/dl which was still ongoing) and one case was judged as moderate. All other reactions were judged mild, except for one instance of moderate eosinophilia. All the adverse reactions, except for the one case of hyperbilirubinemia, resolved without treatment.

Thus, mild reversible liver toxicity (hyperbilirubinemia with or without liver enzyme elevations), mild fluctuations in blood pressure, or a discomfort at the infusion site occurred in ≤1% of patients. Manifestations of hypersensitivity (pruritus, rash) were even less common. HAMA did not seem to be a problem.

X. OVERVIEW OF CAPROMAB PENDETIDE-In IMAGING

NPV of this agent would be: $1-X \div X + 1-X = 1-X$.

The technical image quality in the phase II studies is adequate for interpretation, but does not reflect the image acquisition and image processing improvements that were implemented during the pivotal trials. The following discussion of Capromab Pendetide-In imaging will integrate the imaging protocols used in the pivotal trials, and contained in the sponsor's imaging guidance documents.

SPECT imaging of the pelvis is performed 30 minutes following the Capromab Pendetide-In administration. This 30-minute SPECT imaging study is not intended to identify prostatic tissue sites. The object is to demonstrate the vascular structures, the blood pool, potential patient rotation and the anatomical details of the pelvis. Patient preparation is oral hydration. The urinary bladder is not emptied to allow for localization for a comparison to the 72-120 hour SPECT scan. The patients must remain motionless for 30-60 minutes during the image acquisition.

Planar and SPECT imaging are performed 72-120 hours after Capromab Pendetide-In administration. Patient preparation includes cathartics the night before the imaging study, enemas prior to the imaging study, and the placement of an indwelling urinary catheter with bladder irrigation during the imaging study. Patients must also remain motionless during both the planar imaging (30-60 minutes) and SPECT imaging (30-60 minutes) sessions.

The planar imaging is whole body imaging and/or multiple spot imaging of major body regions. Planar imaging evaluates the biodistribution of Capromab Pendetide-In, potential infiltration of the radiolabeled antibody at the injection site, the vascular anatomy in the pelvis and lower abdomen, as well as Capromab Pendetide-In intensity in the blood pool. Planar imaging demonstrates any bowel and urinary tract clearance activity that may require repeat clearance of the bowel and urinary tract and repeat delayed imaging. Finally, planar imaging attempts to demonstrate any patient-specific anatomical variant structures, and also any sites of abnormal localization beyond the SPECT imaging field of the pelvis and lower abdomen.

SPECT imaging of the lower abdomen and pelvis is performed to detect abnormal localization in the prostatic fossa and adjacent regions, and in the retroperitoneal pelvic lymph nodes. The interpretation of the SPECT scan of the pelvis is highly dependent on the bilateral symmetry of the pelvis and the iliac blood vessels. These vascular structures, filled with the Capromab Pendetide-In blood pool, have multiple anatomical variations of normal—as well as patient specific—anatomical variation and distortion due to atherosclerosis. The patient's vascular anatomy is demonstrated in the 30-minute SPECT scan, and those images correlated with the 72-120 hour SPECT scan. If the patient's anatomical position is misaligned between the two scans—or if the patient is rotated—the study should be repeated. Comparison of the two SPECT studies provides anatomical detail of bone and bone marrow and also the relationship of the urinary bladder to the prostatic fossa.

X. A Technical Aspects

As the clinical trials were ongoing, the sponsor reviewed the imaging performance of Capromab Pendetide-In, determined technical performance limitations, and implemented technical changes to improve image quality. Thus, the imaging procedures and patient preparation evolved during the course of clinical development. These improvements addressed image acquisition, image processing, and image interpretation. Following the conclusion of the pivotal trials, the imaging

protocols and procedures utilized were consolidated into two guidance documents—a *TECHNICAL USER'S GUIDE* and a *PROSTASCINT™ IMAGING CLINICAL REFERENCE GUIDE*.

The *TECHNICAL USER'S GUIDE* was submitted in draft form, with notations for items required for completion of the document. The *TECHNICAL USER'S GUIDE* defines image acquisition, image processing, and provides information for basic image evaluation and interpretation. It is oriented to the technologist performing the Capromab Pendetide-In study—and it adequately reflects the experience and design of the imaging protocols as performed in the pivotal trials. Implementation of the *TECHNICAL USER'S GUIDE* has the potential for improved image quality at the individual clinical sites; however, data confirming improved image quality after using this guide has not been submitted.

The *PROSTASCINT™ IMAGING CLINICAL REFERENCE GUIDE* was also submitted in draft form. This manual is oriented to the physician responsible for imaging performance and image interpretation. The technical issues associated with image acquisition and image processing are appropriate summaries of the discussion in the *TECHNICAL USER'S GUIDE*. Guidance is provided for patient preparation and image acquisition. In addition it provides instructive anatomical representations of the region of the prostate and pelvic lymph nodes to be imaged. It also provides an outline discussion of the anticipated causes of image interpretation variances, with directed comments on potential pitfalls leading to both false positive and false negative interpretations. The implementation of this guide also has the potential for improved image quality and image interpretation at individual clinical sites, but no data to confirm the improvement of image quality and image interpretation after using the guide has been submitted.

X.B. Capromab Pendetide-In Biodistribution

Biodistribution evaluation in the 30-minute SPECT images of the pelvis demonstrates the blood pool vascular structures and clearance activity the bladder.

Biodistribution evaluation in the 72-120 hour SPECT and planar images demonstrate blood pool localization in the vascular structures, liver, spleen and bone marrow localization. Clearance of Capromab Pendetide-In through the bowel and urinary tract is identified.

Altered biodistribution of the radiolabeled antibody is characterized by clearance of the blood pool activity and increased activity in the liver, spleen, and bone marrow.

X.C. Capromab Pendetide-In Dosimetry

A dosimetry evaluation of Capromab Pendetide-In with whole body and organ exposure estimates was submitted. The exposure estimates were within the expected ranges for a diagnostic imaging agent labeled with In-111. The estimated absorbed radiation dose to a 70 kg adult from an intravenous administration of 0.5 mg Capromab Pendetide labeled with 5 mCi of In-111 is given in the following table:

Dosimetry

Organ/Tissue	Mean Absorbed Radiation Dose (Rad/mCi)	Organ/Tissue	Mean Absorbed Radiation Dose (Rad/mCi)
Total Body	2.5	**Bone**	3.8
Prostate	N/A	**Stomach Wall**	2.9
Spleen	18.1	**Upper Colon**	2.6
Liver	15.9	**Small Intestine**	2.4
Kidney	9.0	**Bladder Wall**	2.1
Heart Wall	7.4	**Lower Colon**	1.9
Bone Marrow	6.1	**Thyroid**	1.5
Pancreas	4.7	**Testes**	1.2
Adrenal	4.6	**Skin**	1.1

X.D. Imaging Review

Review of the phase II and pivotal imaging studies confirmed the prospective, on-site interpretations of the Capromab Pendetide-In imaging studies. No pattern of interpretations suggested the need for revision or reinterpretation of the on-site reports.

The review noted that the imaging studies were technically adequate for the on-site interpretation—and for the regulatory review. The imaging studies demonstrated significant variations in image acquisition, image processing, and image quality. The variations were compatible with the clinical use of different imaging systems, imaging protocols, and computer image processing protocols.

The design of the clinical trials for detection of metastatic disease in pelvic lymph nodes required the CT scan to be negative for metastatic disease in the lymph nodes. This requirement removed patients with pelvic lymph nodes >2.0 cm in diameter. The routine SPECT imaging resolution of In-111 is estimated to be limited to 1.0 cm lymph nodes. The pelvic lymph nodes are adjacent to iliac vascular structures which have Capromab Pendetide-In blood pool activity. If patient rotation or patient motion should occur during the SPECT imaging, the vascular blood pool may be asymmetric and misinterpreted for a positive lymph node—or the vascular blood pool may obscure a true positive lymph node localization. Review identified several studies with apparent asymmetry and possible rotation artifact.

The clearance of Capromab Pendetide-In is through the bowel and urinary tract. These clearance patterns of Capromab Pendetide-In activity are easily misinterpreted with SPECT imaging as false positive localizations in lymph nodes and the pelvis. During the phase II and pivotal trials the sponsor delineated and updated a patient preparation to empty the bowel and urinary tract of

Capromab Pendetide-In activity. During both the phase II and pivotal imaging trials, studies with incomplete clearance of the bowel and urinary tract clearance of Capromab Pendetide-In produced SPECT images with potential for false positive sites of activity. These artifacts were correctly disregarded in some patient studies; however, in other studies they appear to be incorrectly identified as false positive sites.

Imaging of the prostatic fossa and adjacent regions presents many potential sites of false positive localization. Superior to the fossa is the bladder and posterior to the fossa is the rectum. Both are pathways of Capromab Pendetide-In clearance. Lateral to the fossa blood pool imaging activity is present in the iliac vessels, and in the midline and inferior to the fossa is the blood pool activity in the penis. Surrounding these structures is the pelvis with the bone marrow cavity and its variable Capromab Pendetide-In activity. If a patient is rotated during image acquisition and/or there is patient motion during image acquisition, misinterpretation of the prostatic fossa region may occur. Patient rotation and/or motion may have been a source of misinterpretation for false positive and/or false negative interpretation of the prostatic fossa.

Several cases of extra-pelvic, abdominal metastatic lymph node disease were submitted. These were from ongoing clinical trials, not trials submitted for review as part of the PLA. These cases were reviewed: Two were confirmed to have negative CT imaging and the positive localization was histologically verified.

Several cases of skeletal metastases identified by Capromab Pendetide-In imaging were also submitted. Patient studies from the dose-ranging trial (356In11) demonstrated bone scan patterns of wide spread metastatic disease. The Capromab Pendetide-In imaging did not identify most sites of abnormal bone uptake, and it did not demonstrate occult sites of metastasis. Two cases of bone/bone marrow metastases imaged by Capromab Pendetide-In were submitted, and confirmed to be bone scan negative. Both cases were adequately confirmed by MRI imaging.

Secondary review of the images determined to be false positives from the phase II and pivotal trials was performed. The studies were technically adequate, with diagnostic image quality. The areas of abnormal localization were demonstrated—and adequately defined to have been interpreted as positive studies in the on-site interpretations. Rotational artifact, incomplete bowel clearance, incomplete bladder clearance, and vascular variations did not appear to be more common as compared to other studies.

The identification of metastatic prostate cancer involvement of lymph nodes of <2.0 cm in size and the detection of CT negative prostatic fossa recurrence is a significant technical challenge for an antibody labeled with 5 mCi of In-111. Clearance pathways through the urinary tract and bowel present an array of variable potential positive imaging artifacts. To reduce the potential for clearance pathway artifacts, patients must submit to an aggressive protocol to reduce Capromab Pendetide-In activity in both the bowel and urinary tract. The Capromab Pendetide-In SPECT imaging protocol is technically challenging and the imaging community's current clinical quality of SPECT and planar imaging In-111 is variable. These limitations are reflected in the quality of the images, and results of the image interpretation. It is anticipated that the performance in the clinical trials will be reflected in the community experience. However it is expected that increased experience with this imaging agent will improve image acquisition, quality and interpretation.

X.E. Clinical Pharmacokinetics.

The clinical pharmacokinetics of 111-In-labeled CYT-356 were determined after a single intravenous dose. Doses of 0.5 mg of CYT-356 which contained 3.99 - 5.52 mCi of 111-In were administered to five patients. Blood and serum samples were collected at various times over an eleven day period. Samples of urine were obtained over a three day period. Serum levels of 111-In-CYT-356 declined in a monoexponential manner. The serum average elimination half-life was 67+/-11 hr. and serum clearance averaged 42+/-22 ml/hr. Urinary excretion accounted for 9.7+/-3.6% of the dose. The volume of distribution was 4.0+/-2.1 L and was similar to the plasma volume. Pharmacokinetics based comparisons of CYT-356 from different manufacturing processes did not reveal any significant changes.

XI. DATA INTEGRITY

Bioresearch monitoring Inspections of seven clinical investigators were performed in support of the subject PLA. The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual 7348.811, Inspection Program for Clinical Investigators.

The seven sites selected for audit encompassed the conduct of the clinical trial for approximately 64% (102 patients) of the total patient population in protocol 356In15. Two of the audited sites were selectyed to review the conduct of a small patient population in the pivotal study. Two of the audited sites were selected to review readministration of the test article in protocols 356In11 and 356In14.

The results of the Bioresearch Monitoring clinical investigator data audits for five of the seven sites indicate that the submitted data, with some exceptions, can be considered reliable and accurately reported. The results of data audits for two sites indicate that the submitted data are accurately reported, with noted exceptions, but data reliability is questionable due to numerous protocol violations at the Lahey Clinic Medical Center, (Burlington, MA) and missing and incomplete pharmacy records at George Washington University Medical Center.

XII CONCLUSIONS.

In assessing the relative impact of the benefits and risks associated with administration of Capromab Pendetide the clinical data obtained support the notion that, when used in conjuction with other diagnostic agents and in the patient population for which it is intended, Capromab Pendetide will improve the diagnosis of prostate carcinoma and metastatic disease.

XIII REVIEW BY THE ADVISORY COMMITTEE

The clinical data were reviewed by the Medical Imaging Drug Advisory Committee on July 22, 1996.The committee voted unanimously to recommend approval of Capromab Pendetide for use in high-risk patients with biopsy-proven prostate cancer in whom there is a high clinical suspition of occult or recurrent metastatic disease and a negative or equivocal standard evaluation.

XV. APPROVED PACKAGE INSERT

A copy of the approved package insert is attached.

SIGNATURE PAGE:

Jorge Laborda, Ph.D., Chair — Date: 7/31/97

Debra Bower Ph.D. Member — Date: 7/30/97

Leon Epps, Ph.D. Member — Date: 7/30/97

Martin D. Green, Ph.D. Member — Date: 7/30/97

George Mills, M.D. Member — Date: 7/30/97

Satish Misra, Ph.D. Member — Date: July 30, 1997

Robert Sausville, Member — Date: July 30, 1997

Richard Steffen, M.D. Member — Date: 30 July 97