

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device generic name	Cardiac Ablation Catheter and Accessories
Device trade name	CryoCor Cryoablation System (CryoCor CryoBlator Cryoablation Catheters & Model 2020 Console)
Applicant's name and address	CryoCor, Inc. 9717 Pacific Heights Blvd. San Diego, Ca 92121
PMA number	P050024
Date of Panel recommendation	June 27, 2007
Date of notice of approval to the applicant	August 1, 2007

II. INDICATIONS FOR USE

The CryoCor Cryoablation System is intended for use in the ablation of isthmus-dependent right atrial flutter in patients 18 years of age or older.

III. CONTRAINDICATIONS

The CryoCor Cryoablation System should not be used:

- in patients with active systemic infection
- in patients with intracardiac mural thrombus or in patients who have had a ventriculotomy or atriotomy within the preceding four weeks
- in patients with cryoglobulinemia.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions for the CryoCor Cryoablator System can be found in the CryoBlator™ physician labeling and the Model 2020 Console User Manual.

V. DEVICE DESCRIPTION

The CryoCor Cardiac Cryoablation System consists of the Cryocor Cryoablation Console (which features an articulating arm housing a pre-cooler) and the CryoCor CryoBlator Catheter (a sterile, disposable, single-use percutaneous cryoablation catheter). The System is designed to be operated as a unit, and will not function without both components.

A. The CryoCor™ Cryoablation Console

The CryoCor Cryoablation Console operation is based on a microprocessor controlled two-stage cooling process initiated by activation of the system's freeze cycle. The console delivers a primary refrigerant to the catheter. This primary refrigerant operates in an open loop, and is liquefied by the closed loop pre-cooling refrigeration stage. Pre-cooling occurs in a heat exchanger located near the catheter/console interconnect, at the end of the console's articulating arm. The primary refrigerant reaches its lowest temperature via the phase change of the fluid (liquid to gas) after it exits the capillary tube at the catheter's distal end. The primary refrigerant gas is then returned from the catheter through the console to an outlet (hospital scavenge line). Deactivation of the freeze cycle stops primary refrigerant flow to the catheter, ending cooling of the catheter tip.

B. The CryoCor CryoBlator Catheter

The CryoCor CryoBlator Catheters interface with the Cryoablation Console and deliver cryoablation therapy to the target tissue to cause a block of electrical conduction through local cardiac cell death. The CryoBlator Catheters included in this application are the (1) CryoBlatorX-05 Catheter and (2) CryoBlatorX-07 Catheter.

Each catheter features a 6.5mm tip. The catheter handle facilitate steering and placing of the catheter tip, and the distal portion of the catheter is capable of being deflected (uni-directionally) to 180°. The metal tip of the catheter is the point of application for heat transfer to the tissue. A temperature sensor located within the catheter tip provides continuous temperature monitoring while the catheter is attached to the console. An additional 1.3mm wide band electrode is incorporated for sending or receiving cardiac electrical signals. A summary of the general specifications of the catheter is provided in Table 1 below.

TABLE 1 – General Specifications of CryoBlatorX-05 and CryoBlatorX-07

Component or Feature	CryoBlator X-05, CryoBlator X-07
Catheter Diameter	10 Fr.
Catheter Tip Diameter	3.1 mm
Catheter Tip Length	6.5 mm
Tip Material	Stainless Steel
Distal Articulation Segment Material	Pebax™ (polyether block amide thermoplastic)
Distal Articulation Segment Length	5cm (CryoBlatorX-05) 7cm (CryoBlatorX-07)
Shaft Material	Nylon 12 w/ black colorant; Pebax with blue colorant, SS wire.
Shaft Length	95cm (CryoBlatorX-05) 97cm (CryoBlatorX-07)
ECG Electrode Band	90% Platinum, 10% Iridium
ECG Electrode Band Placement	2-4mm from the proximal edge of metallic tip
ECG Connector	Lemo Type
Handle Material (molded)	ABS (Acrylonitrile Butadiene Styrene)

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies for atrial flutter include direct surgical ablation, irrigated and non-irrigated radiofrequency (RF) catheter ablation, use of drugs for arrhythmia control, and antiarrhythmia pacing.

VII. MARKETING HISTORY

The CryoCor Cryoablation System Console (Model 2020) has been marketed in the European Union and Hong Kong since receipt of the CE Mark in April 2002. The Console has not been withdrawn from marketing for any reason related to safety and effectiveness of the device.

The CryoCor CryoBlator Catheter has been marketed in the European Union and Hong Kong since June 2005. The CryoBlator Catheter has not been withdrawn from marketing for any reason related to safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse events that maybe associated with catheterization and/or cardiac ablation are described in Table 2 below.

TABLE 2 – Potential Adverse Events

• Abnormal vision	• Laceration
• Adult Respiratory Distress Syndrome (ARDS)	• Local hematomas/ecchymosis
• Air embolism	• Myocardial infarction
• Anaphylaxis	• Neck/pain/groin pain
• Anemia	• Obstruction or perforation or damage to the vascular system
• Allergic reaction (anesthesia)	• Palpitations
• Arrhythmias	• Pericardial effusion
• Atrioventricular fistula	• Pericarditis
• Bleeding	• Pleural effusion
• Cardiac perforation/tamponade	• Pneumonia
• Cardiac thromboembolism	• Pneumothorax
• Catheter rupture and release of refrigerant	• Pseudoaneurysm
• Cerebrovascular accident (CVA)	• Pulmonary edema
• Chest pain/discomfort	• Pulmonary embolism
• Complete heart block	• Radiation injury
• Component damage to implantable cardioverter defibrillator or implantable pacemaker	• Respiratory Depression
• Congestive heart failure/exacerbation	• Seizure
• Coronary artery spasm	• Syncope/near syncope
• Death	• Temporary complete heart block
	• Thrombi

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| <ul style="list-style-type: none"> • Dislodgement of implantable cardioverter defibrillator or permanent pacing leads • Dizziness • Endocarditis • Exacerbation of pre-existing atrial fibrillation • Expressive aphasia • Heart Failure • Hemothorax • Hypoxia/shortness of breath • Infections/sepsis | <ul style="list-style-type: none"> • Thromboembolism • Transient ischemic attack (TIA) • Unintended (in)complete AV, sinus node or other heart block or damage • Valvular damage/insufficiency • Vascular bleeding • Vasovagal reactions • Ventricular tachycardia • Worsening chronic obstructive pulmonary disease |
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Please refer to Section X – Summary of Clinical Sections – for information on the adverse events observed in the clinical study.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Biocompatibility Testing Summary

In accordance with ISO 10993-1, biocompatibility testing was performed on the blood-contacting materials of the device system. The purpose of the testing was to subject the catheter, in its finished form, to standardized biocompatibility tests based on ISO 10993-1. Test selection was based on the nature of body contact and contact duration, as called out in the standard. The catheter components are considered to be “external communicating devices” that contact circulating blood for less than 24 hours. The following tests were performed on the CryoBlator Catheters:

- Cytotoxicity
- Sensitization
- Irritation
- Systemic Toxicity
- Hemolysis
- Thrombogenicity
- Pyrogenicity
- Genotoxicity

The CryoBlator Catheters met all applicable test requirements in the ISO 10993 standard.

B. Sterilization Validation

The sterilization validation qualified a 25kGy dose for the sterilization of the CryoCor 10 French Cryoablation Catheter for delivering a minimum sterility assurance level (SAL) of 10⁻⁶. The validation method used was consistent with AAMI TIR 27:200.

C. Catheter Testing Summary

1. Catheter Functional and Performance Testing

Testing was performed on sterilized catheters to verify whether the catheters met their design specifications. Where appropriate, the catheter shaft was submerged in 37°C bath for the testing. Table 3 below reflects the results of this testing.

TABLE 3 - Catheter Functional and Performance Testing

Qty Tested	Test	Acceptance Criteria	Results
30	Deflection Force	≤ 7 lbs	Pass
30	Deflection Radius	0.75" ± 0.10"	Pass
30	Curvature of deflection	180°, circular and smooth	Pass
30	Lateral Stiffness	> 5 grams	Pass
30	Off Axis deflection	< 15°	Pass
30	Wire Continuity: Tip to connector	<10 Ohms Resistance	Pass
	Tip to connector	<100 Ohms Resistance	Pass
	Marker Band to connector	<25 Ohms Resistance	Pass
30	Articulation Performance	Pass / Fail	Pass
30	Catheter Bubble Leak Resistance	Leak free at 90 psig for 30 seconds	Pass
30	Catheter Thermal/Mechanical Stress	Pass leak resistance (90 psig) post stress cycling (200 articulations)	Pass
30	Catheter Articulation Cycling	Pass leak resistance (90 psig) and Product Performance post 200 Articulation Cycles minimum	Pass
30	Catheter System Performance Test	Achieve T <-60° C post 200 Articulations (minimum) and 400 articulation cycles (lot average)	Pass
30	Tip Corrosion Resistance	No Corrosion	Pass
30	Catheter Tensile Test (Tip to Shaft)	No damage at 15 N (3.37 lbs)	Pass

2. Catheter Mechanical and Torsional Testing

Mechanical testing was performed on sterilized catheters to verify whether the catheters met their design specifications. Table 4 below reflects the results of this testing.

TABLE 4 - Catheter Mechanical Testing

Qty Tested	Test	Acceptance Criteria	Results
30	Tensile Test Flex Interface, Connector to Handle	Minimum tensile force of 15 lbs	Pass
30	Tensile Test Results - Catheter Shaft to Handle Bond	Minimum tensile force 3.37 lbs	Pass
30	Retention Test Results – Catheter Connections (Dual Line Connector, 4-Pin Connector and Pressure Gage Luer)	Minimum tensile force 30 lbs. (In Operation), Minimum tensile force 5 lbs. (Not In Operation)	Pass
30	Retention Results – 4 Pin Connector (Male on Catheter/Female on Console)	minimum tensile force of 5 lbs	Pass
30	Pressure Gauge Luer Torque Test Results (Female on Catheter/Male on Console)	<1 ft/lb torque	Pass
30	Tensile Results – Pull Wire to Steering Knob	Minimum tensile force 7 lbs	Pass
30	Pressurization Results of High Pressure Tube Assembly	No Leaks up to 1000 psia At <-90° C	Pass
30	Pressurization Results of Catheter Shaft / Low Pressure Exiting Tube Assembly	No Leaks up to 90 psia.	Pass
30	Torsion Fatigue Results – Catheter Shaft	A 30” span of shaft, twisted 180 degrees, shall produce a minimum torque of 1.00 in-oz	Pass

3. Catheter Aging Testing

Functional and Performance testing was performed after aging, extreme conditioning, drop testing, vibrational testing, and load testing in order to verify a 12-month shelf life of the catheter. Table 5 below reflects the results of this testing.

TABLE 5 - Catheter Functional and Performance Testing after 12-Month Real-Time Aging

Qty Tested	Test	Acceptance Criteria	Results
30	Deflection Force	< 7 lbs	Pass
30	Deflection Radius	0.75" ± 0.10"	Pass
30	Curvature of deflection	180°, circular and smooth	Pass
30	Lateral Stiffness	> 5 grams	Pass
30	Off Axis deflection	< 15°	Pass
30	Wire Continuity: Tip to connector Marker Band to connector	Pass/Fail	Pass
30	Articulation Performance	Pass / Fail	Pass
30	Catheter Bubble Leak Resistance	Leak free at 90 psig for 30 seconds	Pass
30	Catheter Thermal/Mechanical Stress	Pass leak resistance (90 psig) post stress cycling (200 articulations)	Pass
30	Catheter Articulation Cycling (in 200 cycle increments)	Pass leak resistance (90 psig) and Product Performance post ≥ 400 Articulation Cycles (lot average)	Pass
30	Catheter System Performance Test	Achieve T < -60° C post 200 Articulations (minimum) and 400 articulation cycles (lot average)	Pass
30	Tip Corrosion Resistance	No Corrosion	Pass
30	Catheter Tensile Test (Tip to Shaft)	No damage at 15 N (3.37 lbs)	Pass

D. Console Testing Summary

1. Electrical Safety and EMI/EMC Testing

Electrical safety and characterization of the console during operation for EMI and EMC characteristics were evaluated using the relevant portions of IEC 60601, CISPR 11 and IEC 61000. The purpose of these tests was to demonstrate that the console is safe to use and complies with recognized safety standards in order to protect patients, users and those servicing the console. The following sections of these standards were utilized:

Emissions

- CISPR 11

Immunity

- IEC 61000-4-2, Section 2: Electrostatic Discharge Immunity Test
- IEC 61000-4-3, Section 3: Radiated, Radio Frequency, Electromagnetic Field Immunity Test
- IEC 61000-4-4, Section 4: Electrical Fast Transient / Burst Immunity Test
- IEC 61000-4-5, Section 5: Surge Immunity Test
- IEC 61000-4-6, Section 6: Conducted Surge Immunity
- IEC 61000-4-8, Section 8: Magnetic Field Immunity
- IEC 61000-4-11, Section 11: Voltage dips & short interruptions Test

Safety

- IEC 60601-1, General Requirements for Safety
- Section 17, Protective earthing, functional earthing and potential equalization
- Section 18, Protective earthing, functional earthing and potential equalization
- Section 19, Continuous Leakage Currents and Patient Auxiliary Currents
- Section 20, Dielectric Strength
- Section 21, Mechanical Strength
- Section 42, Excessive Temperatures
- Section 56, Components and General Assembly
- 56.1.b. General, Marking of components
- 56.1.d. General, Component fixing
- 56.1.f. General, Fixing of wiring
- 56.3.a. Connections - General, Construction of connectors
- 56.4. Connections - General, Connections of capacitors
- 56.5. Connections - General, Protective Devices
- 56.6. Connections - General, Temperature and overload control devices.
- 56.8. Connections - General, Indicators
- 56.10.a. Connections - General, Actuating parts of controls, Protection against electric shock
- 56.10.b. Connections - General, Actuating parts of controls, Fixing, prevention of maladjustment
- Section 57.10, Creepage Distances and Air Clearances.

One console was tested. The conclusion of these tests was that the design of the console meets the requirements of these standards, should be safe for use to the patient and the users and should not cause, or be influenced by, electromagnetic radiation.

Additional testing was performed to acquire NRTL Certification to UL2601.

2. Software Testing

In accordance with the FDA Guidance Document titled “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices,” the console software level of concern was major. Documentation per this level of concern was supplied. Validation testing of system performance and functionality was performed to determine whether the operational behavior of the Model 2020 Console correctly implemented the software and safety specifications. All software testing passed the acceptance criteria.

3. Shipping Testing

A fully finished and packaged console was subjected to standardized ASTM shock and vibration testing to simulate commercial transportation. One console was tested for performance before packaging, then subjected to the shock and vibration testing, then evaluated for performance again and visually inspected. The console met the requirements of this test; the console operated normally after exposure to the shock and vibration test conditions. No connectors or fasteners were loosened.

4. Storage Condition Testing

The console was subjected to temperature extremes of potential storage conditions. The limits chosen for storage conditions are as follows: (1) Temperature: -20 to +60 °C and Relative Humidity: 10 to 90% (non-condensing).

To allow proper equilibration at the temperature and humidity extremes, a test cycle allowed 5 hours for the assembly to approach the test conditions, an 8-hour dwell, followed by a 5-hour return period before the console was evaluated for performance. The results of this test showed the device operated normally after exposure to the storage conditions. One console was tested and met this requirement.

E. System Testing Summary

The Cryoablation system was tested to ensure performance across variations expected during normal operation. For the catheter, the variations included low and high heat load, straight and actuated articulation segment, use with or without a sheath, and catheter model (i.e. different articulation segment length). For the Console, the variations included a Pre-Cool Circuit (PCC) charge in the low and high range. Table 6 below reflects the results of this testing.

TABLE 6 - Temperature performance of System under operational variables

	Consoles with Low PCC (n=2)	Consoles with High PCC (n=2)
Model 1205-6.5/ CRYOBLATOR X-05 (n=5)	Total = 40 ablations All maintained an average tip temperature of below -60°C	Total = 40 ablations All maintained an average tip temperature of below -60°C
Model 1207-6.5/ CRYOBLATOR X-07 (n=5)	Total = 40 ablations All maintained an average tip temperature of below -60°C	Total = 40 ablations All maintained an average tip temperature of below -60°C
Model 1205-6.5 catheters with flow rate at the bottom of the specification (n=2)	Total = 16 ablations All maintained an average tip temperature of below -60°C	Total = 16 ablations All maintained an average tip temperature of below -60°C
Model 1205-6.5 catheters with flow rate at the top of the specification (n=2)	Total = 16 ablations All maintained an average tip temperature of below -60°C	Total = 16 ablations All maintained an average tip temperature of below -60°C
	Ablations per console = 56	Ablations per console = 56

F. Animal Studies

1. Model 1100 Catheter Studies

Pre-clinical studies were performed using an earlier catheter model (Model 1100) and the Model 2020 console. Thirteen canines were treated by applying a cryoablation catheter tip sequentially along the cavo-isthmus region of the right atrium. The findings of these studies were as follows:

- Catheter-delivered cryotherapy can be used to ablate cardiac tissue producing controlled myocardial necrosis.
- Effective creation of electrically inactive myocardium in the targeted regions demonstrated the intended electrophysiological effect.
- The endocardium was intact in the area of ablation. The extra-cellular matrix was preserved without contraction.
- The CryoCor Cryoablation System was appropriately operated.

2. CryoBlator (Model 1200 Series) Catheter Study

An acute pre-clinical study was performed comparing the Model 1100 catheter to Model 1200 (CryoBlator) catheters to ensure that the lesions created with the CryoBlator were equivalent to that created with the earlier catheter models. Two porcine subjects were ablated with both catheter models, one model per thigh. The lesion size was found to be equivalent between the models of catheters. Thus, the animal data previously acquired for the 1100 are applicable to the newer version of the device.

X. SUMMARY OF CLINICAL STUDIES

A. Study Design

The safety and effectiveness of the CryoCor™ Cardiac Cryoablation System was evaluated in a prospective, non randomized single-arm, multicenter trial conducted in 160 subjects at 24 U.S. sites.

Subjects with a recent history of symptomatic, cavo-tricuspid isthmus-dependent atrial flutter were eligible. Subjects were evaluated at discharge, one, three, and (via telephone) six months post-procedure as well as weekly via trans-telephonic event recordings collection. Subjects who met the inclusion and exclusion criteria were enrolled. Subjects with concomitant atrial fibrillation (AF) requiring drug therapy, other than with class IC or class III antiarrhythmic drugs, for conversion to atrial flutter were excluded from the study. The study allowed inclusion of subjects with a history of AF who had converted to symptomatic atrial flutter when placed on anti-arrhythmic drugs (specifically class IC and class III drugs). After cryoablation was performed, the continuation, discontinuation, or modification of all pre-procedure class IC and class III drugs for the purpose of AF control was at the discretion of the investigator.

B. Study Endpoints

The endpoints for the study are described below.

Primary Endpoints

The primary safety and effectiveness endpoints were as follows:

- **acute safety:** measurement of all serious adverse events (SAEs) that occurred within seven days after the procedure
- **acute effectiveness:** creation of bi-directional block (BDB) with cryoablation as the surrogate measure of procedural effectiveness.

Secondary Endpoints

The secondary safety and effectiveness endpoints were as follows:

- **chronic safety:** measurement of serious adverse events that occurred more than seven days after the cryoablation procedure
- **chronic effectiveness:** long-term absence of recurrences of atrial flutter
- **re-treatment effectiveness.**

C. Objective Performance Criteria (OPC)

Objective Performance Criteria (OPC) were prospectively established for this study. The performance goals for this study were taken from the FDA guidance document "Cardiac Ablation Catheters Generic Arrhythmia Indications for Use; Guidance for Industry, July 1, 2002." See Table 7 below for the OPC used.

TABLE 7 - Objective Performance Criteria

Study Endpoint	Target Value	95% Confidence Bound
Acute Success	> 95%	≥ 80%
Chronic Success	>90%	≥ 80%
7 Day SAEs	< 2.5%	≤7%

D. Patient Enrollment and Disposition

Table 8 below documents the enrollment and disposition of the patients screened for the study.

TABLE 8 - Patient Enrollment and Disposition

Patients screened for the study	189
Screen Failures	28
Isthmus-dependent atrial flutter not inducible	26
Persistent atrial fibrillation	1
Non-investigational device failure	1
Patient withdrew consent before treatment	1
CryoCor cryoablation investigational catheter inserted (Intent-to-Treat)	160

E. Demographic Data

Of the 160 treated patients, 122 (76.25%) were men and 155 (96.88%) were Caucasian. The mean age of patients enrolled in the study was 63.06 ± 9.25 years. One hundred and four (104) (65%) of these patients reported concomitant arrhythmias in addition to atrial flutter. Atrial fibrillation was the most common among these reported concomitant arrhythmias (58.75%). The majority of patients presented with counterclockwise atrial flutter (78.75%). Treated patients had a mean ejection fraction (EF) of 54.62 ± 10.44%.

F. Procedural Data

An effective cryotherapy application was determined to be a freeze which resulted in an electrophysiological effect as seen on the electrogram. Patients enrolled in the study had an average of 20 (±11.34) freezes delivered during the ablation with an average of 18 (±9.3) considered to be effective. The average temperature of each freezes was -81.52 (±3.73)°C with the lowest temperature of -85.56 (±3.61)°C being reported. Table 9 below summarizes the procedural data with respect to the delivered cryotherapy.

TABLE 9 - Characteristics of Delivered Cryotherapy

Description	Mean	SD
Number of Freezes	20.45	11.34
Number of Effective Freezes	18.61	9.30
Freeze Duration(min:sec)	47:36	24:34
Average Temp (°C)	-81.52	3.73
Minimum Temp (°C)	-85.56	3.61

G. Primary Endpoint #1: Acute Safety

Ten SAEs occurred in 9 patients. Of the 10 SAEs, 4 events were classified as device- or procedure-related (post procedural hematoma, atrioventricular block complete, cardiac tamponade and acute respiratory failure). All four of these SAEs were resolved by the end of the procedure. Table 10 below lists the specific 7-day SAEs that occurred in the study. Table 11 below provides the overall 7-day post-ablation SAE patient rates.

TABLE 10 - Acute Safety (7-day Serious Adverse Events)

Description	Events				Patients	
	Mild	Mod	Severe	Total	Total	Percent
Atrial Flutter	0	1	0	1	1	(0.63%)
Sick Sinus Syndrome	0	1	1	2	2	(1.25%)
Acute Respiratory Failure *	0	0	1	1	1	(0.63%)
Atrial Fibrillation	0	0	1	1	1	(0.63%)
Atrioventricular Block-Complete*	0	1	0	1	1	(0.63%)
Cardiac Tamponade *	0	0	1	1	1	(0.63%)
Dizziness	0	1	0	1	1	(0.63%)
Hyperthyroidism	0	0	1	1	1	(0.63%)
Post Procedural Hematoma*	0	1	0	1	1	(0.63%)

*device and procedure related events

TABLE 11 - Acute Safety (n=160)

	Patient Count	Percent	95% One-Sided CL
7-Day SAEs	9	5.63%	UCL: 9.61%
7-Day SAEs*	4	2.50%	UCL: 5.63%

*device and procedure related events

H. Primary Endpoint #2: Acute Effectiveness

The acute effectiveness results are summarized in Table 12 below. One subject had the catheter inserted, but no cryoablation was performed. This patient was removed from the analysis.

TABLE 12 - Acute Effectiveness

N	Successes	Percent	95% One-Sided CL
159	140	88.05%	82.96 %

I. Secondary Endpoint #1: Chronic Safety

The rate of SAEs which occurred over 7 days after the ablation procedure is listed in Table 13 below. None of these were related to the device or procedure.

TABLE 13 - Chronic Safety (n=159)

Study Endpoint	# of events	Percent	95% One-Sided CL
SAEs post-7 days	28	17.50%	UCL: 23.06%

Three (3) subjects died during the course of the study. The deaths were not related to the device or ablation procedure. The causes of death were suicide, illicit drug overdose and pulmonary emboli.

J. Secondary Endpoint #2: Chronic Effectiveness

The chronic effectiveness was conditional on acute effectiveness and was determined by clinical follow-up with clear documentation of recurrences in addition to weekly event recordings to evaluate asymptomatic recurrences. Patients were considered a success if they were without any objective evidence (i.e., documented on event recordings, Holter, ECG, etc.) of atrial flutter for 6 months. The primary analysis for the secondary objective was a time-to-event analysis (or Kaplan-Meier nonparametric survival analysis). Subjects who did not have a complete set of data for the six-month post-procedure follow-up period were censored at their last known visit or documented event recording if they had not yet recurred. The chronic effectiveness results are summarized in Table 14 below.

TABLE 14 - Chronic Effectiveness

Analysis	Proportion Free From Recurrence	95% CI (lower bound)	95% CI (upper bound)
Survival Estimate	81.60%	74.70% (Peto)	88.40%

A *post hoc* analysis of chronic effectiveness was conducted which considers all subjects in whom the cryoablation catheter was inserted and cryoablation energy was applied, regardless

of whether the subject was an acute effectiveness success. Patients who died (all for reasons unrelated to the procedure) and those patients that were non-compliant with follow-up were excluded from this analysis. Using this definition, 106 out of 151 (70.2%) of all patients undergoing cryoablation treatment exhibited long-term freedom from cavo-tricuspid isthmus dependent atrial flutter. In a worst case scenario where all censored patients are considered failures, the long-term freedom-from-flutter rate is 66.7% (106 out of 159).

K. Secondary Endpoint #3: Retreatment Effectiveness

Five subjects were re-treated with cryoablation and five subjects were re-treated with RF ablation after recurrence of atrial flutter. One subject was first re-treated with cryoablation, and after an additional recurrence, was re-treated with radio frequency ablation. Subjects re-treated with cryoablation were asked to continue sending in weekly random and symptomatic event recordings until they completed the study. The subjects re-treated with radio frequency were optionally offered the opportunity to continue with event recording. Of the five subjects who were re-treated with cryoablation after recurrence of atrial flutter, one subject experienced recurrence after re-treatment, and was subsequently treated with radiofrequency ablation. Due to the small sample size, no statistical calculations were performed.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Pre-clinical testing adequately demonstrates that the CryoCor Cryoablation System should maintain mechanical and electrical integrity and that materials which come in contact with patients should be biocompatible under the proposed conditions for use. Bench testing has established an acceptable degree of energy delivery accuracy and control.

Clinical testing and statistical analysis demonstrates that there is a reasonable assurance of safety and effectiveness for the CryoCor Cryoablation System for the treatment of isthmus-dependant right atrial flutter.

Thus, the Center for Devices and Radiological Health (CDRH) has determined that there is a reasonable assurance of safety and effectiveness for the CryoCor Cryoablation System based on the results of the pre-clinical testing and the results of the clinical study.

XII. PANEL RECOMMENDATION

On June 27, 2007, the Circulatory System Devices Panel met to review the sponsor's request for approval of the CryoCor Cryoablation System. The Panel recommended that FDA approve the PMA subject to the submission to, and approval by, CDRH of the following:

- a post-approval study to further evaluate the short and long term safety and clinical effectiveness in the population indicated for the device
- an in-person training program for physicians and medical staff
- modifications to the device labeling to describe the clinical study.

XIII. CDRH DECISION

CDRH concurred with the Panel recommendation of June 27, 2007 that there is a reasonable assurance of safety and effectiveness of the CryoCor Cryoablation System based on the results of the pre-clinical testing and the results of the clinical study. Specifically, CDRH believes that the events observed in the clinical study that contributed to the safety endpoint are consistent with the frequency and types of events that would be expected for right atrial flutter ablation procedures in the study population and that the many of events observed were not related to the procedure. Further, CDRH believes that the study demonstrated an acceptable level of acute and chronic effectiveness. Therefore, CDRH believes that a reasonable assurance of safety and effectiveness has been demonstrated.

Below is a discussion of FDA action on each of the Panel's recommendations:

- (1) The sponsor should develop a post-approval study to further evaluate the short and long term safety and clinical effectiveness in the population indicated for the device.

The sponsor agreed to conduct a post-approval study to further evaluate the short and long term safety and effectiveness in the population indicated for the device.

- (2) The sponsor should develop an in-person training program for physicians and medical staff.

The sponsor developed a training program based on an in-person site visit by a CryoCor representative. A checklist of items to be covered must be signed by the trainee prior to use. FDA reviewed the proposed training program and found it to be acceptable. The approval order addresses this condition by restricting the use of the device to individuals who have received training.

- (3) The sponsor should modify the device labeling to describe the clinical study.
The sponsor made the recommended labeling changes prior to approval.

FDA issued an approval order on August 1, 2007. The final condition of approval cited in the approval order is as follows. In addition to the periodic report (often referred to as annual report) requirements outlined in the enclosure, the sponsor has agreed to conduct a post-approval study to further evaluate the safety and effectiveness of their device. The post-approval study will consist of a two-arm registry which will include a total of approximately 650 subjects who receive ablation for the treatment of right atrial isthmus-dependent flutter. Half of the subjects will be treated with the CryoCor Cryoablation system and half will be treated with other ablation systems approved for the treatment of typical (Type I) atrial flutter. Subjects will be followed for 12 months. Short and long-term safety and effectiveness will be assessed in all subjects. The sponsor has agreed to submit reports every six months during the first two years and annually, thereafter. The sponsor will submit post-approval study status reports separate from their PMA annual reports and clearly label them as post-approval study reports.

The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Direction for Use: See the labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post approval Requirements and Restrictions: See Approval Order.