SUMMARY OF SAFETY AND PROBABLE BENEFIT

1. General Information

Device Generic Name: Transcatheter Cardiac Occlusion Device

Device Trade Name: CardioSEAL® Septal Occlusion System

Applicant's Name and Address: Nitinol Medical Technologies, Inc
27 Wormwood Street
Boston, Mass. 02210

Humanitarian Device Exemption (HDE) Number: H99004

Date of Humanitarian Use Device Designation: January 8, 1999

Date of Panel Recommendation: Not Applicable (Refer to Section 12 for discussion)

Date of Good Manufacturing Practices Inspection: May 27, 1999

Date of Notice to the applicant: SEP 8 1999

2. Indications for Use

The CardioSEAL Septal Occlusion System is authorized by Federal (USA) law as a Humanitarian Use Device for use in the following indication only:

> Patients with complex single ventricle physiology who have undergone a fenestrated Fontan palliation procedure and require closure of the fenestration.

The effectiveness of this device in this indication has not been demonstrated.

3. Device Description

The CardioSEAL Septal Occlusion System consists of two primary components:

- The CardioSEAL, which is constructed of a metal (MP35N) framework to which polyester fabric is attached, and
- The Delivery Catheter, a coaxial polyurethane catheter designed specifically to facilitate attachment, loading, delivery and deployment of the CardioSEAL to the defect.

For this humanitarian indication, the CardioSEAL will be available in sizes 17mm and 23mm.

4. Contraindications

Presence of thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the defect is gained.

Active endocarditis, or other infections producing a bacteremia.

Patients whose vasculature, through which access to the defect is gained, is inadequate to accommodate the appropriate size sheath.

Patients whose defect is too small to allow the 11 F sheath to cross the defect.

Anatomy in which the CardioSEAL size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins.

Patients with coagulation disorders who are unable to take Aspirin, Coumadin, or other anticoagulants.

5. Warnings and Precautions:

See Warnings and Precautions in the final labeling (Information for Use).

6. Adverse Events

6.1 Observed Adverse Events:

A total of 83 patients with a fenestrated Fontan were enrolled in a 292 patient multi-center High-risk study. A total of 93 adverse events were recorded among the 83 patients enrolled in the study for closure of their fenestrated Fontan. These adverse events were classified as Serious (2), Moderately Serious (26), Not Serious (65) and were linked to either the device, the implant procedure, the catheterization procedure, or other causes, such as a pre-existing condition. Adverse events (13) that were classified as Serious or Moderately Serious and definitely or probably related to the device, the implant procedure or the catheterization are shown in Table 1.

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	Moderately Serious		Serious	
	Early Event*	Late Event**	Early Event*	Late Event**
Device Related				
None	0	0	0	0
Implant Procedure Related				
Hematoma	1	0	0	0
Catheterization Procedure Related				
Hypotension	1	0	0	0
Medication reaction/allergy	1	0	0	0
Respiratory acidosis	1	0	0	0
Respiratory insufficiency	1	0	0	0
Retroperitoneal hematoma	1	0	0	0
Stridor	1	0	0	0
Urinary retension	1	0	0	0
Vocal cord paresis	0	1	0	0
Catheter induced arrhythmia	0	0	1	0
Cyanosis (new cardiac disease)	1	0	0	0
Pleural effusion	0	1	0	0
Supraventricular tachycardia	1	0	0	0

* = Early event is ≤ 30 days from implant
** = Late event is > 30 days from implant

One fenestrated Fontan patient died 7 months post implant. The death occurred after many weeks of worsening symptoms of heart failure. An independent safety committee reviewed this case and determined that the death was attributed to the patient's underlying cardiac condition.

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6.2 Potential Adverse Events:

Placement of the CardioSEAL involves using standard interventional cardiac catheterization techniques. Complications commonly associated with these procedures include, but are not limited to:
Air Embolus
Allergic dye reaction
Anesthesia reactions
Apnea
Arrhythmia
Death
Fever
Headache / Miigraines
Hematoma and/or Pseudoaneurysm including blood loss requiring transfusion
Hypertension; Hypotension
Infection including Endocarditis
Perforation of Vessel or Myocardium
Stroke / Transient Ischemic Attack
Thromboemobolic events
Vavular regurgitation.

Fractures of the framework have been reported in some patients implanted with the CardioSEAL and a previous generation device when used in applications other than Fenestrated Fontan repair. In the independent, multicenter clinical trial sponsored by Children's Hospital, Boston, Massachusetts, the arm fracture rate was 0% in the Fenestrated Fontan population.

6.3 Observed Device Malfunctions:

There was one report of difficulty in releasing the device from the delivery system. The device was successfully released and delivered to the defect site.

7. Alternative Practices and Procedures

Alternative methods to close the fenestrated Fontan repair include surgical closure or closure with sutures placed at the time the fenestration was created.

8. Marketing History

The CardioSEAL Septal Occlusion System has received the CE mark for marketing in Europe. Since 1997 approximately 1600 devices have been sold in the European Community, Latin America, and certain Pacific Rim countries. The CardioSEAL has been used for a variety of defects including fenestrated Fontan closure.

The CardioSEAL has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

9. Summary of Preclinical Studies

9.1 Biocompatibility Testing

Biocompatibility testing of the implant and delivery system was shown to be acceptable by the following tests which were performed in accordance with the provisions of the ISO 10993-1 and Good Laboratory Practice (GLP) Regulations, 21 CFR 58:

Hemolysis	Cytotoxicity
Systemic Toxicity	Pyrogenicity
Intracutaneous Toxicity	Sensitization

Additional testing of the CardioSEAL included a 7-day Muscle Implant test and an Ames Mutagenicity Assay. The delivery system was also tested for Thromboresistance, Coagulation: Plasma Recalcification Time and Complement Activation. The results of this additional testing found that the implant material was non-toxic and non-mutagenic and the delivery system material was non-thrombogenic and does not activate complement.

9.2 Bench Testing

9.2.1 CardioSEAL – Bench Testing

1. Chemical analysis – MP35N wire

A chemical analysis was conducted to verify the material composition for all of the components of the permanent implant, specifically the MP35n, polyester fabric, solder, polyester suture, and platinum wire. All of these materials were tested and met their raw material specifications.

2. Mechanical Properties – MP35N wire

   Testing was conducted to determine conformance of the MP35N wire to specifications and the corrosion resistance of the wire.

   a) Tensile strength/Elongation
      Tensile strength and elongation was tested on 124 MP35N wire samples (60 as received and 64 annealed). All samples met the specifications for these characteristics.

   b) Corrosion Resistance
      To evaluate the susceptibility of the CardioSEAL to stress corrosion cracking, 27 spring arm subassemblies were subjected to static deflections in simulated body fluids. Nine samples were exposed to these conditions out to 6, 9 and 12 months. Scanning electron microscope analysis of the test samples found no evidence of stress corrosion cracking after an exposure of up to 12 months.

3. Mechanical Testing – CardioSEAL

A summary of the bench testing conducted to evaluate the performance of the CardioSEAL is provided in Table 2.

Table 2: Summary of CardioSEAL Testing

Test	Sample Size	Specification	Results
Fatigue Testing:			
Accelerated Life Testing (Springarm)	N=48 (40mm)	Must withstand 10 yrs. Equivalent (pediatric heart rate) of *in vitro* fatigue cycle testing with no fractures.	No fractures occurred in 630 million cycles.
Other Mechanical Testing:			
Arm/Body Joint Strength	N= 14	10 lbs min	Mean = 25.66lbs S.D. 2.02lbs
Ball/Body Joint Strength	N=21	8 lbs min	Mean = 10.21lbs S.D. = 0.74lbs
Arm/Fabric Strength	N=30	1 lb min	Mean = 4.23lbs S.D. 0.70lbs
Dislodgement Resistance	N=10 (17mm) and N=10 (23mm)	Force required to pull an occluder out of a circular hole (50% of the size of the occluder) must be 38 grams minimum.	17mm = Mean = 169.7g S.D. 13.07g 23mm= Mean = 103.4g S.D. = 9.52g
MRI Compatibility			
MRI Compatible	5 Implants	MR safe up to 1.5 Tesla	Non-ferromagnetic Generated artifact < the size of the implant with 1.5 Tesla

A finite element analysis (FEA) was also performed to compare the springback of the model with the laboratory springback testing, determine the stresses (static and dynamic) during the loading cycle and deployment, and compare the model's fatigue prediction with spring arm fatigue test data.

9.2.2 Delivery Catheter - Bench Testing

To demonstrate the strength of the bonded joints and their ability to resist failure, tensile testing was performed on a minimum of 10 samples for each of the bonded locations. The results found that the strength of each of the bonded joints exceeded the test specification.

9.2.3 CardioSEAL Septal Occlusion System - Bench Testing

A summary of the bench testing conducted to evaluate the performance of the CardioSEAL occluder loaded on the delivery catheter is provided in Table 3.

Table 3: Summary of CardioSEAL Septal Occlusion System Testing

[illegible]	[illegible]	[illegible]	[illegible]
Load and Deployment			
Minimum side length	17mmN=136 23mmN=88	17mm: 10.4 mm min. 23mm: 14.0 mm min.	17mm Mean= 12.54mm S.D. = 0.61mm 23mm Mean= 16.42mm S.D. = 0.55mm
Force into Loader	17mm N=17 23mm N=11	5 lbs max (applies to both)	17mm Mean = 0.93lbs S.D. = 0.35lbs 23mm Mean= 1.14lbs S.D. = 0.36lbs
Force into Pod	17mm N= 17 23mm N=11	6 lbs max (applies to both)	17mm Mean= 1.43 lbs S.D. = 0.46lbs 23mm Mean= 1.74lbs S.D. = 0.61lbs
Force out of Pod	17mm N= 17 23mm N=11	8 lbs max (applies to both)	17mm Mean= 1.33lbs S.D. = 0.49lbs 23mm Mean= 1.64lbs S.D. = 0.30lbs
Springback gap	17mm N= 68 23mm N=44	After being subjected to a loading and deployment cycle, the distance between the proximal and distal sides must be ≤4mm. (applies to both)	17mm Mean = 0.25mm S.D. = 0.40mm 23mm Mean= 0.015mm S.D. = 0.098mm
Ball to Ball Strength	N=30	6 lbs min (applies to both)	Mean= 9.22lbs S.D. = 0.68lbs

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9.3 Sterility and Shelf Life Qualification Studies

The method of sterilization for both the CardioSEAL and delivery system is 100% ETO. The product may be sterilized no more than twice and is validated to achieve a SAL of 10^{-6} using method C of the International Document #ISO 11135, 1994 (adopted by the Committee for the Advancement of Medical Instrumentation.).

To support a 4 year shelf life, the sterility and integrity of CardioSEAL and delivery catheters, aged out to 4 years (real-time plus accelerated aged) was tested. This involved testing both the packaging and the device.

Shipping tests in accordance with the ASTM D4169, ISTA 1A tested the packaging of the CardioSEAL and delivery catheters. All packages were found intact without evidence of physical damage. Fifteen packages each of CardioSEAL devices and delivery catheters were burst tested and found to be within the test specification.

Sterility testing was conducted on 6 samples each of the CardioSEAL and delivery catheter. All samples were found to be sterile. Bond strength and functionality testing were conducted on 5 to 20 samples real time and accelerated aged out to 4 years and exposed to shipping stresses. All test results indicate that the product performs within specification and that sterility is maintained over a period of four years.

9.4 Animal Testing

Following successful initial acute studies, three chronic animal studies were conducted to evaluate the CardioSEAL using both sheep and dog models. Explants occurred at the following timepoints: 2 weeks, 30 days, 90 days, 6 months, 1 year, and 2 years. Atrial septal defects were created either via blade septostomy or Brockenbrough followed by balloon dilation. In the first study, oversized devices were placed in freshly created defects, which resulted in thrombosis and a device arm fracture. It was later confirmed that devices implanted in freshly created defects had higher levels of protein deposition and thrombosis.

The next two studies were conducted in both the sheep and dog model with defects created a minimum of 2 weeks prior to device implantation. These both resulted in an acceptable histological response. One arm fracture occurred at 30 days in a device, which did not appear to be appropriately placed within the ASD. Friction lesions were noted acutely near the suture coil location of arms not yet healed to the septal wall surface; these healed over time. The 3 month, 6 month, 1 year, and 2 year explants showed good fibrous tissue overgrowth and endothelialization with no recent thrombosis or arm fractures.

10. Summary of Clinical Study

Study Design/Objective: The multi-center clinical trial conducted by Children's Hospital, Boston, Massachusetts, is a prospective, non-randomized trial studying the use of the CardioSEAL® Septal Occlusion System to close a variety of hemodynamically significant defects. The risks of surgical closure for the patients enrolled in this trial are sufficient to justify the known and potentially unknown risks of transcatheter closure with the CardioSEAL device. The study (referred to as the High-risk study) is ongoing and is summarized below. Data from patients undergoing fenestrated Fontan closure was extracted from this study.

Fenestrated Fontan Patient Entry: Patients were considered for enrollment in the High risk study if they had complex single ventricle physiology, and had previously undergone a Fontan procedure that included intentional placement of a fenestration within the Fontan baffle. An independent peer review group determined whether a patient should be enrolled into the trial based on the following criteria:

- the patient had a type of defect that was technically difficult or impossible to close surgically, such that the surgical risks were sufficient to justify the known and potential unknown risks of the device, or

- the patient's overall medical condition was such that the surgical risks were sufficient to justify the known and potential unknown risks of the device.

Methods: After enrollment, patients underwent cardiac catheterization. Position and size of the defect were confirmed by angiography. A hemodynamic assessment was performed pre-implant, and after test occlusion of the defect with a balloon. When these data suggested that the defect contributed to unfavorable hemodynamics and was feasible for transcatheter closure, device placement proceeded. Patients received aspirin, 1mg/kg/day, rounded to the nearest half tablet of 80 mg size, for at least six months following the procedure.

Patients were seen for follow up assessments as described in Table 4:

TIMING OF EVALUATIONS – Table 4						
	Pre-Implant	Pre-D/C	1 month F/U	6 month F/U	12 month F/U	24 month F/U
Cardiac HX/PE	X	X	X	X	X	X
Chest X-Ray	X	X	X	X	X	
Fluoroscopy				X		X
Echo/Doppler	X	X	X	X	X	X
O_2 Saturation	X	X	X	X	X	X
EKG (rhythm)	X	X	X	X	X	X
Severity of illness	X	X	X	X	X	X

Primary Endpoints: A 5-category ordinal scale (Severity of Illness Scale) was used to measure clinical status. The scale took values from 1 to 5, and was constructed so that an improvement by one category (e.g., from category 1 to category 2, or from 2 to 3) would be considered clinically meaningful (refer to table 5). Any patient who died during the study would receive a value of 0. Data used in the construction of the scale were measured objectively by diagnostic laboratory tests, documented clinical status, or echocardiography. The data were collected prospectively before device implantation, at discharge from the hospital, and at each follow-up visit, so that patient classification at each time point could be implemented using a computer algorithm.

The major criteria by which severity was categorized for patients undergoing device placement for Fontan baffle fenestration closure, were the measurements of oxygen saturation in room air and hematocrit. In addition to decreasing oxygen saturation and increasing hematocrit, a patient could be placed in category 1 if cyanosis was sufficiently severe to cause the patient to be ventilator dependent. The 5 categories and corresponding oxygen saturation and hematocrit values are provided in Table 5.

Severity of Illness Scale – Table 5				
1	2	3	4	5
≤ 70% O_2 sat in room air or ventilator dependent or Hct ≥ 70	79-71% O_2 sat in room air or Hct > 65-69	80-87% O_2 sat in room air or Hct ≥60-64	88-94% O_2 sat in room air	≥ 95% O_2 sat in room air

Additionally an assessment of the echocardiographic closure status was made at each time point both at the evaluating facility, and by an unaffiliated core laboratory. Residual flow was assessed using Doppler color flow mapping, and graded using the following guidelines:

"Trivial" to "Absent": barely detectable or no detectable residual color flow through the defect. If flow present, it was a single color flow jet, well-circumscribed, with a proximal jet width measuring less than 1 mm in diameter in all views.

"Small": single color flow jet, well-circumscribed, and measuring 1-2mm (maximal proximal width) in all views in infants and children weighing less than 20 kg, or between 1 and 3 mm in diameter in larger children and adults.

"More than small": single color flow jet, well-circumscribed, measuring greater than 2 mm in diameter in all views in infants and children weighing less than 20 kg, or greater than 3 mm in diameter in all views in larger children and adults.

Results: At the time the fenestrated Fontan data was analyzed, 83 patients with no additional anatomic lesions were enrolled in the study for closure of a fenestrated Fontan. Enrollment occurred at three investigational sites, with one site enrolling 92% of the patients. Sixteen of these patients did not have a device implant attempted due to defect smaller than anticipated (10), defect larger than anticipated (1), unfavorable anatomy (2), did not tolerate test occlusion (2), and the decision to surgically close the defect at the time of pacemaker implant/lead replacement (1).

Among the 67 patients treated with a CardioSEAL device, there were 39 (58.2%) males and 28 (41.8%) females. The age of the patients ranged from 2 years to 43 years, with a median age of 7 years.

Device placement was successful in all 67 patients in whom an implant was attempted. A single device was implanted in each patient. Because of the small size of baffle fenestrations, only 17mm and 23mm devices were used. All of the implanted devices remained stable throughout the follow-up period. None of the devices embolized or were explanted.

Table 6 reflects the number of patients observed within each oxygen saturation category at each visit. The available data column presents the number of patients with data available (numerator) and the number of patients who were expected to be seen at the respective visits (denominator).

Oxygen Saturation Results – Table 6						
	Category					
Time point	**70 %**	**71 - 79 %**	**80 - 87%**	**88 - 94%**	**95%**	**Available Data**
Initial	1	10	39	16	0	66/67
Discharge	0	0	3	45	17	65/67
1 Month	0	0	1	28	28	57/65
6 Month	0	0	0	28	21	49/52
12 Month	0	0	3	13	22	38/38
24 Month	0	0	1	8	4	13/13

Table 7 reflects the number of patients observed within each Severity of Illness category at each visit.

Severity of Illness Results – Table 7							
	Category						
Time point	**0**	**1**	**2**	**3**	**4**	**5**	**Available Data**
Initial	0	1	10	39	16	0	66/67
Discharge	0	0	0	2	45	16	63/67
1 Month	0	0	0	2	26	26	54/65
6 Month	1	1	0	0	28	22	52/52
12 Month	0	0	0	3	13	18	34/35
24 Month	0	0	0	0	6	4	10/10

Table 8 reflects the number of patients observed within each echo closure category at each visit.

Echo Closure Status Results – Table 8				
	Category			
	None - Trivial	Small	More than small	Available Data
Initial	7	48	7	62/67
Discharge	52	3	0	55/67
1 Month	33	0	0	33/65
6 Month	46	1	1	48/52
12 Month	23	0	0	23/35
24 Month	6	0	0	6/6

11. Conclusions Drawn from the Studies

The pre-clinical studies indicate that the CardioSEAL Septal Occlusion System is biocompatible and has the appropriate physical and performance characteristics for its intended use, as stated in the labeling.

The clinical data generated from the High-risk study at Children's Hospital, Boston, Massachusetts indicates patients will not be exposed to an unreasonable or significant risk of illness or injury, and that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of alternative forms of treatment.

The preclinical studies and the clinical data from the High-risk study provide reasonable assurance of the safety and probable benefit of the CardioSEAL Septal Occlusion System when used in accordance with its labeling.

12. Panel Recommendations

A Circulatory System Devices Panel advisory meeting was not held to discuss this device. However, a general Panel meeting was held on October 24, 1997, where a lengthy discussion of clinical requirements for this category of devices, i.e., occlusion devices intended to treat congenital heart disease, took place. Based on a review of these recommendations and the data in the HDE, it was determined that a Panel meeting was not necessary for this device.

13. FDA Decision

CDRH determined that, based on the data submitted in the HDE, the CardioSEAL Septal Occlusion System will not expose patients to an unreasonable risk of illness

or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval on SEP 8 1999

14. Approval Specifications

Indications for Use: See the Instructions for Use (Attachment 1)

Hazards to Health from Use of the Device: See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, and ADVERSE EVENTS in the Instructions for Use (Attachment 1)