SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. General Information

Device Generic Name: Heart valve replacement (21 CFR 870.3925) and Pulmonic valved conduit (unclassified)

Device Trade Name: Shelhigh Pulmonic Valve Conduit, Model NR4000 with "No-React®" Treatment

Applicant's Name and Address: Shelhigh, Inc.
P.O. Box 884
Millburn, New Jersey 07041

Humanitarian Device Exemption (HDE) Number: H980007

Date of Humanitarian Use Device Designation: August 12, 1998

Date of Panel Recommendation: The HDE was not taken to Panel. Please see Section XI of this document for a discussion of this issue.

Date of Good Manufacturing Practices (GMP) Inspection: A routine GMP inspection was performed on August 23, 1999

Date of Notice of Approval to the Applicant: September 30, 1999

II. Indications for Use

The Shelhigh Pulmonic Valve Conduit Model NR4000 with "No-React®" treatment is indicated for replacement of diseased, damaged or absent pulmonic artery in small children or infants up to age 4 years with Transposition of the Great Arteries, Truncus Arteriosis, or Tetrology of Fallot with associated cardiac anomalies or with Pulmonary Atresia, or to replace failed conduits in young patients with accelerated conduit failure.

III. Device Description

The device is a glutaraldehyde-fixed porcine pulmonic valve and pulmonary artery, to which segments of bovine pericardial tissue are attached to allow for trimming to fit. The valve will be available in sizes 11, 12, 13, 14, 15, 16, 17, and 18 mm. The device has been treated with a proprietary "detoxification" process called "No-React®" for the purpose of reducing or delaying the onset of calcification.

IV. Contraindications, Warnings, and Precautions

There are no contraindications for the Shelhigh Pulmonic Valve Conduit, Model NR4000 with "No-React®" treatment.

The warnings and precautions can be found in the Instructions for Use (Attachment 1).

V. Potential Adverse Effects of the Device on Health

Potential adverse events for this device include endocarditis, calcification, thrombosis, thromboembolism, primary tissue failure, hemorrhage, unacceptable hemodynamics, arrhythmia, and congestive heart failure. These events could result in patient re-operation or death.

VI. Alternative Practices and Procedures

Alternatives available for infants and small children with cardiac anomalies or pulmonary atresia include use of homografts (aortic or pulmonic) or polyester conduits with or without valves sewn into them. Homografts are often not available in the smaller sizes needed by the young target population for this Humanitarian Device Exemption. It is theorized that the non-tissue elements in the polyester conduits may be the impetus for the formation of the "peel" layer leading to their ultimate occlusion.

VII. Marketing History

The marketing history of this device has been limited. Since November 1997, 70 patients have been treated in Europe. Most of the conduits (n = 47) were implanted in infants when a homograft was not available. The device has not been withdrawn from marketing for any reason.

VIII. Summary of Studies

A. Pre-Clinical Testing

Multiple *in vitro* and *in vivo* tests were performed on a variety of devices treated with the "No-React®" process, e.g., bovine patch material, tubular grafts, or valves. The tables on pages 5 and 6 present an overview of the *in vitro* and *in vivo* testing that was performed.

Hydrodynamic testing was done to assess device performance. Five pulmonic valves (sizes 14 [n=2], 18 [n=1], 19 [n=1], and 25 [n=1]) were cycled at 85, 100, 110, and 120 bpm with a stroke volume of 24-30 ml (CO ~2.3 L/min) and a closing pressure over 100 mm Hg. The pressure gradients were acceptable for use in the pulmonic position (ranging from 2.78 to 8.88 mm), as were the effective orifice area (EOA, ranging from 0.99 to 2.29) and regurgitation (ranging from 1.18 to 5.8 percent).

Durability/fatigue testing was conducted on 6 valves (sizes 19, 18, 17, 16, 14, and 14 mm) at 1400 beats per minute, with a closing pressure of between 40 and 70 mm Hg, and using a 2% benzyl alcohol fluid. The samples were cycled for a 2-3 years equivalent (20 million cycles), which is an adequate time frame for this patient population. Valves were monitored daily for damage, and weekly to verify correct pressure. No damage to any valve was noted at the completion of the testing.

B. Clinical Experience

This valve has limited clinical experience to date. A total of 70 patients had the device implanted in the U.K., Italy, Germany and the Czechoslovakian Republic. Of these, a total of 47 patients were under 1 year of age. Sizes used in these young patients ranged from 11 to 15 mm. The implants occurred between November 1997 through January 1999. Only limited, preliminary information is available for some of the 70 patients. To date, the early mortality is 5.8% in this group (out to 14 months). This is similar to the rates reported in the literature, with children younger than one year having much higher late mortality (29%) than those over 1 year (4%)[1].

IX. Conclusions Drawn from Studies

The *in vitro* studies suggest that the "No-React®" process results in tissue that: (1) leaches significantly less glutaraldehyde than traditionally fixed tissues; (2) is biocompatible; and (3) possesses adequate hemodynamic function and durability as a pulmonic valve replacement. Continued glutaraldehyde leaching is hypothesized to be one possible impetus for calcification observed in the alternative devices. It is unknown if this decrease in leaching of glutaraldehyde will result in a decrease in calcification in the human, but animal studies suggest that this reduction in leaching of glutaraldehyde will be associated with a reduction or delay in the onset of calcification. If calcification can be mitigated, then the durability of these valves may be improved in young children, who tend to calcify valves more rapidly than older children and adults.

Information provided in the HDE indicates that the Shelhigh Pulmonic Valve Conduit with "No-React®" treatment will not expose patients to an unreasonable or significant risk of illness or injury. The "No-React®" treatment may prevent or delay calcification of the valve or pericardial wall tissue. The use of all tissue materials in this conduit may prevent the formation of "peel" (prolific neointimal formation that may eventually occlude the conduit). Additionally, the availability of these smaller device sizes will facilitate correct sizing and provide sizes that are not readily available in homografts. Therefore, 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 currently available devices or alternative forms of treatment.

X. Panel Recommendation

A formal Circulatory System Devices Panel advisory meeting was not held to discuss this device. However, several Panel members were consulted and reviewed pertinent sections of the submission. The Panel members agreed that the performance of alternative devices is inadequate for young children and infants due to the "peel" formation phenomenon and to the lack of availability of sizes for infants and young children. The Panel members agreed that the HDE could be granted for sizes 11 – 18 mm for use in children up to age 4 years. The members further recommended that use in patients needing replacement of a failed conduit should be limited to young patients with accelerated conduit failures.

XI. CDRH Recommendation

CDRH concurs with the recommendation of the Panel members that device sizes 11 – 18 mm can be used in patients up to 4 years of age (first implant) or in patients with accelerated conduit failure (subsequent surgery) for the anomalies indicated above under this HDE.

CDRH has determined that, based on the data submitted in the HDE, the Shelhigh Pulmonic Valve Conduit, Model NR4000 with "No-React®" treatment will not expose patients to an unreasonable risk of illness or injury, and the probable benefit to health from using the device outweighs the risks of injury or illness, and issued an approval order on September 30, 1999.

XII. Approval Specifications

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

Hazards to Health from Use of the Device: See Sections IV and V above.

XIII. References

1. Clarke, DR, Bishop, DA. Ten year experience with pulmonary allografts in children. J Heart Valve Dis 4:384-385, 1995.

Table 1—*In Vitro* Tests

Test Performed	# Test Samples	# Control Samples	Pass/Fail Criteria	Results
Pull Strength	Treated conduit (n = 20 measurements)	Fresh conduit (n = 20 measurements)	Suture tear ≥ 1.75 lb	Range 2.0-4.75 lbs; 2 to 3 times stronger than fresh samples
Pressure Leak	All valves manufactured (lot release)	N/A	No leaks at 150 mm Hg	Only samples that pass are marketed
Bioburden	Routine test	N/A	<10,000 CFU/device	Pass
Sterility	Lot release test	N/A	Sterile (SAL 10^{-6})	No lots non-sterile to date
Pyrogenicity	Lot release test	Standard control	<20 EU/device	Pass
Hemolysis (ASTM F756093 method)	1		Standard defines passing	Pass
Glutaraldehyde Leaching (done by a contract facility)	4 treated fixed samples	4 fixed but untreated samples	<5 ppm/patch of 5 x 5 cm	<1 ppm (via chromatography) in treated samples, all controls failed
Glutaraldehyde Leaching (Shelhigh)	2 No-React treated size 27 mm conduits	2 glutaraldehyde fixed size 27 mm conduits	<5 ppm in 24 hours	No-React samples 0 ppm in 24 hours; all controls failed.
Glutaraldehyde Leaching (done by a second contract facility)	4 No-React treated pericardium and 1 stented porcine valve	4 samples glutaraldehyde fixed pericardium and 1 Carpentier-Edwards porcine valve	<5 ppm/device	No detectable glutaraldehyde in No-React samples; control leached >50 ppm at 24 hours; > 600 ppm at 500 hours
Cytotoxicity	Routine test; 2 pulmonic wall, 3 pericardial, and 5 cusps	Pulmonic wall and pericardial samples plus vehicle control	>95% viability in area near tissue	All No-react samples 95-100% viability; all controls 95-100% cell death near tissue
Shrink Temperature	24 samples (lot release)	6 fresh non-fixed tissue samples	<84 °C fails	Pass
Pronase Digestion (done by a contract facility)	10 No-React treated pericardial samples	10 fresh pericardial samples	45-85% undigested in 24 hours	No-React tissue passed; fresh tissue failed
Pronase digestion (done by a second contract facility)	8 pericardium, 8 cusp and 8 aortic wall No-React samples	8 samples each type of glutaraldehyde fixed samples	45-80% undigested	No-React pericardium 10.4±0.5% digested versus 14.8±0.8% fixed. Cusps 36.0±4.2 for No-React versus 49.3±1.6. Wall 41.1±2.3 No-React versus 52.3±3.0
Shelf Life	13 tested for sterility after 3 years aging	N/A	Sterile	Pass

Table 2—*in Vivo* Tests

Test Performed	**# Test/Control Animals and Implant Duration**	**# Test/Control Samples**	**Pass/Fail Criteria**	**Results**
Subcutaneous Implant in Rats	No-React cusps in 20 rats. Sacrifice at 3, 6, and 14 weeks	Each rat received 2 No-React and 2 glutaraldehyde fixed cusps	N/A	Mean Ca^{++} content at 14 weeks 1.3±0.7 g/mg in the No-React samples and 190.6±89.5 in the controls. Histology showed similar results.
Pericardial replacement in sheep	13 sheep sacrificed at 3-18 months	Peri-Guard gutaraldehyde fixed, polyester, ePTFE, and PGA membrane used as controls	Mild or no adhesions, no calcification	No-React samples were adhesion-free or mildly adherent and non-calcified (gross and histologically). Tissue controls severely adherent ; ePTFE non-adherent but with thick fibrin layer on both sides; polyester very adherent; PGA mesh absorbed with a fine layer of fibrin, non-adherent but no physical protection of the heart.
Tricuspid valve replacement in sheep	4 no-react valves in 4 sheep; historical control from same lab	Historical controls	Normal function at 6 months	Sheep sacrificed at 8, 12, 14, and 18 months. Valves functional at explant, cusps soft and pliable, some negative healing response on the polyester sewing ring
Carotid Artery in Sheep	2 No-React bovine internal mammary arteries	2 glutaraldehyde treated controls placed contralaterally in each animal	Full patency at 2 months	Control arteries occluded in a few days; No-React samples patent until sacrifice at 2 and 3 months; clean intimal layer.