SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

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I. General Information

Device Generic Name:	Intravascular Coronary Stent
Device Trade Name:	MULTI-LINK VISION™ RX Coronary Stent System MULTI-LINK VISION™ OTW Coronary Stent System
PMA Number	P020047
Applicant (Name & Address)	Guidant Corporation Advanced Cardiovascular Systems 3200 Lakeside Drive Santa Clara, CA 95054 USA
Date of Panel Meeting:	N/A
Date of Notice of Approval: to Applicant	July 16, 2003

II. Indications for Use:

The MULTI-LINK RX VISION™ and MULTI-LINK OTW VISION™ Coronary Stent Systems are indicated for improving coronary luminal diameter in the following (See Individualization of Treatment):

- Patients with symptomatic ischemic heart disease due to discrete *de novo* or restenotic native coronary artery lesions (length $\leq$ 25 mm) with reference vessel diameters ranging from 3.0 mm to 4.0 mm;

- Patients with symptomatic ischemic heart disease due to lesions in saphenous vein bypass grafts (length $\leq$ 25 mm) with reference vessel diameters ranging from 3.0 mm to 4.0 mm;

- Restoring coronary flow in patients experiencing acute myocardial infarction, as confirmed by ST segment elevation or angiographic findings, who present within 12 hours of symptom onset with native coronary artery lesions of length $\leq$ 25 mm with a reference vessel diameter of 3.0 mm to 4.0 mm.

Outcome (beyond 9 months) for this permanent implant is unknown at present.

III. Device Description

The MULTI-LINK Rapid Exchange (RX) VISION™ and MULTI-LINK Over-the-Wire (OTW) VISION™ Coronary Stent Systems (CSS) are comprised of two main components: the Stent and the Delivery System.

The MULTI-LINK VISION™ Stents consist of two designs: The Small VISION™ Design for the 3.0 mm diameter and the Medium VISION™ Design for the 3.5 mm and 4.0 mm diameters. Both designs are available in the 8 mm, 12 mm, 15 mm, 18 mm, 23 mm, and 28 mm lengths. In addition, both designs are fabricated from L-605 Cobalt Chromium (CoCr) alloy.

The MULTI-LINK RX VISION™ and MULTI-LINK OTW VISION™ CSS were developed in parallel as two platforms, i.e., the MULTI-LINK RX VISION™ CSS is a Rapid Exchange (RX) platform and the MULTI-LINK OTW VISION™ CSS is an Over-the-Wire (OTW) platform. The distal portion of both delivery systems is similar; however, the proximal portions are different to accommodate either the RX or OTW platform.

IV. Contraindications, Warnings and Precautions

Contraindications

The Guidant MULTI-LINK VISION™ RX and Guidant MULTI-LINK VISION™ OTW Coronary Stent Systems are contraindicated for use in:

- Patients in whom anti-platelet and / or anti-coagulant therapy is contraindicated.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon.

Warnings and Precautions

A list of warnings and precautions can be found in the device labeling.

V. Alternative Practices and Procedures

Patients with early coronary artery disease receive exercise, diet, and drug therapy. If the disease progresses, PTCA, coronary artery bypass graft (CABG) surgery, or stenting may be performed. Stenting may be performed with commercially available stents.

VI. Marketing History

The MULTI-LINK RX and OTW VISION™ CSS have not been marketed in the United States. The MULTI-LINK RX and OTW VISION™ CSS had been approved for commercial distribution in the European Union, Australia, Canada and various other countries when the sponsor implemented a voluntary recall of the MULTI-LINK VISION™ CSS on March 31, 2003. The sponsor received a small but concerning number of complaints from customers regarding stent retention and felt this conservative measure was appropriate at that time.

The sponsor implemented improvements to the stent manufacturing processes and has made modifications to the current test methods to assure adequate stent retention is achieved. The sponsor submitted these changes to this PMA and to various other regulatory agencies, as appropriate. The sponsor received CE approval for these modifications on June 27, 2003 and the MULTI-LINK VISION™ CSS has been reintroduced into the market. The MULTI-LINK VISION™ CSS is currently approved to be marketed in the following countries.

Australia	El Salvador	Italy	New Zealand	Sweden
Algeria	Finland	Jordan	Norway	Switzerland
Austria	France	Lebanon	Pakistan	Thailand
Bahamas	French Polynesia	Lebanon	Portugal	Trinidad, Tobago
Bahrain	Germany	Liechtenstein	Qatar	Tunisia
Belgium	Greece	Luxembourg	Reunion	Tunisia
Bermuda	Guadeloupe	Malaysia	San Marino	Uganda
Bolivia	Guyana	Malaysia	Saudi Arabia	United Kingdom
Burma/Myanmar	Hong Kong	Malta	Singapore	Venezuela
Chile	Iceland	Martinique	Slovenia	Vietnam
Costa Rica	India	Morocco	South Africa	Zimbabwe
Denmark	Indonesia	Netherlands	Spain	
Dominican Republic	Ireland	New Caledonia	Suriname	

VII. Summary of Preclinical Studies

Biocompatibility Testing:

The Guidant MULTI-LINK RX and OTW VISION™ CSS were subjected to biocompatibility testing in accordance with the following general regulations and guidance documents:

-The Federal Good Laboratory Practices Regulations (21 CFR § 58)

-International Standards ISO 10993-1 Part 1: 1997 (*Biological Evaluation of Medical Devices*)

Biocompatibility testing conducted on the MULTI-LINK VISION™ CSS

BIOCOMPATIBILITY TEST	MULTI-LINK VISION™ CSS
Carcinogenicity Test	Literature Reference – carcinogenicity testing not necessary
Cytotoxicity Test	Non-cytotoxic - PASS
Hemolysis Test	Non-hemolytic - PASS
Systemic Injection Test	Non-toxic - PASS
Intracutaneous Test	Non-irritating - PASS
Intramuscular Test	Non-toxic - PASS
Ames Mutagenicity Test	Non-mutagenic - PASS
Sensitization test	Non-sensitizing - PASS
Subchronic Test	Non-toxic - PASS
Rabbit Pyrogen Test	Non-pyrogenic - PASS
LAL Pyrogen Test	Non-pyrogenic - PASS
Coagulation Prothrombin Time	No adverse effect on coagulation prothrombin time - PASS
Unactivated Partial Thromboplastin Time (UPTT) Assay	No adverse effect on UPTT - PASS

Sterilization:

Sterilization testing (dose setting, dose-mapping, and dose audit results) was completed in accordance with the "*Sterilization of health care products - Requirements for validation and routine control - Radiation sterilization*", ANSI/AAMI/ISO 11137-1994 and the *Sterilization of Medical Devices – Validation and Routine control of Sterilization by Irradiation* – EN 552. The sterilization testing results demonstrate that the MULTI-LINK RX and OTW VISION™ CSS can be sterilized to achieve dosing values within the 25 kGy minimum and the 50 kGy maximum qualification dose.

In Vitro Bench Testing

In vitro bench testing was conducted on the MULTI-LINK RX VISION™ and the MULTI-LINK OTW VISION™ CSS in accordance with the U.S. FDA May 1994 *Guidance for the Submission of Research and Marketing Applications for*

Interventional Cardiology Devices: Intravascular Stents. The relevant tests outlined in the guidance were conducted to demonstrate the safety and effectiveness of the MULTI-LINK RX VISION™ CSS and the MULTI-LINK OTW VISION™ CSS. Certain tests were performed only on the OTW or RX stent system, when the attribute to be tested was not delivery system specific. When the attribute was specific to the delivery system, both stent systems were evaluated. All test units were sterilized by E-beam radiation which is the sterilization method that will be used for production purposes. A summary of the testing conducted follows:

Material Specification Conformance Testing:

Chemical Analysis:

The MULTI-LINK VISION™ Stent is fabricated from medical grade L-605 cobalt chromium alloy tubing. This material conforms to ASTM Standard F90 for both the chemical analysis and the inclusion/ impurity content. The MULTI-LINK VISION™ Stent tubing is analyzed according to ASTM Standard A751, "Practices and Terminology for Chemical Analysis of Steel Products". The tubing is initially subjected to an optical emission vacuum spectrometric analysis according to ASTM Standard E1086, which detects all elements except nitrogen and in some instances carbon. Nitrogen is detected according to gas fusion thermal conductivity as described in ASTM Standard E1019. Additionally, carbon is detected using the combustion method outlined in ASTM Standard E1019. The chemical analysis of the MULTI-LINK VISION™ Stent met the product specifications.

Scanning Electron Microscopy (SEM) Analysis:

SEM analysis was conducted to identify and analyze trace contaminants, which may be present on the MULTI-LINK VISION™ Stent. The elemental analysis of these particles determined that they included carbon, oxygen, sodium, chlorine, potassium, sulfur, silicon, magnesium and fluoride, all of which can be traced to contact with gloves, glove residue, balloon materials, and biocontaminants (fingers, skin, saliva, etc.). Other elements that were observed were titanium, aluminum, cobalt*, iron, chromium*, tungsten*, nickel, calcium, and phosphorus. The size and quantity of the particles evaluated do not exceed USP requirements for small volume injections.

* Note: The elements cobalt, chromium, and tungsten are contributed by the adjacent and underlying stent alloy.

Tensile Strength and Elongation:

The tensile strength and elongation test was performed to determine the tensile strength and percent elongation of the MULTI-LINK VISION™ Stent tubing. The yield strength and elongation of the MULTI-LINK VISION™ Stent met the product specifications.

ASTM Conformance:

The MULTI-LINK VISION™ Stent is fabricated from medical grade L-605 cobalt chromium (CoCr) alloy tubing. This material conforms to ASTM Standard F90-01. To ensure compliance with ASTM Standard F90-01, the L-605 CoCr alloy tubing is also tested or required to meet the following ASTM Standards:

ASTM Standards used to Evaluate the MULTI-LINK VISION™ Stent Tubing

ASTM Standard	Title
ASTM A751-96	Standard Test Methods, Practices, and Terminology for Chemical Analysis of Steel Products
ASTM E8-01e1	Standard Test Methods for Tension Testing of Metallic Materials
ASTM E45-97e2	Standard Test Methods for Determining the Inclusion Content of Steel
ASTM E112-96e1	Standard Test Method for Determining Average Grain Size
ASTM E345-93(1998)	Standard Test Methods of Tension Testing of Metallic Foil
ASTM E354-93(2000)e1	Standard Test Methods for Chemical Analysis of High-Temperature, Electrical, Magnetic, and Other Similar Iron, Nickel and Cobalt Alloys.
ASTM E1019-00	Standard Test Method for Determination of Carbon, Sulfur, Nitrogen and Oxygen in Steel and in Iron, Nickel and Cobalt Alloys.
ASTM E1086-94	Optical Emission Vacuum Spectrometric Analysis of Stainless Steel by the Point-to-Plane Excitation Technique

ASTM F90-01	Standard Specification for Wrought Cobalt-20 Chromium-15 Tungsten-10 Nickel Alloy for Surgical Implant Applications (UNS R32605)
ASTM F138-00	Standard Specification for Wrought 18 Chromium-14 Nickel-2.5 Molybdenum Stainless Steel Bar and Wire for Surgical Implants (UNS S31673)
ASTM F2129-01	Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices.
ASTM G5-94(1999)e1	Standard Reference Test Method for Making Potentiostatic and Potentiodynamic Anodic Polarization Measurements
ASTM G15-99b	Standard Terminology Relating to Corrosion and Corrosion Testing
ASTM G71-81(1998)e1	Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes
ASTM G78-95	Standard Guide for Crevice Corrosion Testing of Iron-Base and Nickel-Base Stainless Alloys in Seawater and Other Chloride-Containing Aqueous Environments
ASTM G102-89(1999)	Standard Practice for Calculation of Corrosion Rates and Related Information from Electrochemical Measurements

A majority of the ASTM standards and test methods for L-605 CoCr tubing generally refer to bar, wire, sheet and strip testing. The sponsor has adopted the relevant sections of these standards to ensure compliance with ASTM F90. The MULTI-LINK VISION™ Stent met the requirements of the aforementioned ASTM Standards.

Corrosion:

The corrosion resistance of L-605 CoCr alloy tubing used to fabricate the MULTI-LINK VISION™ Stent is governed by the presence of a passive oxide film. The film markedly lowers the corrosion rate (approaches a value of zero) by protecting the alloy from its corrosive environment. The metal is susceptible to pitting when there is a breakdown of the passive film or a discontinuity in the oxide film. The metal is unable to re-passivate following breakdown due to the presence of a high chloride ion

concentration. Each stent is electropolished to eliminate surface imperfections and passivation of the stent promotes the formation of a protective oxide layer.

The L-605 CoCr alloy MULTI-LINK VISION™ stent demonstrated acceptable corrosion resistance in all three studies. The MULTI-LINK VISION™ Stent demonstrated acceptable corrosion resistance when in contact with stainless steel or another L-605 CoCr alloy Stent. Additionally, the testing demonstrated that there were no significant differences in the corrosion properties of the stent with the modifications to the hypotube dimensions and polishing parameters.

Stent Integrity Testing:

Dimensions:

The dimensions test was used to evaluate the dimensions of the MULTI-LINK VISION™ Stent. Samples were measured for stent strut width, thickness, length and mass. The dimensions of the MULTI-LINK VISION™ Stent met the product specifications.

Stent Free Area Percentage:

The stent free area percentage was found by subtracting the area of the MULTI-LINK VISION™ Stent from the total stented vessel area, and then dividing the result by the total stented vessel area.

Length Change:

The length change test determined the percent shortening of the MULTI-LINK VISION™ Stent when expanded to the nominal diameter. Each stent was measured prior to and after expansion in tubing. The length change of the MULTI-LINK VISION™ Stent met the product specifications.

Uniformity of Expansion:

The uniformity of expansion test measured the uniformity of the MULTI-LINK VISION™ Stent along its length after balloon expansion in tubing. Uniformity was defined as the mean outer diameter minus the average double wall thickness of the stent to derive the inner diameter plus or minus the standard deviation at three to five locations along the length of the stent (proximal, mid, distal) after balloon expansion. The smallest inner diameter was then subtracted from the largest one. The MULTI-LINK VISION™ Stent expanded uniformly and maintained this uniformity upon withdrawal of the balloon. The uniformity of expansion of the MULTI-LINK VISION™ Stent met the product specifications.

Recoil:

The recoil test determined the percent recoil of the MULTI-LINK VISION™ Stent after balloon expansion. The stent outer diameter was measured with and without the expanded balloon in place and the percentage was calculated. The recoil of the MULTI-LINK VISION™ Stent met the product specifications.

Radial (Hoop) Strength:

The radial (hoop) strength test was performed to determine the radial strength of the MULTI-LINK VISION™ Stent. The test is performed by applying and then releasing an incrementally increasing compressive force on the stent using a controlled instrument. The force deflection curve from the compression test is then transferred into a radial stress-strain curve to determine the radial strength. The radial strength of the MULTI-LINK VISION™ Stent met the product specifications.

Accelerated Fatigue Testing:

The structural integrity of the MULTI-LINK VISION™ Coronary Stent was evaluated utilizing *in vitro* accelerated fatigue testing and finite element analysis modeling. The fatigue test system simulated the arterial environment and the FEA modeling incorporated a conservative assumption on arterial contraction. The models for both the accelerated fatigue test and the finite element analysis are constructed by loading the internal and external boundaries of the stent based on *in vivo* blood pressure and arterial distensibility. In both cases, the stent performed well within product and material specifications. Specifically, the static and fatigue results on the MULTI-LINK VISION™ Coronary Stent structures, from *in vitro* fatigue testing and finite element modeling presented in this report demonstrate that the expanded stent will survive the ten-year fatigue loading as demonstrated by the Goodman Analysis of the FEA model and *in vitro* fatigue testing. The maximum stresses and strains of the expanded stent are below the ultimate tensile stress and fracture strain of the material, as demonstrated by the FEA model.

Magnetic Resonance Imaging

Passed Shellock Testing for MRI safety and was tested in accordance with U.S. FDA draft guidance February 7, 1997 "*A Primer on Medical Device Interactions with Magnetic Resonance Imaging Systems.*" The results of the MRI safety tests for the cobalt chromium stent indicated the following:

1. Magnetic field interactions will not present a hazard with respect to movement or dislodgment of these stents using MR systems operating at 1.5 Tesla or less;

2. RF energy-induced heating will not pose an increased risk to a patient with the cobalt chromium stent; and
3. Artifacts were characterized and may affect the diagnostic MR procedure if the area of interest is in the same area as one of the stents.

Based on these results, the MULTI-LINK VISION™ stents have been shown to be MRI safe immediately following implantation at field strengths of 1.5 tesla or less, a maximum spatial gradient of 450 gauss/cm, gradient magnetic fields of 6.3 mT/m or less and a maximum whole body averaged specific absorption rate (SAR) of 1.2 W/kg for 15 minutes of MR imaging. MR imaging quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

Stent and Delivery System Testing

Delivery System Profiles:

The delivery system profile test was performed to determine the crimped stent outer diameter of the MULTI-LINK VISION™ CSS. The profiles of the MULTI-LINK VISION™ CSS met the product specifications.

Delivery System Preparation Test:

The delivery system preparation test was performed to evaluate the ease of preparing the MULTI-LINK VISION™ CSS using the double-negative aspiration method with 60% contrast diluted 1:1 with water. The double-negative aspiration method adequately prepares the MULTI-LINK VISION™ CSS.

Deflation Times Test:

The deflation times test was performed to determine the deflation times of the MULTI-LINK VISION™ CSS. The delivery systems were inflated to the rated burst pressure, deflated, and the deflation times were recorded. The deflation times of the MULTI-LINK VISION™ CSS met the product specifications.

Stent Movement Test:

Stent movement testing was performed to determine the stent retention of the MULTI-LINK VISION™ CSS. Following receipt of a small number of complaints related to stent retention from customers in countries where the product was approved for marketing, and the implementation of modifications to the VISION™ CSS to address this issue, this test was revised to assure adequate stent retention. The modified test successfully differentiated between the unmodified and modified VISION™ systems.

The performance of the modified VISION™ CSS was also compared to the performance of the PMA-approved MULTI-LINK ZETA™ CSS, which has an acceptably low rate of stent retention complaints and stent movement was shown to be comparable.

In the modified test, the delivery system was inserted into a rotating hemostatic valve and guiding catheter, then through tortuosity and a simulated lesion. The delivery system was then retracted proximal to the distal tip of the guiding catheter. The last two steps were repeated for a specified number of times. At the end of the test, the system was removed from the guiding catheter and inspected for stent movement. The luminal (inner) diameter of the simulated lesion was established at a dimension at which failure of the unmodified VISION™ CSS occurred, but acceptable results were still demonstrated with the ZETA™ CSS. The stent movement of the modified MULTI-LINK VISION™ CSS through the modified test met the product specifications. These results will be confirmed through a post approval monitoring program to evaluate stent retention complaints (see postapproval conditions in Section XIII).

Guiding Catheter Pullback Test:

The guiding catheter pullback test was performed to determine whether the MULTI-LINK VISION™ CSS can be successfully retracted back into a 5F guiding catheter prior to deployment of the stent. The delivery system was inserted into a rotating hemostatic valve and guiding catheter, until the distal tip was approximately 10 cm distal of the guiding catheter tip. The delivery system tip was then retracted proximal to the distal tip of the guiding catheter. The last two steps were repeated for a specified number of times. At the end of the test, the system was removed from the guiding catheter and inspected for stent movement. The guiding catheter pullback of the MULTI-LINK VISION™ CSS met the product specification.

Balloon Rupture and Stent Compliance Tests:

The balloon rupture and stent compliance tests determined the balloon rupture pressure and the inflation pressure/stent diameter relationship of the MULTI-LINK VISION™ CSS. The delivery system was inflated incrementally until failure. The stent outer diameter was measured at each programmed pressure, and the correlation between the inflation pressure and stent inner diameter was determined by subtracting two times the average wall thickness from the stent outer diameter measurements.

The data analysis indicates with 95% confidence that 99.9% of the MULTI-LINK VISION™ CSS balloons will not rupture at or below the rated burst pressure (RBP) of 235 psi (16 atm). The stent diameters did not significantly distend with increasing inflation pressures. The balloon

rupture pressures (rated burst pressures) and stent compliance of the MULTI-LINK VISION™ CSS met the product specifications.

Inner Member Collapse Test:

The inner member collapse test was performed to determine whether the inner member would sustain pressure before irreversibly collapsing. The delivery system was inflated to specified pressures, and then deflated between each inflation. Guide wire movement was inspected. The inner member collapse of the MULTI-LINK VISION™ CSS met the product specifications.

Delivery System Shaft Pressure Test:

The Delivery System shaft pressure test determined the pressure integrity of the shaft of the MULTI-LINK VISION™ CSS. The shafts were pressurized from 0 psi until failure. The pressure integrity of the shaft of the MULTI-LINK RX VISION™ CSS met the product specifications.

Distal Delivery System Tensile Test:

The distal Delivery System tensile test determined the tensile strength of the junction between the distal balloon seal and proximal portion of the delivery systems of the MULTI-LINK VISION™ CSS. All junctions were pulled until failure using an Instron. The distal Delivery System tensile test of the MULTI-LINK VISION™ CSS met the product specifications.

Proximal Delivery System Tensile Test:

The proximal Delivery System tensile test determined the tensile strength of the junction between the luer adaptor and hypotube-intermediate shaft junction of the MULTI-LINK VISION™ CSS. All junctions were pulled until failure using an Instron. The proximal Delivery System tensile test of the MULTI-LINK VISION™ CSS met the product specifications.

Soft Tip Tensile Test:

The soft tip tensile test determined the tensile strength of the proximal and distal portions of the soft tip junction of the MULTI-LINK VISION™ CSS. The junction was pulled until failure using an Instron. The soft tip tensile test of the MULTI-LINK VISION™ CSS met the product specifications.

Delivery System In-Stent Balloon Fatigue Test:

The delivery system in-stent balloon fatigue test was performed to determine whether the balloon will sustain repeated inflations inside the stent without failure. The delivery system was pressurized to expand the

stent in Tecoflex tubing, and then deflated. A pressure tester was then used to perform subsequent inflations inside the stent. The delivery system in-stent fatigue of the MULTI-LINK VISION™ CSS met the product specifications.

Delivery System Coating Friction Test

This test determined the coefficient of friction of the hydrophilically coated portion of the MULTI-LINK VISION™ CSS. These results of this test are functionally acceptable and within the product specification.

Delivery System Coating Dry Adhesion Test

This test demonstrated the integrity of the hydrophilic coating of the MULTI-LINK VISION™ CSS. The testing determined the percent adhesion of the coating on the catheter test surface. The adhesion results are functionally acceptable and within the product specification.

Delivery System Coating Particulate Test

This test determined the number of coating particulates generated by the hydrophilically coated portion of the MULTI-LINK VISION™ CSS when the delivery system is pulled through a constriction. The mean particulate counts generated are acceptable and within the product specification.

Shelf-Life (Aging) Testing:

Samples of the MULTI-LINK RX VISION™ and MULTI-LINK OTW VISION™ CSS were subjected to accelerated aging and evaluated to ensure adherence to the product specification. The data collected to date ensures a product shelf life of three months for the MULTI-LINK RX VISION™ CSS. The shelf life will be extended for up to three years, as sufficient accelerated aging test data are collected, based on the same test protocols and acceptance criteria.

Package Integrity Testing:

The packaging validation testing was conducted through a three-year shelf life. The packaging configuration for the MULTI-LINK VISION™ RX and OTW CSS meets all relevant guidelines and current specifications for Guidant ACS packaging materials. The header bag used to package the MULTI-LINK RX and OTW ZETA™ CSS exhibits acceptable integrity and maintains this functional ability throughout the current product shelf life of up to three-years.

Animal Studies

Acute animal studies were conducted to evaluate the performance and safety of the MULTI-LINK RX VISION™ CSS and MULTI-LINK OTW VISION™ CSS. Device flexibility, pushability, trackability, stent security, stent strut apposition to the vessel wall, stent symmetry following deployment, and vessel wall injury were evaluated using quantitative coronary angiography. The MULTI-LINK RX VISION™ CSS and MULTI-LINK OTW VISION™ CSS met the acceptance criteria and are deemed to be acceptable for clinical use.

Two chronic animal studies were performed which independently evaluated the L-605 Cobalt Chromium (CoCr) alloy Stent. The chronic animal studies were successfully performed.. The objective of the chronic animal studies was to demonstrate that the L-605 CoCr alloy Stent is safe and that the vascular response of the L-605 CoCr alloy stent is equivalent to stainless steel stents.

The summaries of the two chronic studies are included below:

Cobalt Chromium Alloy Animal Evaluation: Chronic Study 1

The objective of this study was to demonstrate an equivalent vascular response in porcine coronary arteries between L-605 CoCr alloy stents as compared to 316L SS stents. The only difference between the stent designs from L-605 CoCr alloy and from 316L stainless steel was that the nominal strut thickness for the 316L stainless steel stents was 0.0055 inches as compared to 0.0033 inches for the L-605 CoCr alloy stents. These thicknesses represent the design thickness of the stents, respectively. The stents were implanted for 28-day, three-month, and six-month time periods. The L-605 CoCr alloy stent demonstrated an equivalent vascular response to the Stainless Steel control stent and that it can be deployed safely into coronary arteries.

MULTI-LINK VISION™ CSS Stent Design Animal Evaluation: Chronic Study 2

The objective of the second chronic study was to evaluate safety, functional performance, and chronic vascular response to the final design of the MULTI-LINK VISION™ Stent at a three-day and a 28-day timepoint. This study was conducted in non-atherosclerotic mini-swine. The study evaluated the angiographic patency and the physiological response of the vessel to the implanted stent which included quantitative angiography and morphometric analysis for the determination of arterial minimal lumen diameters and areas for both the three-day and 28-day timepoints. Scanning electron microscopy to ascertain stent endothelialization at one month was also performed. The results of the study demonstrated that the MULTI-LINK VISION™ Stent can be deployed safely into coronary arteries.

VIII. Potential Adverse Effects of the Device on Health

The VISION Registry was a multi-center, non-randomized, prospective study conducted to assess the safety and efficacy of the Guidant MULTI-LINK VISION™ RX Coronary Stent System in native *de novo* coronary artery lesions in 267 patients. The primary endpoint was target vessel failure (TVF) at 180 days defined as a composite of death, Q-Wave Myocardial Infarction (QMI), Non-Q-Wave Myocardial Infarction (Non-QMI), Target Site Revascularization (TSR) or Target Vessel Revascularization (TVR) by Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI). Secondary endpoints of MACE and in-hospital TVF at 270 days were also evaluated. These results were compared to results of the 202 *de novo* lesion patients treated with the Guidant MULTI-LINK RX TETRA™ Coronary Stent System in the TETRA Registry.

A total of 297 Guidant MULTI-LINK VISION™ Coronary Stents were implanted in 267 patients. For the 180-day time point, there were three (1.2%) deaths, two (0.8%) Q-Wave MIs, two (0.8%) Non Q-Wave MIs, 13 (5.0%) TSR by PCI, 0 (0.0%) TSR by CABG, one (0.4%) Subacute Thrombosis, three (1.2%) Cerebrovascular Accidents, six (2.3%) Serious Bleeding Events, and four (1.6%) Serious Vascular Events.

There were two (0.8%) device malfunctions reported in the VISION Registry: inability to cross the lesion on the first attempt and inaccurate stent placement. These two device malfunctions did not result in adverse events. There was one stent delivery failure that resulted in the stent being lost in the peripheral system. The patient suffered no adverse events and a subsequent Guidant MULTI-LINK VISION™ Coronary Stent was successfully deployed.

Table 1 summarizes the Principal Adverse Events of patients receiving the Guidant MULTI-LINK VISION™ RX Coronary Stent System at 180 and 270 days, along with those receiving the Guidant MULTI-LINK TETRA™ Coronary Stent System at 180 days.

Table 1: VISION Registry - Principal Adverse Events Through 180 & 270 Days

percent [95% confidence interval] (number)

	180-Day Comparison - *de novo* Registries		270-Day Data
Complication	MULTI-LINK VISION (N = 267)[1]	MULTI-LINK TETRA (N = 202)	MULTI-LINK VISION (N = 267)[1]
Any Adverse Event	**13.2%** [9.3%, 17.9%] (34)	**20.9%** [15.4%, 27.3%] (41)	**20.5%** [15.7%, 25.9%] (53)
Early (In-Hospital)	**5.0%** [2.7%, 8 5%] (13)	**7.9%** [4 6%, 12.5%] (16)	**5.0%** [2.7%, 8.4%] (13)
Out-of-Hospital	**8.5%** [5.4%, 12.6%] (22)	**12.8%** [8.4%, 18.3%] (25)	**15.8%** [11.6%, 20.9%] (41)
Death Total	**1.2%** [0.2%, 3.4%] (3)	**0.5%** [0 0%, 2.8%] (1)	**1.2%** [0 2%, 3.3%] (3)
Early (In-Hospital)	**0.4%** [0.0%, 2.1%] (1)	**0%** [0 0%, 1.8%] (0)	**0.4%** [0.0%, 2.1%] (1)
Out-of-Hospital	**0.8%** [0.1%, 2.8%] (2)	**0.5%** [0.0%, 2.8%] (1)	**0.8%** [0.1%, 2.8%] (2)
QMI Total	**0.8%** [0.1%, 2.8%] (2)	**0%** [0.0%, 1.9%] (0)	**0.8%** [0.1%, 2.8%] (2)
Early (In-Hospital)	**0.4%** [0.0%, 2.1%] (1)	**0%** [0.0%, 1.8%] (0)	**0.4%** [0.0%, 2.1%] (1)
Out-of-Hospital	**0.4%** [0.0%, 2.1%] (1)	**0%** [0 0%, 1.9%] (0)	**0.4%** [0 0%, 2 1%] (1)
Non-Q MI Total	**0.8%** [0.1%, 2.8%] (2)	**2.6%** [0.8%, 5.9%] (5)	**0.8%** [0.1%, 2.8%] (2)
Early (In-Hospital)	**0.8%** [0.1%, 2.8%] (2)	**2.0%** [0.5%, 5.0%] (4)	**0.8%** [0.1%, 2.8%] (2)
Out-of-Hospital	**0%** [0.0%, 1.4%] (0)	**0.5%** [0.0%, 2.8%] (1)	**0%** [0.0%, 1 4%] (0)
TSR CABG Total	**0%** [0.0%, 1.4%] (0)	**1.0%** [0.1%, 3.6%] (2)	**0.4%** [0.0%, 2.1%] (1)
Early (In-Hospital)	**0%** [0.0%, 1 4%] (0)	**0%** [0.0%, 1.8%] (0)	**0%** [0.0%, 1.4%] (0)
Out-of-Hospital	**0%** [0.0%, 1.4%] (0)	**1.0%** [0.1%, 3.6%] (2)	**0.4%** [0.0%, 2.1%] (1)
TSR PCI Total	**5.0%** [2.7%, 8.5%] (13)	**8.7%** [5.1%, 13.5%] (17)	**11.2%** [7.6%, 15.7%] (29)
Early (In-Hospital)	**0.8%** [0.1%, 2.8%] (2)	**0%** [0.0%, 1.8%] (0)	**0.8%** [0.1%, 2.8%] (2)
Out-of-Hospital	**4.7%** [2.4%, 8.0%] (12)	**8.7%** [5.1%, 13.5%] (17)	**10.8%** [7.3%, 15.2%] (28)
*SAT Total	**0.4%** [0.0%, 2.1%] (1)	**0%** [0.0%, 1.9%] (0)	**0.4%** [0 0%, 2.1%] (1)
Early (In-Hospital)	**0.4%** [0.0%, 2.1%] (1)	**0%** [0.0%, 1 8%] (0)	**0.4%** [0.0%, 2.1%] (1)
Out-of-Hospital	**0%** [0.0%, 1.4%] (0)	**0%** [0.0%, 1 9%] (0)	**0%** [0.0%, 1.4%] (0)
*Cerebrovascular Accident Total	**1.2%** [0.2%, 3.4%] (3)	**0.5%** [0.0%, 2 8%] (1)	**1.2%** [0.2%, 3.3%] (3)
Early (In-Hospital)	**0.4%** [0.0%, 2.1%] (1)	**0%** [0.0%, 1.8%] (0)	**0.4%** [0.0%, 2.1%] (1)
Out-of-Hospital	**0.8%** [0.1%, 2.8%] (2)	**0.5%** [0.0%, 2.8%] (1)	**0.8%** [0.1%, 2 8%] (2)
*Bleeding Complications Total	**2.3%** [0.9%, 5.0%] (6)	**3.1%** [1 1%, 6.5%] (6)	**2.7%** [1.1%, 5.5%] (7)
Early (In-Hospital)	**0.8%** [0.1%, 2.8%] (2)	**3.0%** [1.1%, 6.4%] (6)	**0.8%** [0.1%, 2.8%] (2)
Out-of-Hospital	**1.6%** [0.4%, 3.9%] (4)	**0%** [0.0%, 1.9%] (0)	**1.9%** [0 6%, 4 4%] (5)
*Vascular Complications Total	**1.6%** [0.4%, 3.9%] (4)	**4.6%** [2.1%, 8.5%] (9)	**1.9%** [0.6%, 4.4%] (5)
Early (In-Hospital)	**1.2%** [0.2%, 3.4%] (3)	**3.0%** [1.1%, 6.4%] (6)	**1.2%** [0.2%, 3.3%] (3)
Out-of-Hospital	**0.4%** [0.0%, 2.1%] (1)	**1.5%** [0.3%, 4.4%] (3)	**0.8%** [0.1%, 2.8%] (2)
Stent Delivery Failure	**0.4%** [0.0%, 2.1%] (1)	**0.5%** [0.0%, 2.7%] (1)	**0.4%** [0.0%, 2.1%] (1)

[1]268 patients enrolled but patient 306-4002 is excluded due to VISION stent being implanted in SVG, so n = 267.

- *Secondary endpoints were analyzed on per protocol evaluable patients. There were n = 258 patients available at the 180 day f/u time point and there were n = 259 patients available at the 270 day f/u time point.
- ANY Adverse event includes death, Q-Wave MI, Non-Q-Wave MI, TSR CABG, TSR PCI, SAT, cerebrovascular accident, serious bleeding event, and serious vascular event.
- Early (In-Hospital) refers to events during the hospitalization for stent placement. If the patient had a prolonged hospitalization, in-hospitalization was considered to be less than or equal to 7 days post-procedure.
- In cases where a patient experienced both an in-hospital and an out-of-hospital event, they are counted once in each group, however they are counted only once in the total patients for that category. Hence, the sum of the in-hospital and out-of hospital rate may not equal the total rate.
- See Table 5 Footnotes for additional VISION Registry definitions.

Adverse events that may be associated with the use of a coronary stent in native coronary arteries include:

- Acute myocardial infarction
- Arrhythmias, including VF and VT
- Death
- Dissection
- Drug reactions to anti-platelet agents / contrast medium
- Emboli, distal (air, tissue or thrombotic emboli)
- Emergent Coronary Artery Bypass Surgery
- Hemorrhage, requiring transfusion
- Hypotension / Hypertension
- Infection and pain at insertion site
- Ischemia, Myocardial
- Perforation
- Pseudoaneurysm, Femoral
- Restenosis of stented segment
- Spasm
- Stent embolization
- Stent thrombosis / occlusion
- Stroke / cerebrovascular accident
- Total occlusion of coronary artery

IX. Summary of Clinical Studies

Background: Studies conducted on the use of 316L Stainless Steel Multi-Link CSSs to support use of those systems in patients with SVGs and in patients undergoing an AMI were also reviewed in support of this product. Both indications were accepted as appropriate for the VISION™ CSS as well. For more information on those studies, see the Summary of Safety Effectiveness Data for P970020/S40 (*insert web link*). A separate study of the Multi-Link VISION™ CSS was conducted as described below.

Title of Study: A Non-Randomized Evaluation Of The Multi-Link Rx Vision™ Coronary Stent System In The Treatment Of Patients With *De Novo* Native Coronary Artery Lesions

Purpose: To assess the safety and efficacy of the Guidant MULTI-LINK VISION™ RX Coronary Stent System in reducing target vessel failure in *de novo* native coronary artery lesions.

Conclusions: In selected patients, the VISION Registry demonstrated the 180-day and 270-day safety and efficacy of this stent for the treatment of patients with *de novo* lesions in native coronary arteries.

Design: A prospective, non-randomized, multi-center, global (18 North American, 1 European and 3 Asia-Pacific sites), consecutive enrollment study. Patients were at least 18 years of age, with angina or a positive functional study, undergoing elective, single *de novo* lesion treatment in a native coronary artery. Patients were required to have a target vessel with the following coronary angiographic features: major coronary artery or major branch with a visually estimated stenosis of $\geq 50\%$ and $< 100\%$, a reference diameter visually estimated to be ≥ 3.0 mm and ≤ 4.0 mm, and a lesion length visually estimated to be ≤ 25 mm.

The primary endpoint for the VISION Registry was target vessel failure (TVF) at 180 days, defined as a composite of death, Q-Wave MI, Non-Q-Wave MI, TSR, or TVR by CABG or PCI. The primary endpoint was analyzed on an intent-to-treat basis defined as patients who had the investigational device introduced into the body (stent system advanced through distal end of the guiding catheter). Secondary endpoints, including but not limited to angiographic in-stent binary restenosis, TVF and MACE at 270 days, were analyzed on a per-protocol evaluable basis defined as patients who had successful procedures and were available for follow-up.

All patients received the hospital's standard anti-coagulant and anti-platelet regimen for coronary stent implantation. The ACT was monitored and recorded on source documentation during the procedure. The ACT was kept at a therapeutic level for percutaneous coronary interventions per the hospital standard.

Demography: The total population consisted of 268 patients, but analysis was performed on 267 patients because one patient had the Guidant MULTI-LINK VISION™ Coronary Stent implanted in an SVG. Baseline characteristics for the VISION Registry indicated 68.2% were male and ranged in age from 37 to 91 years with an average age of 63.6 ± 10.7 (mean $\pm$ SD), 23.2% had diabetes requiring medication, 61.4% had hypertension requiring medication, 23.6% were current smokers, and 63.7% had hyperlipidemia requiring medication. From a clinical perspective, the patient demographics were similar between the VISION and TETRA Registries.

Methods: Eligible patients underwent standard balloon angioplasty after which a MULTI-LINK RX VISION™ CSS of appropriate size was advanced and deployed at pressures ≥ 9 and ≤ 16 atmospheres (atm). MULTI-LINK VISION™ Stents were available in diameters of 3.0 mm, 3.5 mm and 4.0 mm and lengths of 8 mm, 12 mm, 15 mm, 18 mm, 23 mm and 28 mm. Stents were deployed slowly in 2 atm increments every 5 seconds until fully expanded. Pressure was maintained for 30 seconds. To attain optimal stent apposition, the MULTI-LINK RX VISION™ CSS balloon could be re-inflated up to 16 atm. Optimal stent expansion was defined as the attainment of a balloon

to artery ratio of 1.0-1.1:1.0. The fully deployed stent was not to exceed the reference vessel diameter by more than 10%.

Clinical or telephone follow-up was collected in-hospital and at 14, 30, 180, 270 and 365 days. 80.9% (216/267) of VISION Registry patients underwent angiographic follow-up at the 180-day clinical visit. Guidant personnel performed data monitoring. The angiographic core lab adjudicated revascularizations by PCI. An independent Clinical Events Committee adjudicated all other primary endpoints.

Results: In the VISION Registry, the 180-day and 270-day TVF rates were 6.7% and 14.7% (respectively); in the TETRA Registry, the 180-day TVF rate was 12.8%. The representative sample of patients from the VISION Registry followed clinically for up to 9 months (270 days) demonstrates that the clinical outcomes achieved with the MULTI-LINK VISION™ CSS are similar to those observed at 180 days in the TETRA Registry. No unanticipated events that might affect the risk analysis were noted in the VISION Registry. Adverse event rates are presented in Table 2.

Table 2 compares the principal effectiveness and safety results of patients treated in the VISION Registry at 180 and 270 days to those treated in the TETRA Registry at 180 days.

Table 2: VISION Registry - Principal Effectiveness and Safety Results Through 180 and 270 Days

percent [95% confidence interval] (number/denominator), or mean ± SD {range} (number)

	VISION Stent – 180 Days (n = 267) [1]	TETRA Stent – 180 Days (n = 202)	VISION Stent – 270 Days (n = 267) [1]
Effectiveness Measures			
Device Success by QCA	100% [98.6%, 100.0%] (267/267)	99.5% [97.3%, 100.0%] (201/202)	100% [98.6%,100.0%] (267/267)
Procedure Success by QCA	98.9% [96.8%, 99.8%] (264/267)	97.5% [94.3%, 99.2%] (197/202)	98.9% [96.8%, 99.8%] (264/267)
Binary Restenosis Rate	15.7% [11.2%, 21.3%] (34/216)	23.6% [17.5%, 30.6%] (41/174)	N/A
Post-Procedure In-Stent %DS	4.9% ± 9.2% (266) {-20.1%, 31.9%} [3.8%, 6.0%]	5.7% ± 8.4% (201) {-43.1%, 28.9%} [4.6%, 6.9%]	N/A
Follow-up In-Stent %DS	29.2% ± 19.2% (216) {-7.4%, 100%} [26.6%, 31.8%]	34.6% ± 22.7% (173) {-9.2%, 98.0%} [31.2%, 38.0%]	N/A
Safety Measures			
In-Hospital MACE Rate	1.5% [0.4%, 3.8%] (4/267)	2.0% [0.5%, 5.0%] (4/202)	1.5% [0.4%, 3.8%] (4/267)
Out-of-hospital MACE Rate	5.0% [2.7%, 8.5%] (13/258)	10.2% [6.3%, 15.3%] (20/196)	11.6% [8.0%, 16.1%] (30/259)
MACE Rate	6.2% [3.6%, 9.9%] (16/258)	12.2% [8.0%, 17.7%] (24/196)	12.7% [8.9%, 17.4%] (33/259)
TVF Rate	6.7% [4.0%, 10.4%] (18/267)	12.8% [8.4%, 18 3%] (25/196)	14.7% [10.6%, 19.6%] (38/259)
Survival	98.8% [96.6%, 99.8%] (255/258)	99.5% [97.2%, 100.0%] (195/196)	98.8% [96.7%, 99.8%] (256/259)
TVF Free (KM)	92.9%	86.4%	85.5%

Target Site Revascularization Free (KM)	94.8%	88.5%	88.4%
Target Vessel Revascularization (not at Target Site) Free (KM)	98.4%	N/A	97.3%
Subacute Thrombosis *	0.4% [0.0%, 2.1%] (1/258)	0% [0.0%, 1.9%] (0/196)	0.4% [0.0%, 2.1%] (1/259)
Bleeding Complications	2.3% [0.9%, 5.0%] (6/258)	3.1% [1.1%, 6.5%] (6/196)	2.7% [1.1%, 5.5%] (7/259)
Vascular Complications	1.6% [0.4%, 3.9%] (4/258)	4.6% [2.1%, 8.5%] (9/196)	1.9% [0.6%, 4.4%] (5/259)
Hospitalization Post-Intervention (days)	1.3 ± 1.0 {0, 10} [1.2, 1.4] (267)	1.3 ± 0.8 {0, 6} [1.2, 1.4] (201)	1.3 ± 1.0 {0, 10} [1.2, 1.4] (267)

- [1] 268 patients enrolled but one patient is excluded because the VISION stent was implanted in an SVG, so n = 267.
- Primary endpoint (180-day TVF) was analyzed on an intent-to-treat basis, n = 267.
- 180-day clinical data was available on 258 patients for the VISION Registry and 196 patients for the TETRA Registry.
- 180-day angiographic data was available on 216 patients for the VISION Registry and 174 patients for the TETRA Registry.
- Secondary endpoints were analyzed on per protocol evaluable patients. There were n = 258 patients available at the 180 day f/u time point and there were n = 259 patients available at the 270 day f/u time point.
- KM = Kaplan-Meier.

* Subacute Thrombosis is based on 30 days.

VISION Registry Definitions

- **QCA** - Quantitative Coronary Angiography.
- **Device Success** - Attainment of final result of < 50% residual stenosis of the target site using the designated treatment device.
- **Procedure Success** - Attainment of final result of < 50% residual stenosis of the target site using the designated treatment device and any other adjunctive device, including additional stents, without death, emergent bypass surgery, or Q-Wave or Non-Q-Wave MI post procedure prior to hospital discharge.
- **Binary restenosis** - ≥ 50% by QCA.
- **% DS** - Percent diameter stenosis by QCA.
- **In-Hospital MACE** - Any MACE occurring prior to hospital discharge.
- **Out-of-Hospital MACE** - Any MACE occurring from hospital discharge through 180-day clinical follow-up.
- **Major Adverse Cardiac Event (MACE)** – The composite of death, Q-Wave MI, Non-Q-Wave MI and Target Site Revascularization (TSR) by Coronary Artery Bypass Surgery (CABG) or Percutaneous Coronary Intervention (PCI).
- **Target Vessel Failure (TVF)** – The composite of death, Q-Wave MI, Non-Q-Wave MI, Target Site Revascularization (TSR) or Target Vessel Revascularization (TVR) by Coronary Artery Bypass Graft Surgery (CABG) or Percutaneous Coronary Intervention (PCI).
- **Target Site Revascularization (TSR)** – Repeat Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG) surgery.
- **Subacute Thrombosis (SAT)** - Any cardiac death < 30 days. Any subacute (outside of cath lab) closure requiring revascularization of the target site < 30 days with presence of thrombus at the target site, any total closure indicated by Quantitative Coronary Angiography (QCA) < 30 days.
- **Bleeding Complication** – Blood loss necessitating a transfusion.
- **Vascular Complication** – Any hematoma > 5 cm, arteriovenous fistula, pseudoaneurysm, retroperitoneal bleed, peripheral nerve disorder or surgical repair.
- **Q-Wave Myocardial Infarction (QMI)** – The development of new abnormal Q-Waves not present on the patient's baseline ECG – through blinded evaluation by the ECG Core Laboratory – in association with CK enzyme elevation of three times upper normal limit and presence of CK-MB.
- **Non Q-Wave Myocardial Infraction (Non QMI)** – CK enzyme elevations by more than three time the upper limit of normal and presence of CK-MB.
- **CABG** – Coronary Artery Bypass Graft surgery.
- **PCI** – Percutaneous Coronary Intervention.
- **Cerebrovascular Accident (CVA)** – Acute, new neurologic deficit lasting > 24 hours affecting daily activities, or resulting in death, classified by a physician as a stroke.
- **Stent Delivery Failure** – Inability to deliver the stent to the intended target lesion.

X. Conclusions Drawn from the Studies

The safety and effectiveness of the MULTI-LINK VISION™ RX & OTW CSS covered in this submission is based on the results obtained from biocompatibility, sterilization, *in vitro* bench testing, *in vivo* animal testing, and clinical testing. These test results reveal the following:

(1) Biocompatibility Testing:

The biocompatibility testing that was conducted on the MULTI-LINK RX VISION™ CSS and MULTI-LINK OTW VISION™ CSS demonstrated that both devices are acceptable for long-term (implant, circulating blood) invasive use in the cardiovascular system.

(2) Sterilization Testing:

The test results obtained from the sterilization testing demonstrate that the MULTI-LINK RX VISION™ and MULTI-LINK OTW VISION™ CSS can be sterilized to achieve dosing values within the 25 kGy minimum sterilization dose and the 50 kGy maximum qualification dose at SteriGenics International, Inc., AEA Technology, EBIS Limited Sterilization Services, and Guidant ACS and are acceptable for clinical use.

(3) *In Vitro* Bench Testing:

The *in vitro* bench testing conducted on the MULTI-LINK RX VISION™ CSS and MULTI-LINK OTW VISION™ CSS demonstrated that the performance characteristics of both devices met the product specifications and are safe and acceptable for clinical use.

(4) *In Vivo* Animal Testing:

The *in vivo* animal testing that was conducted on the MULTI-LINK RX VISION™ CSS and MULTI-LINK OTW VISION™ CSS demonstrated that the acute and chronic *in vivo* performance characteristics of both devices are safe and acceptable for clinical use.

(5) Clinical Testing:

The clinical testing conducted on the MULTI-LINK RX VISION™ CSS demonstrated that the performance characteristics of the device are safe and acceptable for clinical use.

XI. Panel Recommendation

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CDRH Decision

The applicant's manufacturing facilities were inspected and found to be in compliance with the Quality System Regulation (21 CFR 820). FDA issued an approval order on July 16, 2003.

XIII. Approval Specifications

Directions for use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.