DE NOVO CLASSIFICATION REQUEST FOR ILLUMINOSS PHOTODYNAMIC BONE STABILIZATION SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

In vivo cured intramedullary fixation rod. An in vivo cured intramedullary fixation rod is a prescription implanted device consisting of a balloon that is inserted into the medullary canal of long bones for the fixation of fractures. The balloon is infused with, and completely encapsulates, a liquid monomer that is exposed to a curing agent which polymerizes the monomer within the balloon creating a hardened rigid structure.

NEW REGULATION NUMBER: 21 CFR 888.3023

CLASSIFICATION: II

PRODUCT CODE: QAD

BACKGROUND

DEVICE NAME: IlluminOss Photodynamic Bone Stabilization System

SUBMISSION NUMBER: DEN160062

DATE DE NOVO RECEIVED: December 28, 2016

CONTACT:

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993 Waterman Avenue
East Providence, Rhode Island 02914

INDICATIONS FOR USE

The IlluminOss Photodynamic Bone Stabilization System (PBSS) is indicated for skeletally mature patients in the treatment of impending and actual pathological fractures of the humerus, radius, and ulna, from metastatic bone disease.

LIMITATIONS

Prescription use only: Federal (USA) law restricts this device to sale by or on the order of a physician.

Limitations on device use are also achieved through the following statements included in the instructions for use:

Contraindications:
This product is contraindicated in patients who have an active or incompletely treated infection that could involve the site where the device will be implanted; are allergic to any of the implant materials or to dental glue; have an intramedullary canal measuring smaller than the diameter of the 6.5 mm delivery sheath provided at the site of the fracture; distant foci of infections which may spread to the implant site, have open fractures with severe contamination; or in patients for whom delivery sheath is unable to cross fracture site after proper fracture reduction and realignment.

Warnings:

- Has not been studied in patients who are skeletally immature.
- Correct selection of the implant diameter and length is extremely important, and should be determined before implantation:
    - Ensure the implant is long enough to span the fracture, and is not longer than the canal
    - Ensure that the implant diameter is large enough to ensure cortical contact.
    - Ensure the separation instrument can reach the balloon.
- The polymerization (curing cycle of implant) is a short term exothermic reaction.
- Do not insert or affix sutures, K-wires, or other hardware to or through the stabilization balloon until after it has cured.
- Do not attempt to inflate the balloon catheter by use of any ancillary inflation equipment. Properly sized inflation syringes and the amount of monomer necessary to accomplish the appropriate inflation are provided. The balloon is made of a non-compliant, thin walled PET and does not expand larger than its prescribed size.
- Do not add any material or fluids to the monomer.
- Do not expose the monomer to any light source other than the IlluminOss. Photodynamic Curing System, shield the monomer from light after removal from vial.
- If, upon fluoroscopic examination, the user determines that the inflated balloon is not in contact with the intramedullary canal of the bone, the user should remove the balloon prior to curing the monomer, reassess sizing, and replace it with the appropriately sized balloon.
- Do not activate the light source until the balloon catheter is in the appropriate position and the bone fracture is reduced and ready for stabilization. Activation of the light source in the presence of the monomer will initiate polymerization, an irreversible process.
- The monomer must be exposed to the IlluminOss Photodynamic Curing System for a specific amount of time in order to activate and fully cure the implant. A partially cured implant cannot be used to complete a procedure. If an uncured, or partially cured implant is suspected, or if a curing cycle is interrupted, additional curing cycles should be completed.
- Inadequate postoperative fixation or unanticipated postoperative events may affect the interface between the bone and stabilization balloon, which may lead to

micro-motion of the implanted balloon and balloon surface. Periodic follow up examinations and radiographs are advised for all patients.

- Deep wound infection is a serious postoperative complication and may require total removal of the stabilization system and embedded polymer. Deep wound infection may be latent and not manifest itself for several years post-operatively.

Precautions

- The monomer in liquid form may cause sensitization by skin contact. In case of contact with skin, wash immediately with soap and water

See device labeling for the complete list of Warnings and Precautions.

DEVICE DESCRIPTION

The IlluminOss Photodynamic Bone Stabilization System (PBSS) is intended to be used in the fixation and stabilization of actual and impending pathological fractures of the humerus, radius, and ulna through a minimally invasive procedure. The system uses a catheter to deploy an inflatable, noncompliant, thin wall PET balloon into the medullary canal of the bone across the fracture site. The balloon is infused using a standard 20cc syringe with a photodynamic (light cured) monomer that causes the balloon to slowly expand and fill the intramedullary canal of the fractured bone. Activation of the light system allows for visible spectrum light to be delivered through a radially emitting light pipe that is temporarily positioned within a central lumen of the catheter that runs the length of the balloon. The liquid monomer within the balloon is exposed to light along the entire length of the balloon during the curing process (Figure 1).

Figure 1: Illustration of PBSS

Curing (and hardening) occurs only when the photo initiator within the monomer is exposed to a specific frequency of light causing rapid polymerization of the monomer resulting in a solid intramedullary (IM) rod. The time to cure the IM rod depends on the size of the balloon used to stabilize the fracture. A Timer Key, included within each balloon catheter kit, determines the time the light source is activated during the curing process to ensure the appropriate cure time is used for each balloon size.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

A biological risk assessment was performed and found to be in accordance with ISO 10993-1 and FDA's biocompatibility guidance (issued June 16, 2016) for an implanted

device with permanent contact (>30 days) with tissue/bone and can be considered safe for use as directed. The following biocompatibility testing was performed on the entire PBSS implanted device including the PET balloon and the hardened monomer mixture.

Table 1 – Biocompatibility Testing Summary

Biocompatibility Test	Standard	Results
Cytotoxicity	ISO 10993-5	Non-cytotoxic
Intracutaneous Reactivity/Irritation	ISO 10993-10	Non-irritant
Sensitization	ISO 10993-10	Non-sensitizing
Acute Systemic Toxicity	ISO 10993-11	Non-toxic
Genotoxicity (Ames)	ISO 10993-3	Non-mutagenic
Genotoxicity (mouse lymphoma assay)	ISO 10993-3	Non-genotoxic
Subchronic/Chronic Toxicity	ISO 10993-11	Non-toxic
Implantation	ISO 10993-6	Slight irritant – 2 weeks; Non-irritant – 12 weeks
Pyrogenicity (material mediated)	ISO 10993-11	Non-pyrogenic

An Exhaustive Extraction was performed. The testing, along with characterization of the extract, did not show any extract in concentrations that would be of biocompatibility concern.

An Inked Balloon Polymer Analysis was performed to determine the bulk composition, thermal profile, and molecular weight of the balloon polymer. The analysis found the materials to be indistinguishable by FTIR and TGA indicating the samples contain little to no filler as well as similar bulk chemistry.

Based on all the biocompatibility testing and evaluations, the IlluminOss Photodynamic Bone Stabilization System was determined to be biocompatible.

SHELF LIFE/STERILITY

The Balloon Catheter Delivery System, ball tip guidewires, optional flow spike for monomer transfer and the monomer are provided sterile for single use. These components are sterilized by ethylene oxide in accordance with ISO 11135:2008 "Sterilization of health care products – Ethylene oxide: Requirements for development, qualification, and routine control of a sterilization process for medical devices." to a sterility assurance level (SAL) of 10^{-6}.

The monomer is aseptically filled in the vials and placed aseptically in Tyvek foil pouches.

A combination of real time and accelerated aged product was used in determining shelf life for the device. The tests were comprised of Bubble Leak Test (ASTM D 3078-08), Burst Test (ASTM F 1140-07), Seal Strength (ASTM F 88/F 88M) and sterility confirmation. In addition, monomer testing included viscosity, shore-D, and FTIR properties performance results. All product tested was post sterilization.

The testing confirmed a three (3) year shelf life was supported based on real time and accelerated aged product. The implant and disposable delivery kit, including monomer, are labeled with a three-year shelf life.

The surgical instrument kits and all instruments are supplied non-sterile and must be cleaned and sterilized (reprocessed) by the end user before use, unless otherwise indicated. Validated reprocessing instructions are included in their own separate labeling document.

The recommended methods for steam sterilization have been validated in accordance with AAMI TIR No. 12-2010: Design, Testing, and Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities: A Guide for Medical Manufacturers and ANSl/AAMl/ISO 17665-1: 2006 Sterilization of Health Care Products - Moist Heat - Part 1: Requirements for the Development, Validation, and Routine Control of a Sterilization Process for Medical Devices, to an SAL of 10^{-6}. Instruments may be sterilized using a PreVac steam autoclave or Gravity steam autoclave cycle. For the PreVac autoclave cycle the validated parameters call for a minimum of 4 minutes at 270°F (132°C) and a minimum dry time of 20 minutes at 270°F (132°C). For the Gravity autoclave cycle, validated parameters call for a minimum of 15 minutes at 270°F (132°C) and a minimum dry time of 15 minutes at 270°F (132°C). Users are advised to use an FDA approved CSR sterilization wrap and FDA cleared sterilizers.

Cleaning parameters have been validated using the acceptance criteria for two cleaning endpoints, Protein and Hemoglobin Reduction Methods, in accordance with AAMI TIR No. 30-2011: A Compendium of Processes, Materials, Test Methods, and Acceptance Criteria for Cleaning Reusable Medical Devices, AAMI TIR No. 12-2010: Design, Testing, and Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities: A Guide for Medical Manufacturers, and the Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling (guidance issued March 17, 2015).

ELECTROMAGNETIC CAPABILITY & ELECTROMAGNETIC SAFETY

The IlluminOss Photodynamic Bone Stabilization System has an electro-medical device component as part of the system. The Photodynamic Light Source has undergone complete testing for electrical safety and EMC in accordance with:

- IEC 60601-1 standard, IEC 60601-1:1988 + A1:1991 + A2:1995, Medical electrical equipment Part 1: General requirements for safety EN 60601-1-2, Medical Electrical Equipment, Collateral Standard: Electromagnetic Compatibility dated 2007 (IEC 60601-1-2: 2007.
- 60601-1-2, Medical Electrical Equipment, Collateral Standard: Electromagnetic Compatibility dated 2007 (IEC 60601-1-2: 2007)

IlluminOss Medical has also subjected the light source to testing under IEC 60601-2-18, because the light source possesses certain similarities to that of endoscopic accessories:

- IEC 60601-2-18 (3rd Edition 2009 for use in conjunction with IEC60601-1:2005) Medical electrical equipment Part 2: General requirements for basic safety and essential performance of endoscopic equipment.

The light source passed all required tests and met all applicable requirements. Results from the electrical safety testing have established that the light source meets the general requirements for electrical safety as well as applicable parts of the standard relating to safety of endoscopic equipment and therefore it is suitable for its intended use.

Electromagnetic Compatibility Testing

Electromagnetic Compatibility testing was also performed in accordance with following IEC standards. The required performance criteria are also listed in Table 2.

Table 2: EMC Testing Summary

Applied Standard	Description	Acceptance Criteria	Test Results
EN55011:2007, EN55022: 2006, FCC Part 15 – Radiated Emissions	This test measures the electromagnetic levels of spurious signal generated by the light source that may affect the performance of other nearby electronic equipment	Class B Below Limit	Complied
EN55011:2007, EN55022:2006, FCC Part 15 – Conducted Emissions	This test measures the electromagnetic levels of spurious signals generated by the unit on the AC power line that may affect the performance of other nearby electronic equipment	Class B, Group 1, Below Limit	Complies
EN61000-3-2:2006 – Harmonic Current Emissions	This test evaluated the potential for the unit currents to be injected into the public supply system and cause distortion on the AC power lines	Class A, Below Limit	Complies
EN61000-3-3:1995 + A1:2001 + A2:2005 – Voltage Fluctuations & Flicker	This test evaluates the potential for the unit to cause voltage fluctuation and flicker impressed on the public AC low-voltage system	Per Section 5 of the Standard	Complies
EN61000-4-2:1995 + A1:1999 + A2:2001 – Electromagnetic compatibility (EMC) – Part 4: Testing and measurement techniques- Section 2: Electrostatic discharge immunity testing	This test evaluated the performance of the unit when subjected to electrostatic events from operator directly and to adjacent objects	The light source shall continue to operate as intended without operator intervention	Passed – No degradation of performance was observed
EN:61000-4-3:2006 – Electromagnetic compatibility (EMC)-Part 4-3:Testing and measurement techniques – Radiated, radio-frequency, electromagnetic field immunity test	This test evaluated the performance of the unit when subjected to radiated electromagnetic fields	The light source shall continue to operate as intended without operator intervention	Passed – No degradation of performance was observed
EN61000-4-4:2004 – Electromagnetic compatibility (EMC) – Part 4: Testing and measurement techniques – Section 4: Electrical fast transient/burst immunity test	This test evaluated the performance of the unit when subjected to repetitive fast transients (bursts) on the power and interconnecting lines.	The light source shall continue to operate as intended without operator intervention	Passed – No degradation of performance was observed

Applied Standard	Description	Acceptance Criteria	Test Results
EN61000-4-5:2005 – Electromagnetic compatibility (EMC) – Part 4: Testing and measurement techniques – Section 5: Surge immunity test	The test evaluates the performance of the unit when subjected to high-energy disturbances on the power and interconnecting lines	The light source shall continue to operate as intended without operator intervention	Passed – No degradation of performance was observed during and after application of the test voltage
EN61000-4-6:2007 Electromagnetic compatibility (EMC) – Part 4: Testing and measurement techniques – Section 6: Immunity to conducted disturbances, inducted by radio-frequency fields	This test evaluated the performances of the unit when subjected to radio-frequencies from intentional transmitters on the power and interconnecting lines	The light source shall continue to operate as intended without operator intervention	Passed – No degradation of performance was observed
EN61000-4-8:1993 + A1:2001 – Electromagnetic compatibility (EMC) – Part 4: Testing and measurement techniques – Section 8: Power Magnetic Field Immunity	This test evaluates the performance of the unit when subjected to magnetic fields at power line frequencies	The light source shall continue to operate as intended without operator intervention	Passed – No degradation of performance was observed
EN61000-4-11:2004 – Electromagnetic compatibility (EMC) – Part 4: Testing and measurement techniques – Section 11: Voltage dips, short interruptions and voltage variations	This test evaluated the performance of the unit when subjected to voltage dips, short interruptions and voltage variations	The output of light may be momentarily interrupted. However, the light output must resume, without operator interventions	Passed

Based upon the electrical safety and EMC testing, the IlluminOss Light Source is safe for its intended use within its intended hospital/healthcare facility environment.

PERFORMANCE TESTING – BENCH

The following section provides a summary of the bench performance testing performed on the IlluminOss PBSS to support its use.

The following tests are summarized in this section:

- Bond Strength Test
- Light Pipe Tensile Testing
- Assembly Inflate/Deflate/Burst Test
- Balloon Dimensional Verification
- Balloon Leak – Monomer Cure
- Monomer Removal Simulation
- Four-Point Bend and Torsion on Cured IM rod
- Four-Point Bend in a Bone Construct
- Use of screws with IlluminOss device
  - Pull-out
  - Torsion
  - Four-point bend, static and dynamic
  - Insertion Torque
- Cure Validation Test

- Light Pipe Validation
- Temperature During Cure
- Temperature Effect on Cure
- Power Interruption; effect on Curing
- Balloon Abrasion Test
- Light Source Bulb Life Test
- Degree of Polymerization
- Aseptic Media Fill Process Validation
- Liquid Monomer Aseptic Filtration Process Validation

Bond Strength Test

Since the introduction and removal of the delivery system catheter imparts stresses to the device and all bonds, the strength of the bonds was tested to determine if the device possesses adequate tensile characteristics for safe use. The strength of the bonds were tested per the FDA guidance document "Non-clinical Tests and Recommended Labeling for Intravascular Stent and Associated Delivery Systems" and ISO 10555-1: Sterile, single-use intravascular catheters. Although the ISO standard and FDA guidance referenced here pertain to intravascular catheters, the design of the proposed device and usage/tensile forces encountered during use are expected to be quite similar for the proposed indication.

In all cases, the minimum acceptance criterion was met and the failure occurred at the guide tube. The mechanical strength of the proposed device far exceeds the demands on the catheter assembly and therefore, the device possesses adequate mechanical integrity and is safe and appropriate for its intended use.

Light Pipe Tensile Strength Test

The objective of this test was to evaluate the tensile properties of the radially emitting light pipe being used. Testing was performed to evaluate the tensile characteristics of the radially emitting light pipe. The results demonstrated that the mechanical strength of the light pipe far exceeded the acceptance criterion for the product, as well as pull forces necessary to remove the device from a balloon catheter once the procedure is completed. Testing demonstrates that the forces required to remove a light pipe from a cured implant are below 1 lb. Based on these results, the light pipe possesses adequate strength to be used as intended.

Assembly Inflate/Deflate Burst Test

Balloon catheter burst testing was performed to demonstrate that the device could withstand the pressures necessary to complete the infusion process with the liquid monomer. The mean burst pressure of every OD balloon catheter assembly met the internal acceptance criterion. No individual test sample exhibited burst pressure results below the acceptance criterion. The results of this testing demonstrate that the catheter and balloon assembly are capable of withstanding pressures far in excess of the pressure capable of being generated by the 20cc syringe. The results demonstrate that the balloon catheter assembly design is robust and adequate for its proposed intended use.

Balloon Dimensional Verification Test

As the balloon size may be important for fitting the target defect, balloon dimensional verification testing was performed. The test results demonstrate that the balloons met their respective test criteria for dimensional measurements. Based upon these results, it is concluded that the physician can accurately and reliably size the balloon catheters during a procedure.

Balloon Leak Monomer Cure

The purpose of this test was to determine whether leaked monomer outside the balloon can be adequately cured when using a radially emitting light pipe per the prescribed instructions for use. The testing demonstrates that small amounts of leaked monomer that may occur because of a pin hole leak in the balloon can be adequately cured using the radially emitting light pipe. The testing demonstrated that both the leaked monomer and the monomer remaining in the balloon were fully cured.

Monomer Removal Simulation

The purpose of this test was to demonstrate that the remediation technique detailed in the labeling for removing uncontained monomer in the intramedullary canal can be successfully performed. The testing performed demonstrated that large volumes of monomer could be effectively removed when labeled instructions are followed. Testing showed that greater than 95% of leaked monomer can be recovered out of the canal following labeled instructions. Therefore, the biocompatible nature of the cured and uncured monomer and the fact that both large and small volumes of the monomer can be removed from the intramedullary canal, should a leak occur, support the device's intended use.

Static and Fatigue Four-point Bend and Torsion Test (ASTM F1264-03)

The objective of this test was to validate that the mechanical properties of the IlluminOss IM rod will be sufficient for the indications for use. Testing was performed and compared to the same testing conducted on a legally marketed device with similar indications. Based upon the static four-point bend strength, static torque strength, fatigue four-point bend strength, and fatigue torque strength results, the IlluminOss device possesses adequate mechanical properties capable of sustaining maximum estimated physiological loads encountered during its use.

Four-Point Bend and Torsion in Bone Construct

The objective of this test was to validate the mechanical properties of the humeral balloon implants in a simulated bone fracture model through Four-Point Bend and Torsion testing (ASTM F1264-03). This test validates that the mechanical properties of the humeral balloon implants are sufficient for the range of sizes being developed. The IlluminOss devices were compared to a legally marketed device with similar indications.

Because the results of the testing using the IlluminOss devices compared very favorably to an existing, marketed device that is safe and effective, it is concluded that the IlluminOss device possesses the mechanical properties to be safely used as indicated.

Screw Pullout Strength (3.5mm Screws)
The objective of this test was to evaluate the use of a conventional orthopedic bone screw with the IlluminOss implant. Per ASTM F-1839, 50 pcf Sawbone cylinders were used for testing.

The results demonstrated that the screw pull-out forces in sawbones cylinders with the IlluminOss IM rods in place were significantly greater than those in sawbones cylinders without the IM rod. Therefore, use of screws with the polymeric IM rod appears to be feasible and safe.

Torsion Testing of Simulated Bone Fractures: IlluminOss IM Rod and Screws
The purpose of this test is to evaluate the torsional properties of IlluminOss IM rods used in the repair of a simulated bone fracture model in conjunction with the use of conventional orthopedic screws. The strategy of the testing was to evaluate the impact of cross-locking screw placement on the performance of the IlluminOss IM rod in a repaired bone fracture model. All acceptance criteria for static and dynamic torsion testing were met. The test results demonstrated that adequate performance will be achieved with the use of screws with the IlluminOss rods. Therefore, if required, screws may safely be used with the IlluminOss device.

Four-Point Bend Test of Repaired Bone Fractures Using IlluminOss Pins and Screws
The objective of this test was to evaluate the effect of using conventional orthopedic bone screws in conjunction with IlluminOss IM rods for the repair of bone fractures in a simulated model. This test evaluated the four-Point Bend properties of these repaired bone fracture models. All acceptance criteria were met. In this test sample, a screw distance placement of 15mm or greater from the fracture line did not affect the static or dynamic 4-point bend test. As testing demonstrated that the combination of screws used with the IlluminOss rods could meet all test criteria even under the worst-case simulation, the use of screws with the IlluminOss polymeric IM rod is safe and does not adversely affect the rod or the screw.

Screw Insertion Torque
Testing required that the average peak insertion torque for simulated bone models with the IlluminOss IM rod should be comparable to other marketed orthopedic bone screws. As expected, the insertion torque values rose when the IlluminOss IM rod was inserted into the test bone model. This increase in insertion torque was evident in both “thin-walled” and “thick-walled” models. Although increased in value, the forces necessary to insert the screws remained within the range of forces defined in literature for typical orthopedic screws (Synthes Technical Bulletin #91, July 1993). The use of orthopedic screws with the IlluminOss IM rod in fracture fixation of the proximal humerus, is permissible, when required. Based upon this testing, the use of screws in conjunction with the IlluminOss device is safe when used as indicated.

Cure Validation Test
The objective of this test is to validate the cure times (light exposure time) that will be sufficient to cure all balloons in the range of sizes being developed. Secondarily, light

pipe removal forces were evaluated to determine the forces required to remove the light pipe after the monomer is cured. The data demonstrated that all quadrants in all sections met the required Shore D Hardness specification and therefore, met the acceptance criterion for this parameter. Lastly, the pull-out forces required to remove the light pipe from the catheter once cure was complete were all less than 1.0 lb, thus meeting the acceptance criterion. The minimum cure time for the testing demonstrated that full cure of the polymeric IM rod can be achieved in less time than that for which individual Timer Keys are coded for a given balloon size. Therefore, the cure times proposed for the balloons are more than required to achieve a complete cure of the implant.

Light Pipe Validation

The purpose of this test was to demonstrate that the radially emitting light pipe can achieve its optical specifications as measured through Absolute Irradiance and Area under the Curve. Out of 110 light pipes (109 tested), there were four light pipes that did not meet one or both stated acceptance criteria. Prior to shipment, 100% of the light pipes are inspected. The inspection includes measurement of area under the curve and minimum output of each individual pipe. Therefore, all light pipes shipped with the IlluminOss device meet the necessary optical properties to ensure adequate curing of the monomer.

Temperature During Cure

Curing of the monomer in the IlluminOss Bone Stabilization System exhibits a mild exothermic reaction and therefore, testing has been performed to assess the temperature profile associated with curing. Animal testing performed and submitted demonstrates that there are no short or long-term adverse effects due to the exothermic reaction that occurs during monomer curing; there was no evidence of tissue necrosis. In addition, clinical results from 81 IDE study patients found no adverse events or device failures attributable to the exothermic reaction. Therefore, test results exhibit an acceptable temperature profile during the curing process that minimizes the risk of tissue injury and demonstrate that the IBSS is safe when used as indicated.

Temperature Effects on Curing

The purpose of this test was to determine the effect of temperature on the cure time of the photodynamic monomer. Per the acceptance criteria, the monomer should cure to its durometer specification at normal body temperatures. The testing demonstrated that temperature does influence the thoroughness and depth of cure. The acceptance criteria were met at normal body temperatures.

Power Interruption on Curing

The objective of this test was to demonstrate that a temporary power interruption followed by a complete cure cycle results in an adequately cured IlluminOss IM rods and causes no identifiable effect on implant strength for both four-point bend and fatigue.

For the static four-point bend strength, the samples cured with a power interruption must have average four-point bend strengths within 15% of the control samples' average. Static four-point bend test results indicate there was little difference in mechanical

strength between the control samples (cured with uninterrupted power) and the interrupted samples.

For the fatigue four-point bend strength, both samples passed the 1,000,000 cycle requirement for a predefined load. The testing demonstrated that, in the event of a power interruption, the light source can be re-started and the cure completed.

The overall data demonstrated that samples cured via an interrupted cycle and those cured via an uninterrupted cycle are the same. Therefore, even in the event of a power interruption, the IlluminOss IM rod implant can be safely and effectively cured.

Balloon Abrasion Test

The purpose of the balloon within the intramedullary canal is to contain the liquid monomer prior to curing it with light. Although the intramedullary canal will be prepared to reduce the surface roughness of the canal prior to placement of the catheter balloon assembly, a test was performed to simulate the contact of the balloon surface with any bony spicules that may be present in the canal during liquid polymer infusion and prior to monomer curing.

All balloons tested for each size showed no evidence of any leaks, punctures, tears or ripping. The testing demonstrated that the pressurized balloon was capable of withstanding severe friction along its side multiple times. Based upon this testing, it was concluded that the strength of the balloon material and its resistance to abrasion will enable the balloon to perform as intended while containing the liquid monomer prior to its curing.

Light Source Bulb Life Testing

The purpose of the testing was to evaluate the output of the bulb after repeated use simulating up to two years use.

All bulbs performed similarly in intensity degradation slopes over cycles and time. Based upon the results of the real time testing performed, it was concluded that the bulb maintains sufficient output intensity to adequately cure the liquid monomer through its intended useful life (i.e., 2,000 hours). The Operators Manual was written to reflect the need to replace the bulb after 2,000 hours of use.

Degree of Polymerization

The purpose of this test was to provide data from a chemical perspective, the degree of conversion (DC) of the IlluminOss photo-activated formula at different depths. Fourier transformation infrared spectroscopy (FTIR) was used. The results of this testing characterize the implant curing and confirmed the degree of polymerization for the humerus balloons.

The average degree of conversion for the test samples was > 90%. Once cured the monomer is completely hardened. Although the remaining 10% is not fully converted, it is still hardened and is no longer in a liquid form. This information, along with the other testing information provided in this submission (i.e., clinical, animal, biocompatibility, and performance (bench) testing) indicate that the IM rods resulting from the cured large balloon sizes proposed for use are safe for their intended use.

Aseptic Media Fill Process Validation

The purpose of the validation was to establish documented evidence that the process employed for aseptic processing of IlluminOss photodynamic liquid monomer (IPLM) will produce the desired results consistently, within the specified acceptance limits, and when performed as per the Standard Operating Procedures.

A review of five years of annual concurrent Media Fills was performed. The acceptance criteria for the validation was:

- When filling fewer than 5,000 units (vials), no contaminated units should be detected
- A minimum of 3 successive annual Media Fill Process Simulations illustrating uncontaminated units at batch sizes consistent with manufacturing runs is required.

The acceptance criteria were met. The results validate the Media Fill process for the IlluminOss photodynamic liquid monomer.

Liquid Monomer Aseptic Filtration Process Validation

The purpose of the validation was to establish documented evidence that the process employed for aseptic processing of IlluminOss photodynamic liquid monomer (IPLM) will produce the desired results consistently, within the specified acceptance limits, and when performed as per the Standard Operating Procedures. Validation was performed per FDA Guidance on Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, September 2004; Parenteral Drug Association - Process Simulation for Aseptically Filled Products PDA Technical Report No. 22, 1996; and ISO 13408-1:2015, Aseptic Processing of Health Care Products, Part 1: General requirements, Part 2: Filtration - 2008.

The following acceptance criteria were set for the validation:

- IPLM after filtration must meet and achieve all specifications for viscosity, hardness, UV cure, and FTIR match.
- A minimum of three consecutive lots of filtered and filled vials must be found to be uncontaminated and sterile.

All lots met and achieved all specifications for viscosity, hardness, UV cure, and FTIR match. There were no non-conforming (out of specification) lots observed during the period.

A minimum of three consecutive lots of filtered and filled vials were found to be uncontaminated and sterile. There were no contaminated lots observed during the 4 year period.

From this validation, the process appears to produce IPLM consistently within the specified limits.

PERFORMANCE TESTING - ANIMAL AND/OR CADAVER

The scope of the test was to validate that the devices designed specifically for larger, longer bones (i.e., humerus) could be reliably and effectively implanted into fractured humerus bones and removed after the IM rod was cured.

This test validated both the procedure and instrumentation used to conduct the implantation and removal. Acceptance criteria stated: 1) balloon catheter assembly must be capable of insertion into the intramedullary canal of the humerus bone across the fracture, 2) the un-infused balloon implant must have sufficient length and diameter to fit within the IM canal, 3) the infused and cure IM rod (balloon implant) must provide reasonable stiffness to minimize motion typical of post-operative scenario with minimal deflection, 4) system must be capable of being utilized as outlined in the surgical technique guide, 5) surgical time for the steps of balloon catheter priming, insertion, infusion, curing and separation must be less than 30 minutes (not inclusive of canal cleaning, entry hole, and fracture reduction), 6) cured implant must be removable via the entry hole or by incision at the fracture site location. Implant removal time must be less than 90 minutes.

Testing was completed using full fresh frozen human cadaveric arms from finger-tip to clavicle.

The testing demonstrated that all acceptance criteria were successfully met. This bioskills protocol validates that the larger balloons can be reliably placed and removed if necessary using the information provided to the clinician (IFUs and surgical and removal guides). Based upon the totality of data from various *in vitro*, and animal experience, the balloons can safely and reliably be placed as intended.

SUMMARY OF CLINICAL INFORMATION

IDE Clinical Study

The sponsor conducted an Investigational Device Exemption (IDE) clinical study of the IlluminOss PBSS to support the De Novo request. The study was a prospective, multi-center (13), historically controlled (literature), open label, noninferiority study of 81 subjects implanted with the PBSS for the treatment of impending and actual pathological fractures in the humerus from metastatic bone disease. Follow up visits occurred at 7, 30, and 90 days which was the primary endpoint, with extended follow-up visits occurring at 180 and 360 days following surgery. Subjects were monitored over the study period to evaluate for pain, functional outcomes and safety parameters which included no additional surgical interventions and the occurrence of other adverse device effects. Results were compared to historical literature controls.

The primary efficacy parameters assessed at Day 90 follow-up included pain as measured by the Visual Analog Scale (VAS) pain score and function as assessed by the Musculoskeletal Tumor Society Rating Scale for Upper Extremity (MSTS). Primary safety parameters included the assessment of major device-related adverse events, additional surgical interventions, and radiographic evaluations for device fracture, migrations, mal-alignment, or loss of reduction or fixation.

- Primary Efficacy Endpoints – reduction in VAS pain score *and* improvement in function (Musculoskeletal Tumor Society Rating Scale for Upper Extremity (MSTS)) reported at Day 90 as compared to pre-op baseline scores. Non-inferiority of mean changes over time were compared relative to reference values determined through evaluation of historical literature controls. The literature controls consisted of a wide variability of intramedullary fixation techniques (cement vs. no cement, locking screws vs. no screws), anatomical locations (upper extremity, lower extremity, diaphyseal, metaphyseal), devices, and etiologies (multiple types of cancer, nonmalignant lesions, simple non-unions).

  Success:
  - mean improvement in VAS over 90 days > 80% of historical ref. (>53.8, not inferior)
  - mean improvement in MSTS over 90 days > 80% of historical ref. (>23.7, not inferior)

- Primary Safety Endpoint – success was meeting all the following: no serious device-related adverse events; no additional surgical interventions (revision, removal, supplemental fixations); no device fracture, migrations, mal-alignment, or loss of reduction or fixation as evidenced by radiographic review. The number and percentage of patients achieving the Safety Success endpoint was reported cumulatively for days 7, 30, 90, and 360, with the primary study endpoint being Day 90.

- Secondary Endpoints – evaluated at the Day 90 visit, include:

  - The individual components of the safety endpoint. Other secondary endpoints include:
    - Duration of index procedure and length of hospital stay
    - Activities of Daily Living score through all follow-up intervals
    - Disability status
    - Evaluation of duration of physical therapy prescription
    - Assessment of prescription and over-the-counter analgesic medication use
    - Survivability from time of index procedure to death

  The safety endpoints evaluated through Day 90, also include:

  1. Incidence and number of adverse events.
  2. Incidence and number of procedure and device-related complications.

These secondary endpoints listed above were also examined during the extended follow up portion of the trial at Day 180 and 360.

Study success = if both the safety and efficacy primary endpoints were met.

Subjects responded well to the PBSS treatment with an average VAS pain reduction of 53 points from baseline to Day 90. Other pain outcome measures also demonstrated a large reduction of pain. The BM-22 Pain Characteristics had a reduction average of 32 points from baseline to Day 90. Pain during Palpation also reduced throughout the trial from 87.7% of subjects reporting pain during palpation at baseline to 13.6% of subject reporting pain during palpation at Day 90. These outcomes demonstrate a large decrease in pain due to the implantation of the PBSS device.

Subjects also experienced a substantial increase in function as demonstrated by a 40-point increase in the MSTS from baseline to Day 90. Additionally, other functional outcomes showed a similar result. The BM-22 Functional Interference had a 30-point average increase in function from baseline to Day 90. The ability of the PBSS device to provide functional improvement is supported by the large increases in functional improvement by subjects in the study.

Device and Procedure Related Adverse Events were low in the study (n = 32). The incidence of second surgeries was also low with only five subjects receiving a second surgery related to the device. No bone infections were observed and only one wound site infection occurred in the study.

Clinically, results were comparable to the referenced literature controls. Statistically the IDE study failed to meet one of its co-primary efficacy endpoints. That is, it failed to meet its success criterion of an improvement in VAS score of at least >80% of the literature control's improvement, as compared to baseline. It showed an improvement of about 79% of that seen with the control. However, a significant clinical improvement in pain relief over baseline was noted for these patients. In addition, the study did successfully meet the other primary co-primary efficacy endpoint of mean improvement of the MSTS rating scale at 90 days vs. literature control, and patients with the device do appear comparable to controls in overall clinical function.

The PBSS clinical trial results appear to validate the ability of the PBSS to safely and effectively stabilize a fracture in this patient population with metastatic bone disease as evidenced by the clinically relevant reduction of pain and increased function of subjects treated with the PBSS over baseline.

Prior Studies

In addition to the U.S. clinical experience, the PBSS is CE marked in the European Union (EU). The ability of the device to perform its intended function in other indications provided the rationale for performing this IDE study of the PBSS in acute proximal humerus pathological fractures.

EU Registry Study:

The EU Registry for the IlluminOss Bone Stabilization System, was initiated in September 2010. The aim of the registry was to collect technical and clinical outcomes on treated patients. The subjects were followed either until they were discharged from clinical care, or were followed for up to two years post-index surgery. There were no pre-specified procedures or additional mandatory visits for subjects enrolled into the registry. Research personnel collected and entered standard of care demographic and fracture-related data, including radiographs, into a web-based database for review by IlluminOss personnel. The database prospectively queried for the incidence of adverse device effects.

Enrollment closed in January 2014. A total of 135 bones were treated in 132 enrolled subjects at three centers in Germany and four centers in The Netherlands. The device was used to treat acute fractures and was used in revision surgeries across indications. It was used alone, and with supplemental hardware, at the discretion of the surgeon. No local or systemic device-related complications were reported. The study is closed.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

Labeling has been provided which includes the instructions for use and an appropriate prescription statement as required by 21 CFR 801.109.

Labeling includes the following:

- A detailed summary of the device's (system's) technical parameters.
- Information describing all materials of the device.
- Information identifying and explaining how to perform the procedure and use the device, including the delivery system and devices which initiate the curing process, as well as how to remove the device and any uncured/unpolymerized materials.
- A shelf life.
- Validated methods and instructions for reprocessing all reusable instruments.

RISKS TO HEALTH

Table 3 identifies the risks to health that may be associated with use of the in vivo cured intramedullary fixation rod and the measures necessary to mitigate these risks.

Table 3 – Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Adverse tissue reaction resulting from: • Balloon leakage • Device materials	Biocompatibility evaluation Labeling
Infection, including wound complications	Sterilization validation

	Reprocessing validation Shelf life testing Pyrogenicity testing Labeling
Bone fracture resulting from: • Device bending, cracking, or fracture • Device migration or instability, including initial inadequate fixation • Inability to properly deploy or remove device	Non-clinical performance testing Labeling
Soft tissue damage including transection or laceration of neural, vascular, or muscular structures.	Non-clinical performance testing Labeling
Pain and/or loss of function resulting from: • Balloon leakage • Device bending, cracking, or fracture • Device migration or instability, including initial inadequate fixation • Inability to properly deploy or remove device	Non-clinical performance testing Labeling
Revision	Non-clinical performance testing Labeling
Electric shock or interference with other electrical devices	Electrical safety testing Electromagnetic compatibility testing Labeling
Exothermic reaction leading to tissue injury	Non-clinical performance testing

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the in vivo cured intramedullary fixation rod is subject to the following special controls:

1. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    a. Mechanical testing must be conducted on the final device to assess burst, abrasion, bending, and torsion in static and dynamic conditions.
    b. Mechanical testing must demonstrate the integrity of the balloon including testing for leaks, ruptures, and release of cured/uncured material.
    c. Performance testing must demonstrate that the device can be inserted and removed.
    d. Performance testing must demonstrate the ability, in the event of a leak, to remove the uncured material from its in vivo location.
    e. Performance testing must demonstrate the reliability and accuracy of the curing method used.
    f. Thermal safety testing must be conducted to evaluate the temperature rise during curing.

2. Electrical safety, electromagnetic compatibility (EMC) testing, and electromagnetic interference (EMI) testing must be conducted for all electrical components.

3. All patient-contacting components must be demonstrated to be biocompatible.

4. Performance data must demonstrate the sterility and pyrogenicity of patient contacting components of the device that are provided sterile.

5. Performance data must validate the reprocessing instructions for any reusable components or instruments.

6. Performance data must support the shelf life of the system by demonstrating continued sterility, package integrity, and system functionality over the established shelf life.

7. Technological characterization of the device must include materials, curing agents, and a description of the operating principles of the device, including the delivery system and devices which initiate the curing process.

8. Labeling must include the following:
    a. A detailed summary of the device technical parameters.
    b. Information describing all materials of the device.
    c. Information describing how to perform the procedure and use the device, including the delivery system and devices which initiate the curing process, as well as how to remove the device and any uncured materials.
    d. A shelf life.
    e. Validated methods and instructions for reprocessing any reusable components or instruments.

BENEFIT-RISK DETERMINATION

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study, described above. The probable risks associated with the IlluminOss Photodynamic Bone Stabilization System, beyond those commonly associated with intramedullary fixation rods, include balloon leakage and adverse tissue reaction, insufficient initial fixation, inability to properly deploy or remove the device, failure of the curing process, lack of electrical safety or electromagnetic compatibility, and unacceptable exothermic reaction.

These risks can be mitigated with biocompatibility testing, labeling, EMC/EMI testing, non-clinical bench testing, and technological characterization. The mitigation activities for all the risks identified for in vivo cured intramedullary fixation rods are described in the section above.

The probable benefits of the Photodynamic Bone Stabilization System are also based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study as described above. The benefits of using the PBSS in the alignment and reduction of pathological fractures include decreases in pain and increases in upper extremity function and overall quality of life.

Reduction in Pain

In patients whose pathological humeral fractures were treated with the PBSS, the following reductions in pain were noted:

- VAS Pain: There was an average reduction of 34.2mm at 7 to 14 days, 45.7mm at 30 days, and 53.2mm at 90 days.
- Pain Characteristics via QLQ-BM22: There was an average reduction of 19.84 at 7 to 14 days, 25.81 at 30 days, and 32.12 at 90 days.
- Pain at Palpation: The percentage of patients reporting pain at palpation decreased over time from 87.7% at baseline, to 55.6% at 7 to 14 days, 40.7% at 30 days, and 13.6% at 90 days.
- Patients Prescribed or Using Analgesics: The percentage of patients prescribed analgesics at the visit decreased over time: 21.0% at 7 to 14 days, 12.3% at 30 days, and 9.9% at 90 days. The percentage of patients who had used analgesics since the prior visit decreased over time: 79.0% at 7 to 14 days, 63.0% at 30 days, and 50.6% at 90 days.

Improvement in Function

The following improvements in function were noted in patients whose pathological humeral fractures were treated with the PBSS:

- Upper Extremity Functional Outcome via MSTS: There was an average increase of 25.22 at 7 to 14 days, 32.01 at 30 days, and 40.13 at 90 days.
- Functional Interference via QLQ-BM22: There was an average increase of 21.45 at 7 to 14 days, 24.49 at 30 days, and 30.41 at 90 days.
- Increased Return to Mobility: The percentage of patients not able to perform activities of daily living (ADLs) independently decreased from 87.2% at baseline to 79.5% at 7 to 14 days, 64.1% at 30 days, and 51.3% at 90 days. The percentage of patients not able to perform ADLs with assistance decreased from 90.5% at baseline to 61.9% at 7 to 14 days, 57.1% at 30 days, and 40.5% at 90 days.
- Reduction in Need for Physical Therapy: The percentage of patients prescribed physical therapy (PT) at the visit decreased over time from 35.8% at 7 to 14 days to 32.1% at 30 days, and 21.0% at 90 days.

As discussed above, the risks associated with in vivo cured intramedullary fixation rods, and specifically the IlluminOss Photodynamic Bone Stabilization System, are presented with mitigation methods. These known risks can be adequately mitigated through non-clinical bench testing, biocompatibility testing, sterility, pyrogenicity, and shelf-life testing, EMC/EMI testing, technological characterization, and device labeling, including both package labeling and surgical technique.

PATIENT PERSPECTIVES

Patient perspectives considered for the IlluminOss Photodynamic Bone Stabilization System during the review include:

- VAS Pain: There was an average reduction of 34.2mm at 7 to 14 days, 45.7mm at 30 days, and 53.2mm at 90 days.
- Pain Characteristics via QLQ-BM22: There was an average reduction of 19.84 at 7 to 14 days, 25.81 at 30 days, and 32.12 at 90 days.
- Functional Interference via QLQ-BM22: There was an average increase of 21.45 at 7 to 14 days, 24.49 at 30 days, and 30.41 at 90 days.
- Pain at Palpation: The percentage of patients reporting pain at palpation decreased over time from 87.7% at baseline, to 55.6% at 7 to 14 days, 40.7% at 30 days, and 13.6% at 90 days.

These are all patient reported outcomes that demonstrate a meaningful reduction in pain and increase in function. Additionally, a responder analysis of pain reduction showed that at the Day 90 visit, 91.1% of the subjects had clinically significant reductions in VAS pain.

BENEFIT/RISK CONCLUSION

In conclusion, given the available information above, for the following indication statement:

> The IlluminOss Photodynamic Bone Stabilization System (PBSS) is indicated for skeletally mature patients in the treatment of impending and actual pathological fractures of the humerus, radius and ulna from metastatic bone disease.

The probable benefits outweigh the probable risks for the IlluminOss Photodynamic Bone Stabilization System. The device provides benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The De Novo request for the IlluminOss Photodynamic Bone Stabilization System is granted and the device is classified as follows:

> Product Code: QAD
> Device Type: In vivo cured intramedullary fixation rod
> Class: II
> Regulation: 21 CFR 888.3023