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Example - Early Feasibility Investigational Device Exemption

IDE Section:

Appendix G – Sterilization

G. Appendix G – Sterilization

This section contains:

G.1. Overview and Rationale for Single Lot Batch Release

At the time of submission of this EFS-IDE, we are providing a promissory note for a future device-specific final report for a worst case sterilization validation study for Ethylene Oxide sterilization of the NNP System implanted components.

The single-lot batch release protocol will not result in a fully validated sterilization *process* required for routine sterilization. However, following exposure performed under the CWRU single-lot batch release protocol, the NNP system components will be considered sterile in accordance with ISO 11135-1:2007, and appropriate for human implant use if:

- **An SAL of 10^{-6} is achieved, *and***
- **The EO residual levels are below the allowable limits per ISO 10993-7:2008(R)2012.**

No devices will be implanted that do not meet these two criteria.

We believe this approach is reasonable because the single lot batch release process results in sterile product that can be safely used in humans. While a fully validated procedure is necessary as part of the development of a full quality system, *the validation process itself does not render the components any "more sterile", or any "more safe".* It simply provides reassurance as to the repeatability of the overall sterilization process. In our case, the full validation procedure will require us to manufacture six complete sets of NNP Systems in order to run the procedure three times. At this point, it is the building and qualifying of units that would cause the most considerable cost increases and time delays.

FDA has previously stated that the concern with our approach is that the devices may not be sterile or may pose risks to subjects. **The single-lot batch release method results in products that are <u>confirmed to be sterile</u> because the process itself includes confirmation of SAL and EO levels based on the presence of positive controls.**

With the help of Moog Medical Devices, Inc (formerly Ethox), we have developed a single-lot release Ethylene Oxide sterilization program, based on an overkill methodology, for the implantable components of the NNP System. Additional NNP Systems (batches) may be sterilized by repeating the single-lot release Ethylene Oxide sterilization program with a repetition of the per-lot testing, but without a repetition of the other tests and documentation performed as a part of the protocol development.

The following table indicates the standards applied to the conduct and the validation of the sterilization and sterile packaging of the implantable NNP System components. This table also identifies any significant deviations from or limitations on the application of the standard.

TABLE G-1: STANDARDS USED IN DEVELOPMENT OF STERILIZATION PROTOCOL

Standard	Title	How Used	Any Limitations or Comments
ISO/AAMI/ANSI 11135-1:2007	Sterilization of Healthcare Products - Ethylene Oxide - Part 1: Requirements for development, validation and routine control of a	Primary standard for sterilization process, monitoring, qualification and validation process	Guidance for the Release of Small Batches or Lots provided by AAMI TIR16:2009

	sterilization process for medical devices		
AAMI TIR16:2009	Microbiological aspects of ethylene oxide sterilization	Provides guidance on the use of ISO 11135 for Release of Small Batches or Lots	
AAMI TIR28:2009	Product adoption and process equivalency for ethylene oxide sterilization	Guidance in comparing various components for relative sterilization challenge presented by device materials and construction.	Used as a guidance.Product is sterilized as a single lot release and not adopted into a validation process
ISO 109937:2008	Biological evaluation of medical devices - Part7: Ethylene oxide sterilization residuals	Test methods and limits for EO and ECH residuals in medical devices	
ISO 116071:2009	Packaging for terminally sterilized medical devices Part 1:Requirements for materials, sterile barrier systems and packaging systems	Overall guidance in testing of sterile package and heat sealing process validation	Purchased Peel Pouches comply with this standard and it identifies the ASTM test standards
ASTM F1929:1998 (R 2004)	Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration	Test Methods for seal integrity testing by dye penetration	
ASTM F2054:2007	Standard Test Method for Burst Testing of Flexible Package Seals Using Internal Air Pressurization Within Restraining Plates	Test Methods for Burst Testing of sterile packaging (supplier formed seals and heat seal)	
ATSM F2096:2004	Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test)	Test Methods for Bubble Testing of sterile packaging	
AAMI ST72:2011	Bacterial Endotoxins - Test Methodologies, Routine Monitoring, and Alternatives to Batch Testing	Test methods and limits for endotoxins and pyrogenicity in medical devices	

In addition, for guidance on endotoxin and pyrogenicity testing methodologies, we have consulted FDA Guidance for Industry Pyrogen and Endotoxins Testing Questions and Answers, June 2012.

G.2. Intrinsically Safe Requirement for Power Module

G.2.1. Intrinsic safety

Establishing the “Intrinsically Safe” requirements for the NNP System is a necessary prerequisite to performing sterilization processes.

Intrinsic safety is a requirement that may be applicable to devices that are being operated in areas with flammable gases or fuels. It means that the device is incapable of igniting those gases or fuels. Intrinsically safe equipment is "equipment and wiring which is incapable of releasing sufficient electrical **or** thermal energy under **normal** or **abnormal** conditions to cause ignition of a specific hazardous atmospheric mixture in its most easily ignited concentration." An abnormal condition may be due to accidental damage, failure of electrical components, excessive voltage, or improper adjustment or maintenance of the equipment.

"Intrinsically Safe" is a practice where one is restricting the energy available to electrical equipment in this potentially hazardous area so that a spark or hot surface cannot occur due to any type of electrical fault [or normal operation].

A mixture of hazardous gases and air may ignite in contact with a hot surface. The condition for ignition depends on several factors as surface area, temperature and concentration of gas; moreover, ethylene oxide can exothermally decompose even in the absence of oxygen if momentarily exposed to a hot spot. Approved equipment receives a temperature code indicating the maximum surface temperature of the equipment. The temperature marking specified shall not exceed the ignition temperature of the specific gas or vapor to be encountered.

G.2.2. Simple Apparatus

A Simple Apparatus is an electrical component or combination of components of simple construction with well-defined electrical parameters that does not generate more than 1.5 volts, 100 mA, 20 uJ, and 25 mW; or a passive component that does not dissipate more than 1.3 watts and is compatible with the intrinsic safety of the circuit in which it is used. It may be employed in a hazardous area without certification.

G.2.3. Medical Devices

Medical devices containing batteries or other stored energy must be “Intrinsically Safe” as defined by the *NFPA 70 standard for Class 1, Division 1, Group B* hazard areas such as EtO sterilization chambers.

- Class I locations are those in which flammable vapors and gases may be present
- Division 1 locations are those where ignitable concentrations of hazards exists under normal operation conditions; and/or where hazard is caused by frequent maintenance; or repair work; or frequent equipment failure (leakage)
- Group B includes the gases: Hydrogen, Butadiene, Ethylene Oxide, and Propylene Oxide

G.2.4. EtO Sterilization Process

Most EtO sterilization lines involve three different stages:

- Pre-Conditioning
- Sterilizer
- Degasser

Devices go through a pre-conditioning phase to make micro organisms grow. The batch-load goes through a dwell-time under a controlled environment of temperature and humidity. The device must deal with the pre-humidification stage of the sterilization process, which is conducted under condensing conditions. The device needs to be proof against high-rate electrical discharge in the presence of a condensed water film on circuitry and components.

G.2.5. Intrinsic safety of the NNP System Implanted Components

The NNPS stimulator utilizes three Quallion implant-grade batteries for its power supply, and Quallion has certified that this battery design complies with UL 1642, UL Standard for Safety of Lithium Batteries. We have provided certification to our contract sterilizer, Moog Medical, that the circuit in which these batteries are integrated complies with relevant portions of IEC 60601-1 - Medical equipment/medical electrical equipment - Part 1: General requirements for basic safety and essential performance.

G.3. Single Lot Batch Release Method

The implantable NNP System components will be sterilized in a single lot batch release process developed in conjunction with Moog Medical. The process protocol is based on the overkill methodology using 100% EtO sterilizing exposure in a fixed chamber, and will be compliant with the guidance of AAMI TIR16:2009 (Microbiological aspects of ethylene oxide sterilization) for Release of Small Batches or Lots.

For details on the methods and acceptance criteria, please refer to the attached sterilization protocol provided by Moog Medical that follows this section.

The following table shows the maximum content of a single sterilization batch.

TABLE GT 2: MAXIMUM CONTENT OF SINGLE STERILIZATION BATCH

Implantables Included in Sterilization Batch (Maximum Load)	Quantity in Batch	Quantity in Package (Double Barrier Tyvek Pouch)	Used in Single Surgery NNP Application
Power Module – PM1 + 4 Port Plugs	3	1	1
Stimulator Module – PG4 + 8 Port Plugs	13	1	5
Myoelectric Recording Module – BP2 + 8 Port Plugs	5	1	2
Network Cables - NC	18	1	7
Intramuscular Stimulating Electrode	45	1	16
Intramuscular Recording Electrode	8	1	3
Epimyseal Stimulating Electrode	5	1	4
Epimyseal Recording Electrode	2	1	1
Spare Port Plug	5	5	0-5

G.4. Packaging, Handling and Shelf-Life

G.4.1. Packaging

The Power Modules and Remote Modules undergo a final cleaning and inspection procedure within the CWRU Cleveland FES Center's Technical Development Laboratory (TDL), before being packaged and sealed. All Network Cables, Stimulating Electrodes, Recording Electrodes, and Port Plugs are fabricated, cleaned and packaged at Ardiem Medical, Indiana, PA.

Each of the implantable NNP System components is separately packaged using a Tyvek-poly peel double barrier pouch system. Packaged, as such, none of the NNP System components require any additional protective packaging materials. The Tyvek pouches used for component packaging are purchased in various sizes and a pouch size is chosen for both the inner and outer pouch, appropriate to the size and bulk of each NNP component. The Tyvek pouches also come with three sides pre-sealed by the manufacturer. In the case of the Power Modules and Remote Modules the final, fourth seals are applied at the TDL. In the case of the Network Cables, Stimulating Electrodes, Recording Electrodes, and Port Plugs the final, fourth seals are applied at Ardiem Medical.

This packaging and sealing process and procedure is identical to that used in our prior IDEs G900108, G040214, G110018, where seal integrity and seal strength were evaluated by (then) Ethox International after applying a simulated ship test compliant to ASTM D4169. The IST System implantables used in our previous IDEs, are similar in size, shape, and weight to the NNP System components, and, as such, for this first-in-human EFS-IDE study, no additional testing of the packaging procedure is planned at this stage.

G.4.2. Handling

The packaged product is shipped, along with a shipping traveler, in standard sealed Pelican Cases between CWRU and Moog Medical. This shipping method is identical to that used with an earlier generation system, G110018, where package integrity was evaluated by (then) Ethox International after applying a simulated ship test (performed by UPS) compliant to ASTM D4169. The single batch release composition of the IST System used in our previous IDEs is similar in quantity, bulk, and weight to the NNP System single batch release. Further, given the limited distribution (single investigational site), limited handling, and tight, supervisory control we have of the sterile NNP System components for this first-in-human EFS-IDE study, no additional testing of the handling and shipping procedure is planned at this stage.

G.4.3. Shelf-life

The NNPS System components are all designed and fabricated with methods and materials that do not degrade measurably over long periods of time with reasonable care given to the storage environment. This, together with the long history and demonstrated longevity of the Tyvek Poly-Peel pouch construction, allows us to apply an event-driven sterility (ERS) expiration criteria to the sterile NNP System components, and, for this first-in-human EFS-IDE study, no additional shelf-life testing is planned at this time. This is consistent with other feasibility IDE's for earlier generation systems, such as G110018. All sterile packages will be labeled with the date of sterilization, a lot control number, and will be considered sterile until their packaging is breached or they are exposed to extremes of temperature or moisture. All packages will be labeled: "Sterile unless the package is opened, damaged, exposed to extreme temperature, or wet. Please check before using." Unused sterile stock is stored in a secure area under the control of the investigator.

G.5. EO Sterilization Protocol for NNP System – Moog Medical

NOTE: The sterilization protocol has been omitted due to proprietary information. A new sterilization protocol is in development by COSMIIC with the intention of sharing it with the open-source community once completed.