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Example – Biocompatibility Evaluation Plan (BEP)

Cover Page

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Biological Evaluation Plan

Device Name: **COSMIIC System**

Prepared for:

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1 Revision History

Version	Date	List of Modifications
1	November 25, 2024	Initial release

2 Executive Summary

The COSMIIC System is a modular implant system with an implanted battery and communication module, pulse generators and biopotential recording units, wired connections, and various electrode designs. It is designed to be a flexible, modular, extensible platform technology, allowing for interconnected stimulating and sensing components to reach wide-ranging locations throughout the body to treat multiple symptoms of spinal cord injuries at once. The COSMIIC System is categorized as an implant device with long term (>30 days) contact with tissue or bone per ISO 10993-1.

A biological evaluation plan of the COSMIIC System has been performed based on the requirements of ISO 10993-1:2018, ISO 14971:2019, 2023 FDA Biocompatibility Guidance. A biological evaluation plan identifies areas of concern to be addressed by literature review, clinical experience, and testing. The evaluation of the biological safety of a medical device is a strategy planned on a case-by-case basis to identify the hazards and better estimate the risks of known hazards.

To evaluate the biological safety of the device, consideration was given to the following: type of patient contact and intended clinical use, potential hazards associated with the materials of construction, the history of clinical use of the materials of construction, manufacturing process information, clinical trial data and other information available in the literature.

Based upon examination of this information, additional biological testing and extractables/leachables testing is recommended to establish the biocompatibility of the COSMIIC System.

3 Signature Page

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Signature/Date of Approval

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Reviewer

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Signature/Date of Approval

4 Introduction

4.1 Background Information and Purpose

Cosmiic Inc. has developed the COSMIIC System, a modular implant system with an implanted battery and communication module (PM), pulse generators and biopotential recording units (RM's), wired connections (Network Cables), and various electrode designs. It is designed to be a flexible, modular, extensible platform technology, allowing for interconnected stimulating and sensing components to reach wide-ranging locations throughout the body to treat multiple symptoms of spinal cord injuries at once. The COSMIIC System was approved under an Early Feasibility Study in 2015 (G140225), referred to as the Networked Neuroprosthesis, or NNP. Cosmiic Inc. is seeking to share the technology for adoption of other researchers in the United States through an open-source model, and would like to ensure the COSMIIC System meets current biocompatibility standards.

The purpose of this plan is to evaluate the biological safety of the COSMIIC System giving consideration to the following: type of patient contact and intended clinical use, potential hazards associated with the materials of construction, the history of clinical use of the materials of construction, manufacturing process information, clinical trial data and other information available in the literature.

4.2 Responsibilities

The biological evaluation plan was performed by [redacted] from the information provided by Cosmiic Inc. This biological evaluation plan focuses only on the implantable components of the COSMIIC System described in this report and does not address the biological risks associated with the Control Tower, implantation tools, or other accessories.

4.3 Risk Assessment Guidelines

This document focuses on the requirements and recommendations listed in Table 1.

Table 1: Applicable Documents

Reference	Title
ISO 14971:2019	Medical Devices – Application of risk management to medical devices
2023 FDA Biocompatibility Guidance	Use of International Standard ISO 10993-1, Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process, Guidance for Industry and Food and Drug Administration Staff, September 2023
ISO 10993-1:2018	Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process and applicable ISO 10993 standards[1]
90/385/EEC	Active Implantable Medical Device Directive
ASTM F2901-19	Standard Guide for Selecting Tests to Evaluate Potential Neurotoxicity of Medical Devices

5 Device Description

The COSMIIC System is used to study the restoration of muscular function in adults who have paralysis from spinal cord injury. It has been used to stimulate trunk muscles for core stability, lower extremities for transferring function, and upper extremities for hand grasp patterns.

A typical implantable system for clinical use includes one battery and communication module (Power Module, PM), a combination of multiple pulse generators and biopotential recording units (RMs), wired connections (Network Cables) to connect them, and stimulating and recording electrodes connected to RMs. Each PM has two possible ports, and each RM has four possible ports for Network Cables. RMs have an additional four possible ports for electrodes. The modular design allows for interconnected stimulating and sensing components to reach wide-ranging locations throughout the body to treat multiple symptoms at once.

The PM is implanted in the subcutaneous tissue in either the abdomen or chest. The pulse generator RM (utilized for electrical stimulation of the paralyzed nerve and muscle tissue) and the biopotential RM (recording myoelectric signals or electromyography (EMG) for the purposes of neuroprosthetic control of the muscle under voluntary control) are implanted in the subcutaneous space of the chest or arm. The Network Cables may be implanted anywhere below the head within the subcutaneous tissue. The intramuscular stimulating electrodes are implanted into the belly of the

muscle or sutured to the surface or the muscle. The epimysial stimulating electrodes are designed to be sewn onto the surface of the target muscle. Despite the location of the electrodes on the muscle, electrical pulses delivered through the electrode cause activation of the nerves branching into the muscle, rather than direct activation of the muscle tissue itself (see Figure 1, Figure 2, Figure 3, and Figure 4).

A maximum of one COSMIIC System can be implanted at the same time in adult patients, with an exposure duration to last a lifetime. The maximum number of components for a hand grasp-only system (stimulates the undamaged lower motor neurons by placing electrodes on the innervated muscles) includes 1 PM, 4 RMs, 4 Network Cables, and 14 electrodes. The maximum number of components for trunk stability in addition to hand grasp includes 1 PM, 7 RMs, 7 Network Cables, and up to 26 electrodes, and represents the most conservative case for surface area of patient exposure.

The precise module and electrode placement will vary per individual based on the specific needs and availability to stimulate and/or record electrical activity. Examples of system placement for different functions are described in Table 2.

Table 2. Targeted Muscles for Electrode Placement

FUNCTION	MUSCLE NAME	ELECTRODE PLACEMENT
Hand Grasp	Adductor pollicis	Hand
	Abductor pollicis brevis	Hand
	Flexor pollicis longus	Forearm
	Extensor pollicis brevis / longus	Forearm
	Extensor digitorum communis	Forearm
	Flexor digitorum superficialis	Forearm
	Flexor digitorum profundus	Forearm
Wrist Mobility	Pronator quadratus	Forearm
	Extensor carpi ulnaris	Forearm
	Extensor carpi radialis brevis	Forearm
	Extensor carpi radialis longus	Forearm
	Flexor carpi ulnaris	Forearm
	Flexor carpi radialis	Forearm
Elbow and Shoulder	Triceps	Upper Arm
	Pectoralis Major	Shoulder
	Pectoralis Minor	Shoulder
	Deltoid	Shoulder
	Rhomboid	Shoulder
	Trapezius	Shoulder
	Supraspinatus	Shoulder
	Infraspinatus	Shoulder
	Subscapularis	Shoulder

Figure 1: Illustration of the COSMIIC System (one PM, 4 RMs, multiple Network Cables and Electrodes)

Figure 2: Images of Stimulating Electrodes

Figure 3: Image of a Recording Electrode

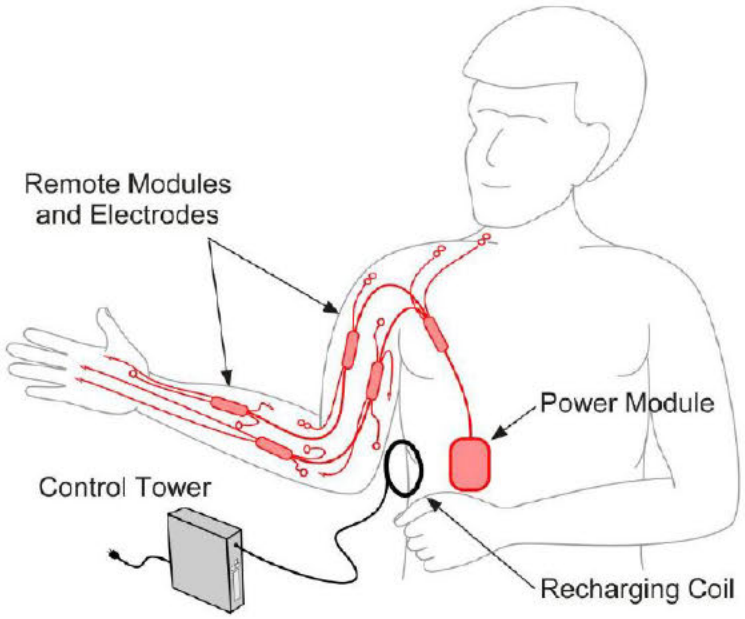


Figure 4. Illustration of Surgical Implementation of the COSMIIC System

A summary of the physical characteristics of the COSMIIC System is provided in Table 3.

Table 3. Physical Characteristics of COSMIIC

Component Name	Device Dimensions
PM	80 x 50 x 15mm
RM	16 x 57 x 7mm
Network Cables	1.3mm diameter 10-30cm long
Stimulating surface of intramuscular electrode	8mm² surface area 2mm long
Polypropylene barbed anchor at tip of electrode	2mm long
Epimysial stimulating electrode	3.3mm diameter disc 8.55mm² surface area

Only direct patient contacting materials of construction are listed in Table 4.

Table 4: COSMIIC System Materials of Construction

Raw Material	Raw Material	Additional Information	Raw Material Manufacturer	Type of Patient Contact
Power Module (PM)				
Capsule	Titanium Grade 23 6AL-4L ELI ASTM F136	Hermetically seals internal electronic components	Synapse	Direct
Capsule Header	Tecothane Lubrizol TT-1075D-M	Encapsulant protections for female interconnect assemblies, wireless antenna, and feedthrough wires	Lubrizol	Direct
Header Adhesion and Back-fill	NuSil MED3-4213	Fast-cure silicone adhesive: attaches header to metal capsule; used as sealant to fill weld access points after header assembly attached	NuSil	Direct

Raw Material	Raw Material	Additional Information	Raw Material Manufacturer	Type of Patient Contact
Header Back-fill	NuSil MED-6215	Low viscosity silicone elastomer: sealant to fill weld access points and vent holes after header assembly attached	NuSil	Direct
Suture Skirt	Silicone SSF-METN-750 Polyester Fabric SSF-FMR-1160	Polyester reinforced silicone sheeting: allows use of non-absorbable sutures to anchor the capsule to the underlying tissues	RMS (supplier) Synapse (manufacturer)	Direct
	NuSil MED-1137	Silicone adhesive: used to adhere suture skirt to capsule	NuSil	Direct
	NuSil MED6-161	Silicone primer: used to promote adhesion of suture skirt to capsule	NuSil	Direct
Remote Module (Pulse Generator and Biopotential Recording modules)				
Capsule	Titanium Grade 1 Commercially Pure Titanium ASTM F67	Hermetically sealed protection for internal electronic components	Synapse	Direct
Capsule feedthrough assembly	Titanium Grade 2 Commercially Pure Titanium ASTM F67	Hermetically sealed protection for internal electronic components	Synapse	Direct
Header	Tecothane Lubrizol TT-1075D-M	Encapsulant protections for female interconnect assemblies, wireless antenna, and feedthrough wires	Lubrizol	Direct
Header Adhesion and Back-fill	EPO-TEK 301	Used to attach header to metal capsule; sealant used to fill weld access points after assembly	Epoxy Technology, Inc.	Direct
Suture Skirt	Silicone SSF-METN-750 Polyester fabric SSF-FMR-1160	Specialty silicone fabricators: allows use of non-absorbable sutures to anchor the capsule to the underlying tissues	RMS (supplier) Synapse (manufacturer)	Direct
Suture Skirt	NuSil MED-1137	Silicone adhesive: used to adhere suture skirt to capsule	NuSil	Direct
Suture Skirt	NuSil MED6-161	Silicone primer: used to promote adhesion of suture skirt to capsule	NuSil	Direct
Electrode Cable and Network Cable				
Insulating tubing	NuSil MED-4750	Silicone elastomer: provides protection for the insulated, stranded conductors	NuSil	Direct
Strain Relief with Dual O-Ring	NuSil MED-4840 or NuSil MED-4850	Provides strain-relieving transition from interconnect pin to cable body, and sealing of interconnect pin assembly into receptacle	NuSil	Direct
Strain Relief with Dual O-Ring	NuSil MED-4800 color pigments for Liquid Silicone Elastomers Lead Type: Stimulating MED-4800-3 Red 1.5% Recording MED-4800-6 Green 1.5% Network MED-4800-7 Dark Blue 2%	Provides color-coding to identify interconnect function	NuSil	Direct
Adhesive	NuSil MED-1137	General assembly	NuSil	Direct
Adhesive	NuSil MED-4211	General assembly	NuSil	Direct
Intramuscular Stimulating Electrode and Recording Electrode				
Tissue Interface	Stainless Steel 316LVM ASTM F138	Stimulating and recording surfaces	Ardiem	Direct

Raw Material	Raw Material	Additional Information	Raw Material Manufacturer	Type of Patient Contact
Tissue anchors	Polypropylene, blue monofilament Non-absorbable (SP137, 3-0)	Barbed anchor at tip of electrode – for intramuscular placement	Surgical Specialties	Direct
Over-molding	NuSil MED-1137	Silicone adhesive: anchors exposed electrode contracts to silicone tubing	NuSil	Direct
Epimysial Stimulating Electrode				
Tissue Interface	Platinum 10% Iridium	Stimulating surfaces for epimysial placement	Ardiem	Direct
Electrode backing and suture skirt	Silicone SSF-METN-750 Polyester fabric SSF-FMR-1160	Allows the use of non-absorbable sutures to anchor the capsule to the underlying tissue	RMS (supplier) Synapse (manufacturer)	Direct
Over-molding	NuSil MED-4211	Encapsulates the electrode termination and backing material	NuSil	Direct
Port Plug				
Insulting tubing	NuSil MED-4750	Provides protection for the insulated, stranded conductors	NuSil	Direct
Strain Relief with Dual O-Ring	NuSil MED-4850	Provides strain-relieving transition from interconnect pin to cable body, and sealing of interconnect pin assembly into receptacle	NuSil	Direct
Dual O-Ring and Plug Body	NuSil MED-4800 color pigments for Liquid Silicone Elastomers	Provides color-coding to identify interconnect function	NuSil	Direct

ASTM F136: Standard Specification for Wrought Titanium- 6Aluminum-4Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications
ASTM F67: Standard Specification for Unalloyed Titanium, for Surgical Implant Applications
ASTM F138: Standard Specification for Wrought 18 Chromium-14 Nickel-2.5 Molybdenum Stainless Steel Bar and Wire for Surgical Implants

Details on the patient-contacting materials of construction are given in Appendix A.

6 Device Manufacturing Process

Following manufacture, the COSMIIC System PMs and RMS are cleaned with isopropyl alcohol wipes and then dried at 50°C in an oven for 10 minutes. They are packaged in double Tyvek bags and sent for ethylene oxide sterilization.

Network Cables and electrodes are ultrasonically cleaned in 1% Liquinox solution (1ml/100ml) with deionized water for 10 minutes, followed by a second ultrasonic rinse in deionized water for 10 minutes. Cables are dried for 10 minutes at 50°C. They are then packaged in double Tyvek bags and sent for ethylene oxide sterilization.

A hazard analysis of the manufacturing process and manufacturing agents used in the construction of the device is presented in Appendix B.

7 Device Categorization

When used as intended, the COSMIIC System is categorized according to ISO 10993-1 as an implant device with long-term contact (>30 days) with tissue/bone. Patient contact consists of muscle, nerve or connective tissue. There is no direct or indirect exposure with blood or cerebral spinal fluid.

Because of the COSMIIC System categorization, consideration must be given to all relevant endpoints defined by ISO 10993-1 and the 2023 FDA Biocompatibility Guidance (see Table 5).

Table 5: Endpoints to be Considered for the COSMIIC System

Endpoint	Applicable ISO 10993 Standard	Title
Physical and Chemical Information	ISO 10993-1	Evaluation and testing within a risk management process
Cytotoxicity	ISO 10993-5	Tests for *in vitro* cytotoxicity
Sensitization	ISO 10993-10	Tests for skin sensitization
Irritation	ISO 10993-23	Tests for irritation
Material Mediated Pyrogenicity	ISO 10993-11	Tests for systemic toxicity
Acute Toxicity	ISO 10993-11	Tests for systemic toxicity
Subacute Toxicity	ISO 10993-11	Tests for systemic toxicity
Subchronic Toxicity	ISO 10993-11	Tests for systemic toxicity
Chronic Toxicity	ISO 10993-11	Tests for systemic toxicity
Implantation Effects	ISO 10993-6	Tests for local effects after implantation
Genotoxicity	ISO 10993-3	Tests for genotoxicity, carcinogenicity, and reproductive toxicity
Carcinogenicity	ISO 10993-3	Tests for genotoxicity, carcinogenicity, and reproductive toxicity

Subclause 3.17 of ISO 10993-1 defines physical and chemical information as knowledge regarding formulation, manufacturing processes, geometric and physical properties and type of body contact and clinical use that is used to determine whether any additional biological or material characterization testing is needed.

Additional relevant endpoints outlined in ASTM F2901-19 should be considered for the COSMIIC System components due to device components used in nervous tissue applications.

Table 6. Summary of ASTM F2901-19 Endpoint Evaluations

ASTM F2901-19 Clause	Biological Endpoints
6.2.1	Cytotoxicity
6.2.2	Genotoxicity
6.2.3	Implantation
6.2.4	Pyrogenicity
6.2.5	Indirect hemolysis (per ISO 10993-4: Selection of Tests for Interactions with Blood)
6.2.7	Developmental neurotoxicity

While all endpoints listed above must be considered, they can be addressed in a number of different ways including biological testing, analytical chemistry testing, written risk assessment with justification, or a combination of the three, if relevant information is available.

8 Method

8.1 Safety Assessment Approach Used

This document assesses the risk posed to patients on whom the device is intended to be used.

The risk management process consists of the following elements:

- Risk analysis
- Risk evaluation
- Risk control and
- Production and post-production activities

8.2 Biological Risk Estimation

Information or data for estimating risks can be obtained from a number of different sources. For example, knowledge of the composition of a medical device, including additives and processing aids, prior use of the relevant material(s) in a predicate device or similar device, and biological safety tests are used to provide predictive evidence of potential hazards to users of the device under consideration.

8.3 Literature Search Methodology

Literature review on the raw materials to construct the COSMIIC System is part of a comprehensive risk analysis approach. Multiple sources were searched for published data. These sources include online databases that typically consider studies peer-reviewed by authorities, or studies conducted following the requirements of recognized standards. The search terms include elements such as CAS numbers (when available), chemical names, safety, chemistry, toxicology, toxicity, or biocompatibility.

Relevant toxicity databases include the following as examples:

- Registry of Toxic Effects of Chemical Substances (RTECS)
- FDA's Select Committee on GRAS Substances (SCOGS) Reports database
- European Chemicals Agency (ECHA) database
- Agency for Toxic Substances and Disease Registry (ATSDR) reports database
- ChemIDplus (which indexes databases such as HSDB, DART, EMIC, CCRIS, IRIS, Medline, and Toxline)
- PubMed
- Environmental Protection Agency (EPA) CompTox Chemicals Dashboard
- ChemFinder
- Various other on-line sources and databases (e.g., FDA.gov)

The literature review on each individual raw material is not intended to be exhaustive as presented in the guidelines of the informative Annex C of ISO 10993-1 but is intended to provide information on actual hazards related to raw materials. To assess the overall toxicological risks, other parameters must also be considered such as the manufacturing process, including implementation, cleaning, packaging and sterilization where applicable, and its potential residues. For this reason, the intent of the literature review is not to review and triage all the existing published data on each raw material and detected extractable, but to identify any documented known toxicological hazards.

9 Results

9.1 Risk Analysis of Device Materials

After an analysis of the materials used to construct the COSMIIC System, it was apparent that all materials used are well characterized with a long history of clinical use in similar or closely related, approved and marketed medical devices. From the information reviewed, there are no novel materials and degradation of the materials would not be expected. Stability of the materials of construction until point-of-use should be demonstrated (e.g., shelf-life validation) and is outside the scope of this assessment.

One substance, found in the NuSil MED-4800 colorants (octamethylcyclotetrasiloxane) is noted to be slightly irritating when tested as a neat material (100%). The substance as part of the NuSil MED-4800 is present at a significantly less amount (<0.25%), and is dispersed in a vinyl-functional silicone polymer which covalently bonds into the matrix of platinum-cured silicone system. Once cured and embedded within the silicone elastomer, is considered to have very low patient risk of exposure. Any residual risk will be mitigated with the recommended biocompatibility testing.

The detailed risk analysis performed on the device materials of construction is presented in Appendix A.

9.2 Risk Analysis of Manufacturing Processes

After an analysis of the manufacturing processes used to construct the COSMIIC System, none are classified as carcinogenic, mutagenic or reproductive toxicants or substances with endocrine-disrupting properties.

For most of the processing agents listed in Table 17, these substances are more of a concern for those individuals within the manufacturing environment with the chemicals in their neat state. The main concern for the manufacturing agents would be irritation and sensitization when the COSMIIC System is used as intended. Hazards associated with these substances can be mitigated by favorable biocompatibility data indicating that all downstream cleaning processes are performing well and the risk of residual manufacturing agents is negligible.

The detailed risk analysis performed on potential residuals from the processing agents used in the construction of

device is presented in Appendix B.

9.3 Biological Tests

Previous biological testing has been conducted on the RM and PM modules only. Since that time, EPO-TEK 301 has replaced the header adhesion and back-fill on the RM (previous testing used the EMIUV Cast 710-2K adhesive). For further details regarding the methods and analyses, the specific reports should be referenced.

Table 7. Previous Biological Testing Conducted

Study Number NAMSA	Conducted according to Standard:Year	Biological Endpoint Evaluated	Test Method and Conditions	Results
12T_28213_01	ISO 10993-5:2009 ISO 10993-12:2007	Cytotoxicity (RM)	MEM Elution (1X MEM) 37°C x 24 hours 3cm²:1mL	Non-cytotoxic
12T_28351_01	ISO 10993-5:2009 ISO 10993-12:2007	Cytotoxicity (PM)	MEM Elution (1X MEM) 37°C x 24 hours 3cm²:1mL	Non-cytotoxic

MEM: Minimal Essential Media

9.4 Clinical Data

The COSMIIC System (also referred to as the Networked Neuroprosthesis, NNP System), has been implanted into 8 individuals for periods of up to 7.5 years.[2] These implants consist of as many as 22 different stimulating and recording electrodes in the muscles of the torso, arm and both legs. The function of these electrodes, either through stimulation or through recording of myoelectric signals, is very sensitive to scar tissue formation around the electrode. In all cases (~150 electrodes to date), the activation thresholds and recorded signals have been within the expected stability of electrodes of this type. This indicates that there is no excessive scarring around the electrodes or around the modules (which serve as the return current path for the electrodes).[2] Similar electrodes, using the same design and materials, have been utilized in earlier generations of the implanted system for more than 30 years.[2]

Across the 8 individuals which have been exposed to complete systems, there have been 55 device modules that have been implanted in the upper chest, abdomen (bilaterally), upper arm, and volar forearm. In addition, network cables connect each device in the body to form an interconnected network and thus 47 network cables have been implanted in the 8 individuals. Total implantation time ranges from 6 months to 92 months. There has been no evidence of adverse tissue reaction due to material incompatibility. The incisions over the modules have healed normally, with typical to minimal visible scarring confined to the incision itself. There is no reported palpable evidence of scar buildup or granulomas around any of the modules. There has been no evidence of tissue erosion caused by any of the implanted components, and no swelling or irritation.[2] The COSMIIC System is designed for upgrades and replacement of individual modules and cables without the need to remove or replace the entire system. Over the course of this clinical study however, 4 patients have undergone removal and replacement of original components which had been implanted more than 4 years. Three of the 4 underwent module replacements due to updated internal electronics or battery; and the fourth patient no longer wanted to participate in the trial due to chronic pain unrelated to the device, hence the entire system was removed. In all cases modules were covered with a <1mm fibrous encapsulation with no indication of irritation, progressive scarring, ongoing tissue reaction, or signs of corrosion. For one patient who had been implanted for more than 7.5 years, four modules were exposed, and multiple tissue samples taken for pathological examination. The results exhibited no organisms, no growth of pyrogens, no polymorphonuclear leukocytes, and 1+ squamous epithelial cells.[2] These results indicate favorable biocompatibility of the COSMIIC System components, including modules, electrodes and network cables. These components have been shown to be safe for chronic implantation in humans for periods of up to 7.5 years.

10 Risk Control

The estimation of risks for the COSMIIC System has been reviewed and the testing strategies and or justifications for the waiving of certain biocompatibility tests are presented in this section to demonstrate that all biological hazards have been considered and relevant risks assessed and controlled.

A summary of the methods of consideration used to address each relevant biological and chemical endpoint appears in Table 8. Where multiple methods are presented in the ISO 10993 individual standards, the recommended method based upon the clinical use of the device is presented in parentheses. Further details regarding testing and justifications follow the table.

Table 8: Methods of Consideration of Biological Endpoints for the COSMIIC System

Testing Program		Standard	Testing Performed, Rationalized, or Recommended (Method Recommended)
Chemical Analysis – Exhaustive extraction			
Chemical Characterization of Degradation Products and Extractables/Leachables		ISO 10993-18	Recommended (2 separate tests) 1. PM/RM modules 2. Cables, electrodes, plug ports
Toxicological Risk Assessment of Chemistry Results		ISO 10993-17	Recommended
Biological Testing			
Cytotoxicity		ISO 10993-5	Performed on PM and RM only (MEM Elution) *and* Recommended with entire system (MEM Elution)
Sensitization		ISO 10993-10	Recommended (Guinea Pig Maximization)
Irritation		ISO 10993-23	Recommended (Intracutaneous)
Acute Systemic Toxicity		ISO 10993-11	Recommended
Pyrogenicity		ISO 10993-11	Recommended (USP <151> Preferred)
Subacute/Subchronic Toxicity		ISO 10993-11	*Rationalized*
Chronic Systemic Toxicity		ISO 10993-11	*Rationalized*
Implantation		ISO 10993-6	*Rationalized*
Genotoxicity	*In vitro* Bacterial Cells Bacterial Reverse Mutation Assay	ISO 10993-3	Recommended
	In vitro Mammalian Cells Mouse Lymphoma Assay (preferred) or Chromosomal Aberration Assay	ISO 10993-3	Recommended
Carcinogenicity		ISO 10993-3	*Rationalized*
ASTM F2901-19			
Cytotoxicity		ISO 10993-5	Recommended as above
Material Mediated Pyrogenicity		ISO 10993-11	Recommended as above
Indirect Hemolysis		ISO 10993-4	*Rationalized*
Local Tissue Effects (Implantation)		ISO 10993-6	*Rationalized*
Genotoxicity		ISO 10993-3	Recommended as above
		ISO 10993-3	Recommended as above
Developmental Neurotoxicity		ISO 10993-6	*Rationalized*

10.1 Representative Device Selection

The COSMIIC System patient contacting components should be tested in their final finished state, including final packaging and sterilization. The maximum number of components of the COSMIIC System is that for trunk stability, which includes a total of 1 PM, 7 RMs, 7 Network Cables, and up to 26 electrodes. This represents the most conservative case for surface area of patient exposure of an entire system and should be used as the worst-case system representative for biological testing.

For chemical characterization testing, because of potential solvent compatibility differences, and because this system is based upon a modular platform, consideration should be given to testing the power and remote modules separately from the cables, electrodes, and port plugs. The toxicological risk assessment may subsequently combine results for a full evaluation of results.

10.2 Chemical Testing Recommended

Chemical characterization of a medical device is the cornerstone of the ISO 10993-1 and ISO 14971 standards for evaluating risk for medical devices. Although the materials of construction are generally known materials that have been characterized and demonstrated biocompatible, information gaps were identified that require additional investigation through chemical analysis using methods prescribed in ISO 10993-18.

Organic chemicals can qualitatively be placed into three classes based on their volatility: volatile organic compounds (VOC), semi-volatile organic compounds (SVOC), and non-volatile organic compounds (NVOC). The analytical techniques used to screen for these classes of organic extractables are different, though one chemical can often be detected using a variety of techniques; for example, gas chromatography with headspace sampling (HS-GC) is typically used to analyze VOC, gas chromatography (GC) is typically used to analyze SVOC and liquid chromatography (LC) is used to analyze NVOC. The chromatographic techniques used for screening are coupled with appropriate sensitive, broadly applicable, and information-rich detection methods, such as mass spectrometry (MS), to ascertain the extractables' identity and concentration. While the chromatographic methods screen solutions for organic extracted compounds, atomic spectroscopic methods such as inductively coupled plasma optical emission spectroscopy (ICP-OES), and inductively coupled plasma mass spectrometry (ICP-MS) screen solutions for elements that may be associated with either organic or inorganic extractables. The ICP analysis is not strictly limited to analysis of inorganic extractables, as several of the elements typically included in ICP analysis can exist in both organic and inorganic forms (e.g. S, Si, Zn, and Sn, etc.).

Considering the clinical use of the device system, initial solvent compatibility testing should be performed on the components.

Following selection of the appropriate solvents, the following chemical characterization program is recommended:

1. Exhaustive extraction in polar, semi-polar, and non-polar vehicles;
2. ICP-MS or ICP-OES for quantification of trace metals (including ICH Q3D elements) in saline extract;[3]
    a. If the use of 0.9% sodium chloride (saline) negatively impacts the analyses (*e.g.*, interference, quantitation limit problems, *etc.*), separate extractions in purified water may be needed.
3. GC-MS for quantification of SVOC from the test article extracts;
4. LC-MS for quantification of NVOC from the test article extracts;
5. HS GC-MS for quantification of VOC from the test article extract;

The COSMIIC System is categorized as a long-term (>30 days) medical device implant, with direct contact with tissue/bone. The worst-case duration of body contact could be > 10 years to a lifetime. The dose-based threshold (DBT) of 1.5 µg/day is considered to be protective for both non-cancer (systemic) and cancer effects (per ISO/TS 21726) for Analytical Evaluation Threshold (AET) calculations.

Once obtained, the extractables data should be subjected to toxicological evaluation per ISO 10993-17:2023 and ISO/TS 21726 to determine if there are unmitigated risks associated with patient exposure to extractable chemicals during clinical use of the subject device.

10.3 Biological Testing Recommended

The COSMIIC System is a permanent implant, and although it is manufactured from well characterized, non-toxic, inert materials with ubiquitous use in medical devices, biocompatibility testing is required to mitigate adverse effects and toxicity subsequent to potential residuals and extractables, as well as any issues that could arise from the device/tissue interface due to design properties or surface effects under the environment to which it will be exposed.

The biological testing recommended should be performed according to the most recent ISO 10993 standards as listed in Table 8 as well as ISO 10993-12:2021.

Recommended studies requiring extraction should use both polar and non-polar extraction vehicles unless the vehicle is incompatible with the test system (e.g., non-polar extracts cannot be intravenously administered).

The extraction conditions of 50ºC for 72 hours are preferred by regulatory agencies assuming these conditions are compatible with the device and test system.

Only the patient contacting portions should be evaluated in any of the biocompatibility testing performed.

All biological tests should be conducted according to GLP regulations (i.e., FDA GLP).

Tests to be performed on the final finished COSMIIC System inclusive of final packaging and sterilization are:

Cytotoxicity (ISO 10993-5): This highly sensitive *in vitro* test intended to screen biologically harmful devices in the absence of protective mechanisms that normally assist cells within the body.

Although cytotoxicity has been conducted on the PM and RM components independently, extractions were only conducted for 24 hours. Per ISO 10993-5:2009, "*medical devices which are in prolonged (>24 h to 30 d) or long-term contact (>30 d), extraction times of 72 h are recommended for cytotoxicity testing because extraction for 24 h may not be sufficient to obtain an extract that represents the chemicals released beyond 24 h of device use*." Therefore, cytotoxicity testing should be repeated under these conditions, and performed inclusive of all patient contacting components together to help mitigate the risk of all interactive chemistry when implanted as a complete system.

For the cytotoxicity study, U.S. FDA recommends that extractions be conducted at 37°C for 72 hours, for devices with patient contacting cumulative exposures exceeding 24 hours, using a vehicle that will allow for extraction of both polar and non-polar constituents from the test article, such as mammalian cell culture media (e.g., MEM) supplemented with 5-10% serum.

Sensitization (ISO 10993-10): This *in vivo* test is intended to determine whether a device could induce Type IV allergic reactions as a result of repeated/prolonged contact with the immune system.

Note: While the Local Lymph Node Assay (LLNA) is recommended for determining the sensitization potential for single chemicals (as per ISO 10993-10, Clause 6.1), the guinea pig maximization test (GPMT) is a reliable method to evaluate the sensitization potential for multi-chemical containing extracts of medical devices.

Intracutaneous Irritation (ISO 10993-23): This *in vivo* test is intended to evaluate irritation potential of a device after a short-term exposure by the intradermal route.

Note: currently, the US FDA does not recognize Clause 6 of ISO 10993-23, which described *in vitro* test methods for irritation (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm).

Material Mediated Pyrogenicity (ISO 10993-11/Ph. Eur./USP): This *in vivo* test is intended to detect substances inducing a material-mediated pyrogenic reaction, that could lead to a febrile reaction in the patient.

The US FDA typically prefers the methods/criteria specified in USP, General Chapter <151>, Pyrogen Test

Acute Systemic Toxicity (ISO 10993-11): This *in vivo* test is intended to estimate, during a period of occurring at any time within 72 hours after exposure of a test sample, the adverse effects on general health status resulting from absorption, distribution, and metabolism of potential toxic leachables in extracts.

Note: Acute systemic toxicity testing may be waived for the EU and the US FDA, if leachables of the device are identified and can be evaluated to demonstrate that all components have been adequately tested for acute systemic toxicity.

Genotoxicity (ISO 10993-3 and ASTM 2901-19): These assays determine the potential of a medical device or material to be mutagenic, clastogenic, genotoxic, or potentially carcinogenic. As per ISO 10993-3:2014, two *in vitro* tests must be considered:

- Ames Test (Bacterial Reverse Mutation Assay, OECD 471): This highly sensitive *in vitro* test is intended to detect gene mutations affecting a small portion of the DNA molecule including frameshifts and base-pair substitutions following contact with test-extracts.
- Mouse Lymphoma Assay (OECD 490) or Chromosomal Aberration Assay (OECD 473): These *in vitro* tests are intended to evaluate whether extracts of the test-article induced gene mutations/chromosomal aberrations in cultured mammalian cells.

10.4 Rationale for Testing not Recommended

The rationale for the omission of subacute, subchronic and chronic systemic toxicity, implantation, carcinogenicity, hemolysis, and developmental toxicity testing of the COSMIIC System is provided below.

Subacute, Subchronic, and Chronic Systemic Toxicity (ISO 10993-11): These assays determine the potential of a

device or material to cause systemic toxicity over a specified duration of time according to ISO 10993-11. Testing of the device for chronic systemic toxicity is unnecessary for the following reasons:

- The materials used to manufacture the COSMIIC System are known materials with an established history of biocompatibility in devices with similar applications. The materials are not known to cause systemic toxicity.
- It is assumed that the extractables testing and associated toxicological evaluation of the results completed on the device will not exhibit a potential for significant patient exposure to specific compounds that could pose a potential risk for systemic toxicity.
- It is assumed that no acute systemic toxicity will be observed when the device is subjected to acute systemic toxicity testing in mice.

Local Implantation (ISO-10993-6 and ASTM 2901-19): These tests determine the local effects of implanting the test device *in vivo.*

It is acknowledged that the long-term clinical data represents a small patient number (n=8), with limited macroscopic and microscopic tissue evaluation. However, local implantation testing of the COSMIIC System is considered unnecessary for the following reasons:

- Traumatic spinal cord injury (SCI) is a life-altering, devastating condition, associated with significant morbidity, psychological and financial stress.[4] Medical management is estimated to be 4 billion dollars, an enormous burden to patient, family and the health care field.[7]
- Currently, there are no successful therapeutic interventions to reverse damage to the spinal cord. Surgical intervention (decompression, spinal alignment, stabilization) helps only 1% to 1.8% of cervical and thoracic SCI patients.[5] Stem cell transplants and bioengineered growth scaffolds have been promising therapies, but results are still inconclusive.[5,8]
- Those with severe spinal cord injury (SCI) have permanent loss of sensation and function. Intended patient population is small. Globally, spinal cord injury (SCI) exhibits an incidence of 10.4-83 cases/million/year.[6] In the United States, the annual incidence rate of SCI is 54 cases per million, with a prevalence rate of 721 to 906 cases per million people.[7]
- Severity depends on extent of injury and location of injury. For complete injuries, there is no nerve communication below the injury site and muscle control, feeling, or function is lost.[8] Patients with acute spinal cord injury have significantly increased mortality in the 1st year following injury, and those that survive have decreased life expectancy.[9] Up to 22.2% of patients with SCI experience anxiety and depression as well.[10] Rehabilitation programs include physical therapy, occupational therapy, vocational rehabilitation.[8] The addition of the COSMIIC System for these patients can positively affect quality of life when accompanied by a certain level of improvement in functional outcomes.
- The risk benefit is significant for this small patient population, who exhibit a high level of paralysis and no credible alternatives to improve quality of life, or functional movement. The risk of an adverse biological effect in rationalizing implantation testing is small in consideration of the enormous benefit for this patient population if implanted with the COSMIIC System. The clinical dataset of COSMIIC System patients has encompassed 55 different modules and 47 network cables, with no concerning trends of increasing stimulation required to maintain functional benefits, providing an adequate safety profile.

Carcinogenicity (ISO 10993-3): Carcinogenicity tests should only be performed if there is a reasonable suspicion that carcinogenicity of a device is a true risk.

Section 6.1 of ISO 10993-3 states: Before a decision to perform a carcinogenicity test is made, ISO 10993-1 shall be taken into account. The decision to perform a test shall be justified on the basis of an assessment of the risk of carcinogenesis arising from the use of the medical device. Carcinogenicity testing shall not be performed when risks can be adequately assessed or managed without generating new carcinogenicity test data.

The COSMIIC System is not considered to be a carcinogenic risk for the following reasons:

- The materials used to manufacture the COSMIIC System are known materials with an established history of biocompatibility in devices with similar applications. The materials are not known to be carcinogenic.

- It is assumed that the extractables testing and associated toxicological evaluation of the results completed on the device will not exhibit a potential for significant patient exposure to specific compounds that could pose a potential risk for carcinogenicity.
- It is assumed that the recommended biological testing completed on the device will not yield adverse or equivocal/conflicting results that indicates potential biological risk.

Indirect Hemolysis (ASTM 2901-19): Indirect (extract) hemolysis testing on the final sterilized medical device is recommended for devices that either directly or indirectly contact cerebrospinal fluid (CSF). Testing of the device is unnecessary as none of the components/implantables of the COSMIIC System have direct or indirect contact with the CSF.

Developmental Neurotoxicity (ASTM 2901-19): Clause 6.2.7 of ASTM F2901-19 lists conditions that may trigger consideration of a developmental neurotoxicity evaluation. It states, "…potential for in utero exposure, intended use of a device in neonates, infants, or vulnerable pediatric populations; the type and duration of exposure; the use of novel materials that have limited toxicity data; and/or the presence of base materials or manufacturing additives that have known neurotoxicities."

- No developmental neurotoxicity testing or assessment is required as the COSMIIC System Implant components are not intended to be used in neonates or infants, the materials are well-characterized, and no material or manufacturing additive has known neurotoxicities. Although limited to a small patient trial of 8 individuals spanning over 7.5 years, the clinical data has not exhibited any biocompatibility concerns. The COSMIIC System is developed for patients with paralysis from a spinal cord injury, so quality of life is an important consideration as well. Evaluation of neurobehavioral assessments and histopathology in animals may not be of added value given the benefit that has already been demonstrated in the trial. With no adverse biocompatibility events documented among the 8 patients, and in-line with ISO 10993-2 (animal welfare guidelines) and the 3 R's (reduce, replace, refine), further animal studies would not be warranted and considered ethical.
- It is assumed that the extractables testing and associated toxicological evaluation of the results completed on the device will not exhibit a potential for significant patient exposure to specific compounds that could pose a potential risk for neurotoxicity.

11 Reassessment of Risk

This risk assessment is valid for the current iteration of the COSMIIC System as presented to [redacted] by Cosmiic Inc. It applies to devices manufactured using the current processes and techniques.

As specified in the Clause 4.9 of the ISO 10993-1 standard, the biological risk assessment of the device shall be re-evaluated if any of the following occur:

- Any change in the source or in the specification of the materials used in the manufacture of the product;
- Any change in the formulation, processing, primary packaging, or sterilization of the product;
- Any change in the manufacturer's instructions or expectations concerning storage, e.g. changes in shelf life or transport;
- Any change in the intended use of the product;
- Any evidence that the product can produce adverse biological effects when used in humans.

12 Conclusion

Based upon the safety assessment of the information evaluated in this biological evaluation plan, additional biological and extractables testing, with subsequent evaluation of results, is recommended to establish the biocompatibility of the COSMIIC System.

This assessment applies only to the device described in this report. Any extrapolation to other devices is the Sponsor's responsibility.

Appendix A Risk Analysis of Device Materials

Evaluation of the chemical nature of the material can take the form of experimental data or information on the chemistry of the materials/components involved. Literature on the materials of construction for the COSMIIC System is provided below.

A.1 Titanium (CAS No. 7440-32-6)

Titanium (Ti) is the chemical element with an atomic number of 22 and atomic weight of 47.90 g/mol. Grade 1 and Grade 2 commercially pure titanium is used as the materials of construction for the RM and the feedthrough assembly of the RM. Titanium is a transition metal with a white-silvery-metallic color known for its excellent biocompatibility. Due to its cost, it is mainly used for specialized purposes in the aerospace and nuclear industries or medicine.

Ti-6Al-4V ELI (capsule of the PM, ASTM F136) is a titanium alloy mainly composed of aluminum (6%) and vanadium (4%).[11] Ti-6Al-4V ELI, where ELI stands for Extra Low Interstitial, is an improved version of Ti-6Al-4V that has a lower content in interstitial impurities (such as oxygen, nitrogen, carbon and hydrogen).[12,13] Since these impurities decrease the fatigue strength, Ti-6Al-4V ELI shows higher toughness than Ti-6Al-4V.[13]

Although Ti-6Al-4V and Ti-6Al-4V ELI were not specifically developed for the biomedical area, their high specific strength, corrosion resistance and biocompatibility has led to their use in biomedical applications in the 1950's.[11,12,13,14] They were one of the first titanium biomaterials introduced in implantable devices and are now the most widely used titanium alloys for implants where high strength is required.[11,14] Of note, ISO 5832-3, as well as the ASTM F1472 for Ti-6Al-4V and ASTM F136 Ti-6Al-4V ELI, specify the requirements of these alloys when used for the manufacture of surgical implants.[11]

There is no known biological role for titanium. There is a detectable amount of titanium in the human body and it has been estimated that humans take in about 0.8 mg/day, but most passes through the body without being absorbed. It is not a poisonous metal and the human body can tolerate titanium in large doses. The extremely low toxicity of titanium and several of its compounds (titanium salicylate, oxides, peroxide, and tannate) when in contact with skin and tissues has been demonstrated by its use in the therapy of skin disorders.[15] When administered to rats as a single intraperitoneal injection of 25 mg (139-156 mg/kg) or an intravenous injection of 250 mg/kg, titanium dioxide behaved as an inert substance. The physical-chemical properties of titanium are summarized in Table 9.

Table 9. Physical-Chemical Properties of Titanium

Property	Value
Boiling Point	3277°C
Melting Point	1677°C
Specific Gravity	4.5
Solubility in Water	Insoluble
Appearance and Odor	Odorless white-silvery metallic solid

The excellent biocompatibility of titanium and its alloys, such as Ti-6Al-4V ELI, is well documented. Titanium has historically maintained the reputation of being an inert and relatively biocompatible metal, suitable for use as both a medical and dental prosthesis. Titanium and titanium alloys show the greatest biocompatibility among metallic materials for biomedical applications.[16]

The biocompatibility of titanium is high as shown by its prevalent use as an implant material in orthopedics, oral surgery, and neurosurgery. Bothe, Beaton, and Davenport were the first to study the tissue reaction of titanium. They implanted titanium and several other metals into the cat femora. While several metals provoked some reaction of the bone, titanium remained inert. Leventhal inserted titanium screws into rat femora.[17] The animals were sacrificed at six, 12, and 16 weeks. Microscopic examination of the bone revealed no reaction to the implant. Plates of titanium were also implanted in the subcutaneous tissue of rabbits and examined at intervals up to 10 weeks. The subcutaneous tissue was normal; therefore, the author concluded that titanium was compatible with the tissue. Implantation of titanium metal in dogs has shown that soft tissue has a high tolerance for titanium metal, indicated by lack of irritation, good wound healing, and encapsulation of the metal by fibrous tissues. The small amounts of titanium occasionally released from implants into adjacent tissues have not caused any adverse effects.[18]

- Acute Toxicity: When administered to rats as a single intraperitoneal injection of 25 mg (139-156 mg/kg) or an intravenous injection of 250 mg/kg titanium dioxide behaved as an inert substance.[19]

- Repeat-Dose Toxicity: NSF International has evaluated the non-cancer oral toxicity data for titanium and titanium dioxide, and calculated a reference dose (RfD) of 3 mg/kg/day based on an oral no observed adverse effect level (NOAEL) of 2680 mg/kg/day observed in F344 rats in a 103-weeks study.[20] NSF International applied a composite uncertainty factor of 1000 (10 each for inter- and interspecies extrapolation and for database deficiencies) to the NOAEL of 2680 mg/kg/day in rats. The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.
- Genotoxicity: Kodama studied the corrosion resistance and mutagenicity of pure titanium, and two different titanium alloys, TI-6Al-4V ELI and Ti-5Al-2.5Fe.[21] Using the bacterial reverse mutation (Ames) assay, the titanium and titanium alloys were found to be non-mutagenic. Nordman and Berlin have also determined that titanium tetrachloride is non-mutagenic.[19] There is sufficient and reproducible data in the literature to indicate that titanium is not genotoxic.
- Carcinogenicity: The carcinogenicity of titanium has not been extensively studied using animal models based on its overall good biocompatibility and widespread use in a number of long-term implants. No evidence of carcinogenic or tumorigenic potential which can be attributed to a titanium implant has been reported in the literature. On the basis of available data, titanium has generally been considered to belong to the group of metals of low carcinogenicity.[19]
- Sensitization: Persons with a history of allergies, including sensitivities to cobalt, chromium, or nickel, generally do not exhibit or develop sensitivity to titanium or other constituents of Ti-6Al-4V alloy.[15]

A.2 Tecothane

Tecothane (Lubrizol TT-1075D-M) is an aromatic polyether-based thermoplastic polyurethane (TPU) used as a material of construction for both the PM and RM, as an encapsulant protection for female interconnect assemblies, wireless antenna, and feedthrough wires. Tecothane TT-1075D-M according to the safety data sheet (SDS) is not classified for hazards.[22] The components are not hazardous or are below required disclosure limits.[22] Per the technical data sheet, it is a medical grade material, that comes in a variety of hardnesses, with good mechanical properties, good chemical resistance, and can be color-matched.[23]

Tecothane® TPU's have been evaluated for biocompatibility by Toxicon Inc. (Bedford, MA), inclusive of MEM elution, hemolysis, pyrogenicity, USP Class VI testing (acute systemic, acute intracutaneous, and 7-day implantation), histopathology from samples of Tecothane subcutaneously implanted into rabbits for up to 90 days, and mutagenicity testing (Ames Assay), all with favorable results.[24] Favorable biostability testing has included an acute 14-day, subacute 30-day and subchronic 90-day subcutaneous testing.

A general toxicological profile of polyurethane is described below.

A.2.1 Polyurethane

Polyurethane (PU) is categorized as a thermoplastic elastomer. PUs can be strong elastomers or rigid plastics, and they can be processed using extrusion, injection molding, film blowing, solution dipping, and two-part liquid molding. PU can be sterilized by dry heat, ethylene oxide, or gamma irradiation. Polyether urethanes were developed to have enhanced hydrolytic resistance and stability and be more stable than their predecessors, poly ester urethanes (PEU).[25] Even so, polyether urethanes are still susceptible to oxidation after extended periods *in vivo*. To make PU polymers even more stable, antioxidants have been added to prevent soft segment oxidation, thereby prolonging the lifetime of the polyurethane.[26]

PUs are among the most versatile construction materials that can be formulated for medical devices and consumer products. Their unique chemistry gives them this versatility. They are segmented polymers, meaning they have a soft segment that provides flexibility and a hard segment that provides strength. PU polymers are made from three basic building blocks: the backbone, the diisocyanate, and the chain extender. The backbone, usually a long chain molecule, provides flexibility to the polymer. The diisocyanate and the chain extender combine to form the hard segment, which acts as a cross-link to provide the polymer with high tensile strength and elongation.[25]

PU polymers are made from either aromatic or aliphatic diisocyanates. Aromatic diisocyanates contain phenyl rings, which create polyurethanes that are generally tougher, stronger, and less costly than the aliphatics. The aromatics

generally have tougher hard segments, which are chemically more resistant and give rise to higher tensile strength and elongation than aliphatics. Aliphatic diisocyanates are made with hydrocarbon backbones and contain no phenyl rings. Aliphatic polyurethanes make strong polymers but lack the chemical resistance of aromatics. They are more expensive than aromatics and are used primarily in applications that require good light stability. There are thousands of possible combinations of the basic building blocks used to create aromatic and aliphatic polyurethanes, thereby providing engineers with a myriad of options for their products. PU polymers are used in medical devices such as wound dressings, catheter components, tensioning ligatures, tubing, connectors, and fittings. Most implantable polyurethane leads are made from polyether urethanes.[27]

PU polymers are tough, biocompatible, and hemocompatible.[28] Segmented polyurethane elastomers have been extensively used in medical devices due to their excellent biocompatibility and unique mechanical properties. Polyurethanes have been used in medical devices for more than twenty years.[29] Results of some of the biocompatibility tests for polyurethane are shown in Table 10.

Table 10. Summary of Referenced Biocompatibility Tests on Polyurethane

Study Description	Biological Effect	Result	Reference
Cytotoxicity	Cellular Toxicity	Non-cytotoxic	29
Muscle implant, rat, 2, 10, 30, 45 and 60 days	Local Tissue Reaction	Negative reaction after 60 days	29

The International Agency for Research on Cancer (IARC) has concluded there was sufficient human or animal information available to classify polyurethane as Group 3, not classifiable as to carcinogenic to humans.[30] The biological evaluation studies give no evidence of potential for carcinogenicity; additionally, the genotoxicity studies do not demonstrate any sign of mutagenicity or toxicity.

A.3 Silicone (CAS No. 7440-21-3)

A polyester reinforced silicone sheeting (Silicone SSF-METN-750) is used to allow the non-absorbable sutures to anchor the device to the underlying tissue for the PM, RM, and intramuscular stimulating and recording electrodes. In addition, several NuSil silicone rubber, silicone adhesives/primers, elastomers/sealants, are used in the construction of the COSMIIC System.

A general toxicological profile for silicone is described below.

Silicone rubbers are synthetic polymers with a backbone of alternating silicon and oxygen atoms (Figure 5). This structural linkage is similar to that found, for example, in a mineral such as quartz. Silicones have superior heat resistance compared to other elastomers. The strong silicon-oxygen chemical bonds of silicone give the polymer its unique performance properties, including biocompatibility, superior temperature and chemical resistance, good mechanical and electrical properties, and natural clarity or translucence. Silicones are resistant to water and many chemicals, including some acids, oxidizing chemicals, ammonia, and isopropyl alcohol. Concentrated acids, alkalines, and certain solvents should not be used with silicones.[31]

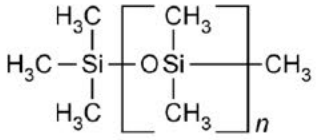


Figure 5. Chemical Structure of Polydimethylsiloxane (Silicone Rubber)

Silicones are made by combining oxygen and silicon at high temperatures and pressures to produce polydimethylsiloxane (PDMS). Silicone fluids are made from linear chains of PDMS whereas the gels are lightly cross-linked to give the material a thicker cohesiveness.

Since the 1960s, silicone has found widespread use in medical, aerospace, electrical, construction, and industrial applications. Flexibility over wide temperature ranges, good resistance to compression set, a wide range of durometers, and inert and stable compounds are among the reasons for its popularity.

Silicones (polydimethylsiloxanes) are very common and versatile substances used in medical and pharmaceutical applications. Common silicone medical components and assemblies include airways, balloon catheters, tubing for

feeding, drainage, and use with peristaltic pumps, compression bars, electrosurgical handpieces, infusion sleeves and test chambers, introducer tips and flexible sheaths, wire/fluid-path coextrusions, ear plugs and hearing aids, shunts and septa, and a variety of seals, stoppers, valves, and clips.[32]

Solid silicone has a long history of use and continued commercial marketing clearance in implanted medical devices (e.g., breast implant shells and gastric banding medical devices). Silicones are also widely used in the many other healthcare applications such as nipples for baby bottles, cosmetic preparations, urinary catheters, breast implants, and blood handling tubing. Many recent applications that utilize silicone materials such as pacemaker Leads, hydrocephalus shunts, heart valves, finger joints, and intraocular lenses have been developed.[33]

The distribution of D4 in rats was studied using radiolabeled D4 administered by inhalation at a dose of 700 ppm.[34] The radioactivity was widely distributed in rat tissues, but only 5-6% of the total dose was retained in the tissues. Based on these results, the authors proposed that there is a high pulmonary and hepatic clearance of D4.

The major metabolites of hexamethyldisiloxane (HMDS) and D5 were identified in urine collected from rats orally and intravenously administered carbon 14 labeled HMDS and D5.[35] There were five metabolites that were commonly present in all HMDS injected animals. No parent HMDS or D5 were present and only polar metabolites were found in the urine. The presence of a hydroxymethyl group, the primary oxidation product of the methyl group, was noted in most of the metabolites of HMDS, while with D5 the presence of multiple hydroxyl groups was a common feature. The study also concluded that the presence of metabolites such as dimethylsilanediol in HMDS and methylsilanetriol in D5 clearly established that some demethylation occurs at the silicon-methyl bond.

Several studies have been conducted in which ^{14}C-labeled polydimethylsiloxanes were subcutaneously injected into animals. The majority of the radioactivity (94-99.97%) remained at the injection sites. In one experiment, less than 0.02% was found to have migrated to different tissues, and very small percentages (approximately 0.1%) of PDMS were detected in expired air, urine, and feces. Raposo do Amaral *et al.* injected rats with 2 mL of silicone gel at two different sites and followed the animals for various time periods up to 450 days.[36] Silicone was not detected in the heart, spleen, liver, stomach, or gonads, but it could be locally detected surrounding the tissue capsules at the injection sites. No silicone was found in the regional lymph nodes.

Silicone KS66 (92% polydimethylsiloxane and 8% silica), used as an antifoaming food additive, was fed to 50 female and 50 male rats to evaluate the potential for carcinogenicity. No treatment related effects were noted regarding survival rate, general condition, body weight, food consumption, hematology, and organ weight data. Detailed histopathological examination revealed no treatment-related increase in the incidences of any non-neoplastic or neoplastic lesions. The results demonstrate that KS66 is not carcinogenic in F344 rats of either sex.[37]

Genotoxicity testing provides an indication of the potential of a material to result in cancer in humans. A comprehensive safety assessment of several low molecular weight cyclic siloxanes (D3-D7) was completed.[38] Overall, the data presented in the assessment indicate that silicone, and its low molecular weight leachable, are not genotoxic. The genetic toxicity and mutagenicity of silicone materials have been extensively evaluated. No evidence of mutagenicity was observed in any of these test systems.

NuSil silicone rubber, silicone adhesives/primers, elastomers/sealants are of medical grade. Master Access Files (MAF) for the NuSil silicone products used in the construction of the COSMIIC System (as listed in Table 4) have been filed by NuSil (Carpenteria, CA) with the U.S. Food and Drug Administration (FDA). The NuSil silicones have been subjected to a significant amount of biocompatibility testing by the manufacturer. In all cases, the materials were found to be biocompatible. The testing results are summarized in Table 11.

Table 11. Biocompatibility Testing Conducted on NuSil Medical Grade Silicones (Master Access File)

Standard/Method	Test	Results
ISO 10993-5 / USP <87>	Cytotoxicity Study Using the ISO Elution Method (1X MEM Extract)	Non-cytotoxic
ISO 10993-4	*In Vitro* Hemolysis Study (Modified ASTM – Extraction Method)	Non-hemolytic
ISO 10993-11 / USP <88>	USP and ISO Systemic Toxicity Study – Extract*	Non-toxic
ISO 10993-10 / USP <88>	ISO Intracutaneous Study – Extract*	Non-irritant
ISO 10993-6 / USP <88>	ISO Muscle Implantation Study	Non-irritant
ISO 10993-3	Genotoxicity: Bacterial Reverse Mutation Study (DMSO and Saline Extracts)	Non-mutagenic
ISO 10993-11 / USP <151>	USP Pyrogen Study – Material Mediated	Non-pyrogenic
ISO 10993-10	ISO Maximization Sensitization Study – Extract	Non-sensitizer

*The products meet USP Class VI test requirements.

The colorants found in NuSil MED-4800, are color masterbatches for liquid silicone elastomers. Each pigment is dispersed in a vinyl-functional silicone polymer which covalently bonds into the matrix of platinum-cured silicone system:[39,40,42] Each is considered for use in human implantation for a period of greater than 29 days.[39,40,42] Each has undergone favorable cytotoxicity testing USP<87> ISO 10993-5.[39,42,40] Pigments are used to provide color-coding to identify interconnect function.

Stimulating Lead:

- MED-4800-3 Red 1.5% (ASTM D2090)
  A Master File for MED-4800-3 has been filed with the U.S. Food and Drug Administration.[39]
  Composition: Octamethylcyclotetrasiloxane (CAS No. 556-67-2 (<0.25%)[41]

Recording Lead:

- MED-4800-6 Green 1.5%
  A Master File for MED-4800-6 has been filed with the U.S. Food and Drug Administration.[42]
  Composition: Octamethylcyclotetrasiloxane (CAS No. 556-67-2 (<0.25%)[43]

Network Cable:

- MED-4800-7 Dark Blue 2%
  Master File for MED-4800-7 has been filed with the U.S. Food and Drug Administration.[40]
  Composition: Octamethylcyclotetrasiloxane (CAS No. 556-67-2 (<0.25%)[44]

A general toxicological profile for octamethylcyclotetrasiloxane is described below.

A.3.1 Octamethylcyclotetrasiloxane (CAS No. 556-67-2)

Cyclotetrasiloxane, octamethyl, also known as D4, is mainly used as a chemical intermediate for silicone fluids and elastomers, including those used in medical devices. One of the most notable medical applications has been for breast implants. D4 is widely used in a variety of applications including fermentation processes, instant coffee production, paper coatings and sizing, diet soft drinks, waste yeast tanks, food washing solutions, adhesives, textiles, boiler treatments, detergents, cleaning solutions, surfactants, cosmetic products, and polishes. Another notable use is the combination of D4 with decamethylcyclopentasiloxane (D5), commonly referred to as cyclomethicone which has a wide range of applications as a formulation aid in personal care products.

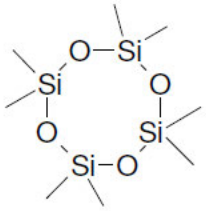


Figure 6. Chemical Structure of Octamethylcyclotetrasiloxane

D4 has been evaluated for its safety in a full range of toxicity studies by a number of routes of exposure. The results of these studies have shown D4 to have very low acute oral, inhalation, and dermal toxicity. In a recent study, the major urinary metabolites of D4 were identified. The urine samples were collected from male and female Fischer rats (F-344) intravenously administered [^{14}C] D4. The HPLC radiochromatogram revealed two major and at least five minor metabolites. The two major metabolites, constituting 75-85% of the total radioactivity, were identified as dimethylsilanediol [$Me_2Si(OH)_2$] and methylsilanetriol [$MeSi(OH)_3$]. Formation of $MeSi(OH)_3$ clearly established demethylation at the silicon-methyl bonds of D4. No parent D4 was present in the urine. The minor metabolites identified were tetramethyldisiloxane-1,3-diol [$Me_2Si(OH)$-O-$Si(OH)Me_2$], hexamethyltrisiloxane-1,5-diol [$Me_2Si(OH)$-$OSiMe_2$-$OSi(OH)Me_2$], trimethyldisiloxane-1,3,3-triol [$MeSi(OH)_2$-O-$Si(OH)Me_2$], dimethyldisiloxane-1,1,3,3-tetrol [$MeSi(OH)_2$-O-$Si(OH)_2Me$], and dimethyldisiloxane-1,1,1,3,3-pentol [$Si(OH)_3$-O-$Si(OH)_2Me$].[45]

The following toxicological information is provided for D4:

- Toxicokinetics: No available data.

- Acute Toxicity: The median lethal dose (LD_{50}) following oral administration of D4 in rats is reported to be more than 4800 mg/kg.[45] The median lethal concentration (LC_{50}) of 36 mg/L was calculated for rats after exposure to D4.[45] The acute dermal LD_{50} in rats and rabbits is >2400 mg/kg and >4640 mg/kg, respectively.[46]

- Repeated Dose Toxicity: D4 has been evaluated for its safety in a range of toxicity studies by different routes of exposure. A NOAEL of 960 mg/kg was found in a study in rabbits with dermal application of D4 for 28 days.[45]

  Four studies were performed with F344 rats. The rats (seven-eight weeks of age when the exposure started) were exposed by whole-body inhalation to concentrations of 0, 10 ppm, 30 ppm, 150 ppm, or 700 ppm D4 (LL084732 >99% pure) (mol weight 296.62, air concentration [0, 121, 364, 1820 or 8492 mg/m^3] six hours/day, five days/week. *Tissue Level Study* (Subgroup A): six rats/sex/group, the animals were sacrificed after six months of exposure. *Chronic Toxicity Study* (Subgroup B): 10 rats/sex/group, the animals were sacrificed after 12 months of exposure. *Chronic Recovery Study* (Subgroup C): 20 rats/sex/group, the animals were exposed to D4 for 12 month and sacrificed after a 12-month recovery period. *Oncogenicity Study* (Subgroup D): Described in section Genotoxicity/Mutagenicity/Carcinogenicity.[45]

  The survival of Subgroup C when assessed after 12 months of recovery showed no significant difference between the exposed and the control groups of either sex. There was no early death in either Subgroup A or B prior to their scheduled sacrifices. There were no clinical signs that were clearly associated with D4 exposure. Ocular examination conducted two weeks prior to the scheduled sacrifices for Subgroups B and D did not reveal eye lesions clearly associated with D4 exposure. Clinical pathology parameters were measured at three, six, nine, and 12 months on study. Overall erythrocyte and urinalysis parameters of either sex were not affected by D4 exposure. Leukocytosis was consistently observed in both sexes of rats exposed to 700 ppm at all time points, resulting from increased lymphocytes. There was an exposure related decrease in aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), and lactate dehydrogenase (LDH) activities in D4 exposed rats of both sexes at three, six, nine, and 12 months of exposure. These decreases were frequently present in a dose-related manner, in particular at the six- and nine-month time-points. No clear toxicological significance of the decrease in serum enzymes was identified relative to histopathology findings. Selected organs were collected and weighed at the scheduled sacrifices. Weight increases in the liver, kidney, and uterus were of particular interest. At six months on study (Subgroup A), the absolute liver weight tended to increase with increasing D4 exposure concentration and the difference was statistically significant at 700 ppm for females and at 30 ppm for males, respectively, relative to the concurrent controls. At 12 months (Subgroup B), the absolute liver weights were significantly increased at 150 and 700 ppm compared with controls for both sexes and the relative liver weights (normalized either to body or brain weight) generally increased with increasing exposure concentrations. The liver weight increase might be associated with centrilobular hypertrophy of hepatocytes diagnosed in 700 ppm males in Subgroup B. The absolute and/or relative kidney weights increased in some exposed males and females at 12 months, but the differences were statistically significant at 700 ppm when compared with the controls. In this study, a NOEL of 10 ppm was identified based on increased liver weights in males after six months. A NOAEL of 150 ppm was set based on increased liver weights and on centrilobular hypertrophy of hepatocytes diagnosed after 12 months in males receiving 700 ppm.[45]

  D4 administration by oral gavage to rats over 28 days does not cause any immune suppression at doses as high as 300 mg/kg/day. In another oral 28-day study in rats, 200-300 mg/kg/day dose of D4 (quantity not precisely determined) led to stress and reduced body weight gains.[45]

  Sprague Dawley rats were treated by gavage with 25, 100, 400, or 1600 mg/kg/day D4 five days per week for 14 days. Liver weights increased by more than 10% in males at 400 and 1600 mg/kg/day. In females, liver weights increased by 8, 17, 24, and 24 per cent at 25, 100, 400, and 1600 mg/kg/day, respectively. A NOAEL of 25 mg/kg/day is identified on the basis that liver weights at this dose are within 10% of control liver weights. At 1600 mg/kg/day terminal bodyweights in males and females reduced slightly to 83 and 89% of control weights, respectively. Histopathology was not assessed in this study.[47]

  Rabbits given 500 or 1000 mg/kg D4, seven days per week for 14 days consumed between 25 and 50 per cent of the amount of food consumed by controls, and terminal bodyweights were up to 20 per cent less than those of controls at both dose levels. A NOAEL for reduced food consumption was not identified from this study. Liver weights were not affected in rabbits given up to 1000 mg/kg/day D4 for 14 days. However, in the case of D4, reduced food consumption occurs in gavage studies and at high concentrations in inhalation studies,

where palatability issues do not apply. The reduced food consumption may therefore represent a pharmacological effect because of the dopamine-like effects of D4.[47]

No adverse effects in one three-week dermal exposure study in which male and female New Zealand white rabbits received doses of 0.1, 0.3, or 1 mL/kg undiluted D4 (equivalent to 96, 288, and 960 mg/kg), five days per week for three weeks. The lack of any adverse effects in dermal exposure studies is consistent with the minimal dermal penetration measured for D4. The NOAEL for the effects of repeated dermal exposure lies above 960 mg/kg/day, which is the highest dose administered in any study to date.[47]

- Reproductive/Developmental Toxicity: There is no evidence that D4 causes developmental toxicity in rats or rabbits or an adverse effect on male rat fertility. However, the following effects on female rat fertility were identified:[45]
    - An effect on fertility which occurs at ovulation apparently with reduced numbers of eggs ovulated as demonstrated by the 'phased' studies in female rats.
    - Decreases in number of corpora lutea, number of uterine implantation sites, total number of pups born, and mean live litter size were noted in the one-generation general reproduction and fertility studies at high exposures. Two multi-dose studies (0, 70, 300, 500 or 700 ppm) allow estimates of NOAELs. In one study, reductions in reproductive parameters were recorded only at 700 ppm, while in the other study, reduced implantation sites and viable fetuses and increased pre-implantation losses were noted at 500 and 700 ppm. In addition, reduced numbers of corpora lutea were found at 300 ppm. However, as the reduction in corpora lutea was marginal at 300 ppm (14.6/dam vs. 16.2/dam in controls) without a clear exposure-related response and within the range of values in the historical control database, (14.2/dam-20.5/dam), the NOAEL was considered to be 300 ppm.[45]
    - Similar reproductive changes were recorded in the two-generation study at 500 and 700 ppm, but, in addition increased estrous cycle length in F1 females at 700 ppm as well as increased pituitary gland weights were noted. Also in F1 females there were histopathological changes in ovaries and mammary glands at all exposure levels. These histopathological changes were:

        1) Minor, and not clearly treatment-related except at 700 ppm,

        2) Reported only in the F1 and not in the F0 generation,

        3) Similar in nature to those found in concurrent controls and,

        4) Considered to be probably a combination of D4's effect on the luteinizing hormone (LH) surge, as well as a manifestation of the spontaneous, age-related waning of the female reproductive system in the rat (i.e. F1 female Sprague Dawley rats were about 274 days of age at sacrifice).[45]

  Considering these points, it appears justified to set 300 ppm as the NOAEL. From the reproductive toxicology studies and taking the weight of evidence approach for reproduction parameters, the NOAEL was established as 300 ppm.[45]

  In an oral study in rabbits, animals were administered the test material a 0, 50, 100, 500, or 1000 mg/kg/day (Day 7 of gestation through to Day 19 of gestation). Clinical signs included mucoid stool at 500 and 1000 mg/kg/day, anogenital staining and hair loss at 1000 mg/kg/day, and tissue and/or red fluid on cage tray (often associated with abortion) at 500 and 1000 mg/kg/day. Body weight and food consumption reductions were recorded at all D4 dose levels. Treatment-related abortions were observed at 500 and 1000 mg/kg/day with markedly increased post implantation losses at 1000 mg/kg/day. This correlated with reductions in the number of live fetuses and gravid uterine weights at 1000 mg/kg/day. By Day 13 of gestation most rabbits at 500 or 1000 mg/kg/day were consuming less than 20 g/day or not eating at all. Therefore, it was considered likely that the increase in abortions and post implantation losses are the consequence of reduced food consumption and not a direct effect of D4.[45]

- Genotoxicity/Mutagenicity: D4 (in ethanol) was tested for mutagenicity in the reverse mutation assay on bacteria. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to the test substance at concentrations ranging from 100 µg/plate to 5000 µg/plate (with and without S9 mix). No

mutagenic activity was observed in any of the five strains tested, either by evidence of a dose-response relationship or a doubling of the mean number of colonies over the mean control level, either in the absence or presence of S9 activation. D4 is not mutagenic or genotoxic.[45]

- Carcinogenicity: In a six-month carcinogenicity study in rats, D4, administrated by inhalation at doses of 0, 10, 30, 150, and 700 ppm (air concentration of 0, 0.12, 0.36, 1.82, and 8.49 mg/L), was shown to induce uterine (endometrial) adenomas and hyperplasia at the highest dose level of 700 ppm. The NOAEL of the study was considered to be 150 ppm. The neoplasms observed in female rats after chronic exposure to 700 ppm D4 were considered related to a mode of action that is not relevant for humans because of pronounced differences in the endocrine regulation between rats and humans.[45]
- Irritation: D4 is reported as slightly irritating to the skin of rabbits.[45]
- Sensitization: D4 produced no skin hypersensitivity response when evaluated in Magnusson-Kligman maximization test on guinea pigs.[45]

A.3.2 Polyester

The reinforced silicone sheeting (Silicone SSF-METN-750), used to allow the non-absorbable sutures to anchor the device to the underlying tissue for the PM, RM, intramuscular stimulating and recording electrodes, also has a has a polyester reinforced fabric (SSF-FMR-1160) skirt.

A general toxicological profile for polyester is described below.

Polyethylene terephthalate (PET; Figure 7), also known as polyester, is a blend of synthetic fatty acid esters, ethoxylated alcohols, and long chain fatty acids. It can be formed by an esterification reaction of ethylene glycol with terephthalic acid, or through transesterification of ethylene glycol and dimethylterephthalate. Polymerization by either method is conducted under controlled conditions of heat and vacuum, with the aid of catalysts and stabilizers.[48]

Migration and degradation studies have been documented in the literature. PET can be highly crystalline and is highly hydrophobic, which prevents degradation via a hydrolytic mechanism. Knitted and woven PET fabrics have very good stability in the *in vivo* environment, exhibiting negligible deterioration even after implantation for durations greater than 10 years.[49]

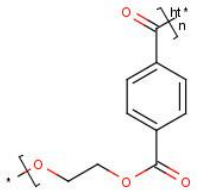


Figure 7. Structure of Polyester

PET is one of the standard biomaterials currently used for the manufacture of permanently implanted prosthetic vascular grafts. Its history of use in this application goes back to Ku in 1957 and DeBakey in 1958.[50] Other uses for PET yarns and fabrics include coverings of annuloplasty rings and sewing rings for heart valve assemblies, arterial graft repair of aneurysms, and carotid patch angioplasty.[51] Per US FDA 21 CFR 870.3470, cardiovascular prosthetic devices (i.e., intracardiac patch or pledget) can be manufactured from PET. An intracardiac patch or pledget is a fabric device placed in the heart that is used to repair septal defects, for patch grafting, to repair tissue, and to buttress sutures.[52]

The use of permanent PET implants in ACL reconstruction has been well documented. Tsuda and others secured a soft-tissue graft to the ACL using polyester tape (Acufex, Smith & Nephew) to study the motion of an ACL replacement graft within the femoral bone tunnel when secured with polyester tape.[53] The authors found the tape to be as good as use of the EndoButton fixation method. Polyester tape is also used for treating ruptured Achilles tendons which allows for earlier mobilization.[54]

Polyester fiber has been in use in a wide variety of approved implantable medical devices. It is a well-known biocompatible material.

The following toxicological information was located for PET:

- Irritation/Sensitization: Patch tests with humans resulted in no skin irritation.[55] Prolonged contact with PET is essentially non-irritating to skin. Human patch tests determined PET is not irritating or sensitizing.[56] Repeated contact may cause flaking and softening of skin. PET may cause slight temporary eye irritation; corneal injury is unlikely.[57]

- Acute Toxicity: In a 1-month study, rats received wine extracts obtained after several months contact with PET. The treatment produced no harmful effect on animals.

- Repeat Dose Toxicity: Rats were given 5.0 to 400 mg technical grade PET/kg-day and 5.0 to 100 mg pure PET/kg-day over a 3-month period. There were no changes in their behavior, body weight gain, biochemical indices of blood serum, urine, or hematology analyses, or in relative weights of internal organs.[58]

  A 13-week dietary study in Sprague-Dawley CD rats was performed on spunbond, non-woven fabric consisting of polyethylene and polyethylene terephthalate, which met the requirements of US FDA 21 CFR 177.1630 and 177.1520 for food contact applications. The test material was ground into a fine powder and orally administered at levels of 0.5, 2.5, and 5% of the basal diet. Feed consumption and body weights were recorded weekly. Cage-side clinical observations were performed daily. Detailed clinical observations, including activity levels and locomotion, skin and coat condition, eye and mucous membrane condition, and any altered behavior or other relevant observations were performed weekly. Hematology, coagulation, and clinical chemistry were performed on surviving animals prior to study termination. Complete necropsies were conducted and selected organs were weighed. Microscopic examination of selected tissues was conducted on the control and 5% dose group animals. No toxicologically relevant treatment-related effects were observed in any of endpoints evaluated at dietary concentrations up to 5% of milled fabric.[59] Based on the average food consumption over 13 weeks, the doses were determined to be 143, 714, and 1571 mg/kg-day for males and 100, 500, and 1071 mg/kg-day for females (using an average food consumption rate of 200 g/week (males) and 140 g/week (females) for the 0.5 and 2.5% doses, and 220 g/week (males) and 150 g/week (females) for the 5% dose).

- Genotoxicity: A *Salmonella* reverse mutation assay per OECD Guideline 471 was performed on the spunbond, non-woven fabric consisting of polyethylene and polyethylene terephthalate. The non-woven material was extracted in phosphate-buffered saline (PBS) and dimethyl sulfoxide (DMSO), and mutagenicity was determined in five different *Salmonella typhimurium* tester strains (TA98, TA100, TA102, TA1535, and TA1537) with and without exogenous S9 metabolic activation. No mutagenic response was observed at any dose level tested.[59]

  PET was tested as a source of mutagen contamination from bottles used for beverage packaging. PET bottles were filled with mineral water and stored in daylight and in the dark for different periods of time. The water samples were concentrated and the concentrates (non-volatile compounds) tested for mutagenicity with the Ames test (static tests). Total organic carbon (TOC) leaching was concurrently determined. Leaching of mutagens was also studied using dynamic tests (shaking distilled water in PET bottles). New methods were also used to test the leaching potential of both volatile and non-volatile compounds (directly testing the mutagenicity in unconcentrated water stored in PET bottles and growing *Salmonella* strains directly in the plastic bottles). The results were positive only for the static test, which identified leaching of mutagens after 1 month of storage in PET bottles. This activity was higher after storage in daylight.[58]

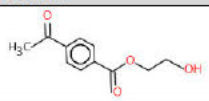
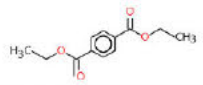
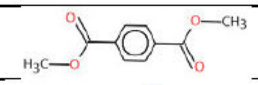
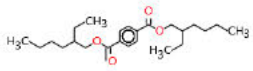
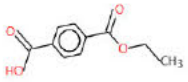
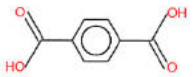
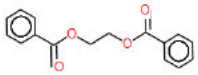
  In several tests of water stored in PET for up to 6 months, the water was not mutagenic to *Salmonella typhimurium* (strains TA98 and TA100) with or without metabolic activation except for one test where the water was mutagenic after storage for 1 month but not at 3 and 6 months.[52]

- Reproductive/Developmental Toxicity: Animal studies demonstrate no developmental or reproductive effects.[60] In addition, polyester and the terephthalate-related chemicals listed in Table 12 are not listed on California's Proposition 65 list.[61] Considering the use of PET in long term medical devices such as surgical sutures, meshes, and intravascular grafts and intracardiac patches, PET poses minimal risk of reproductive/developmental toxicity.

- Carcinogenicity: Subcutaneous administration of polyethylene terephthalate is not classifiable as to its carcinogenicity to humans (Group 3).[62] Considering the use of PET in long term medical devices such as surgical sutures, meshes, and intravascular grafts and intracardiac patches, it poses minimal risk of carcinogenicity. In addition, genotoxicity data on PET, as well as similar chemicals (i.e., monomers or surrogates) demonstrate negligible risk of genotoxicity (Table 12).

Genotoxicity and carcinogenicity data were gathered for pertinent polyester-related chemicals from the ECHA database (Table 12). When data were not available, Toxtree was used to determine the presence of structural alerts for these biological endpoints.[63] Considering the many uses of PET in medical devices and consumer goods, and the negative genotoxicity results for PET and related chemicals, the risk of carcinogenicity from PET is minimal.

Table 12. Genotoxicity and Carcinogenicity of PET-related Chemicals

Chemical Name	Structure	CAS No.	Genotoxicity	Carcinogenicity
Polyethylene terephthalate		25038-59-9	No alerts for Ames mutagenicity; one alert for *in vivo* micronucleus* [63]	No alerts for genotoxic and nongenotoxic[63]
Diethyl terephthalate		636-09-9	No alerts for Ames mutagenicity or *in vivo* micronucleus[63]	No alerts for genotoxic and nongenotoxic[63]
Dimethyl terephthalate (DMT)		120-61-6	Negative (*in vitro* and *in vivo*)[64]	Negative[64]
Di-2-ethylhexyl terephthalate		6422-86-2	Negative (*in vitro*)	Negative† [64]
1,4-Benzenedicarboxylic acid, monoethyl ester		713-57-5	No alerts for Ames mutagenicity or *in vivo* micronucleus[63]	No alerts for genotoxic and nongenotoxic[63]
Terephthalic acid (TPA)		100-21-0	Negative (*in vitro* [WOE] and *in vivo*‡) [64]	Negative (human prediction based on rat study) [64]
Ethylene dibenzoate		94-49-5	Negative (*in vitro* and *in vivo*)[64]	No alerts for genotoxic and nongenotoxic[63]
Ethylene glycol		107-21-1	Negative (*in vitro* and *in vivo*)[64]	Negative[65]

*H-acceptor-path3-H-acceptor.
†Despite having structural alert for non-genotoxic carcinogenicity.[63]
‡Despite having structural alert for H-acceptor-path 3-H-acceptor.[63]
WOE: Weight of evidence.

A.4 Polypropylene

Polypropylene suture, blue monofilament (3-0), is used as the non-absorbable tissue anchor for the intramuscular stimulating and recording electrodes.

A general summary for polypropylene is provided below:

Polypropylene or polypropene (PP) (Figure 8) is a thermoplastic polymer, extensively used in the manufacture of sterilizable medical devices because of its low cost, clarity, high modulus, and chemical resistance. Polypropylene, an addition polymer made from the monomer propylene, is rugged and unusually resistant to many chemical solvents, bases, and acids. Polypropylene has a melting point of approximately 165°C making it autoclavable. The chemical additives and degradation products of polypropylene have been thoroughly studied and reported in peer-reviewed publications.[66,67]

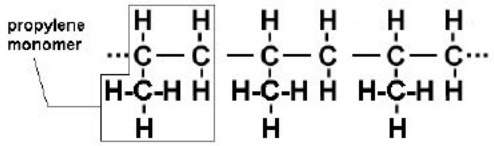


Figure 8. Chemical Structure of Polypropylene

The biological safety of polypropylene (PP) has been demonstrated in numerous studies and by years of safe medical

and pharmaceutical applications. It was introduced in the 1950s, and since then has become one of the most commonly employed polymers by the device industry.[68] PP has been used to manufacture syringes, vials, eye glasses, and containers for food and medicines.

Polypropylene has been used as a non-absorbable suture material for decades. Prolene® Sutures, manufactured by Ethicon (Somerville, NJ), have been on the market since 1969. Prolene® Sutures are indicated for use in general soft tissue approximating and/or ligation, including use in cardiovascular, ophthalmic, and neurological procedures. Prolene® Sutures, and other polypropylene sutures, have been used in internal applications, which can be considered implants, millions of times without any indications of bio-incompatibility.[69] Many other manufacturers have introduced polypropylene sutures into the market; a small sampling of these products is listed in Table 13.

Table 13. Sampling of Cleared Polypropylene Non-Absorbable Surgical Sutures

Suture	Manufacturer	510(k) Number
Modified USS Polypropylene Suture	United States Surgical	K050947
Trulene® Non-Absorbable Polypropylene Suture	Sutures India Pvt.	K041511
Polypropylene Non-Absorbable Surgical Suture	C.P. Medical	K001185
Polypropylene Non-Absorbable Surgical Suture	R.K. Medical	K961389
Quill™ Polypropylene Knotless Tissue Closure Device	Angiotech	K130078

Polypropylene has been used as a filament around the outside of arterial graft prostheses. In this study, the PP caused no foreign body response and the authors concluded that PP was considered to be the suture of choice in peripheral vascular graft surgery.[70]

Prolene® filaments have also been used to construct mesh materials for use in the repair of hernia or other facial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result. These devices include the Modified Prolene® polypropylene mesh nonabsorbable synthetic surgical mesh (K962530) and the Prolene® Soft (polypropylene) Mesh (K001122). Many other manufacturers have introduced polypropylene meshes into the market; a small sampling of these products is listed in Table 14.

Table 14. Sampling of Cleared Polypropylene Non-Absorbable Meshes

Mesh	Manufacturer	510(k) Number
Minimesh® Polypropylene Mesh	Mpathy Medical Devices	K041632
Caldera Large Pore Monofilament Polypropylene Mesh	Caldera Medical	K060004
Parietene™ Duo/Quadra Polypropylene Mesh	Covidien	K072951
Restorelle™ Polypropylene Mesh	Mpathy Medical Devices	K092207
Restorelle™ L	Coloplast A/S	K122440

The blue colorant was not provided, however would be embedded within the non-absorbable polypropylene material and unavailable to the patient systemically. If the recommended biological testing to be conducted exhibits favorable extractions (colorless, clear, no particulates), these data can be supportive and informative for a lack of colorant leaching. The recommended chemical characterization testing, can help mitigate for any colorant that may be detected, if detected at levels below that which may cause a toxic response. These data, if favorable, would indicate that patient risk is negligible. The identical polypropylene blue monofilament has been used in previous versions of the COSMIIC System for Investigational Device Exemption (IDE) G8890084, G900108, G950116, and G040214. The same material is also marketed and approved for use with the FreeHand System by Neurocontrol (P950035).

Per the FDA U.S. Food and Drug Administration, for a device categorized as an implant device with long-term contact (>30 days) with tissue/bone, the chemical name/CAS No., purity information (CFR color listing, raw material's Certificates of Analysis, or final device testing for impurities), and estimated/calculated maximum amount of the colorant (in weight) per device, should be disclosed.[71] No additional colorant information is needed if the colorant is less than or equal to a comparator device (with the same colorant, type and duration of tissue contact, same matrix material and intended use); or, colorant impurity amounts are less than the tolerable intake for the colorant detected.[71]

A.5 Stainless Steel

Stainless Steel 316LVM ASTM F138 is used as the tissue interface for the intramuscular stimulating and recording electrodes of the COSMIIC System.

Based on their chemical composition, stainless steels are divided into:[72]

- **Ferritic stainless steels**, mainly consisting of iron and chromium (10.5-20.0%)

- **Martensitic stainless steels**, mainly consisting of iron, chromium (10.5-18%) and carbon (0.2-1.0%)
- **Austenitic stainless steels**, mainly consisting of iron, chromium (16-28%), nickel (6-38%) and low carbon content (<0.08%)
- **Duplex stainless steels** (austenitic-ferritic stainless steels), mainly consisting of iron, chromium (18-30%), nickel (1.35-8%), molybdenum (0.1-4.5%), copper and nitrogen.

Common designations in the United States include the AISI (American Iron and Steel Institute) system, used in the United States. In the AISI system, austenitic grades are in the 200 and 300 series (representing the intramuscular stimulating and recording electrodes of the COSMIIC System); martensitic and ferritic grades are in the 400 series.

Stainless steels have remarkable mechanical properties, including hardness, wear resistance, tensile strength, elongation, fracture toughness, creep resistance.[73,74] But one of the most important properties of stainless steels is their resistance to corrosion, which is due to the presence of chromium. Of note, austenitic stainless steels exhibit superior corrosion resistance to both ferritic and martensitic stainless steels.[72] Moreover, the addition of nitrogen in duplex stainless steels further improves corrosion resistance.

These mechanical properties along with the high corrosion are the main reasons for the wide use of stainless steels in various industries.[73,73]

Recognized as biocompatible, stainless steels have been extensively used in the medical industry. They are the most commonly used materials for medical instruments, such as surgical instruments or spinal instruments.[73,74] Moreover, stainless steels, particularly stainless steel AISI 316L, are also commonly used in orthopedic, cardiovascular and dental implants, including joint replacements (hip and knee), shoulder prostheses, bone plates for fracture fixation, coronary stents, heart valves, dental implants for tooth fixation, dental root implants and orthodontic braces.[76,75] Of note, in developed countries, there is a shift towards nickel-free austenitic stainless steel or other metals, like unalloyed titanium, titanium alloys and chromium alloys, to replace stainless steel AISI 316L in medical implants.[72,76]

The most commonly used stainless steels for medical devices are austenitic and martensitic stainless steels. Indeed, the applications of ferritic stainless steels are limited to devices such as solid handles for guide pins, tools and clamps, while duplex stainless steels do not have a significant impact in the medical field. The austenitic stainless steels can be found in medical devices with lower corrosion resistance including cannula, dental impression trays, containers, hypodermic needles, steam sterilizers, storage cupboards and work surfaces or thoracic retractors. The martensitic stainless steels are widely used for dentistry and surgical devices. These stainless steels can be hardened and tempered by heat treatment. Thus, they are capable of developing a large series of mechanical properties like high hardness for cutting tools: scalpels, curettes, chisels, forceps, orthodontic pliers, retractors etc.[74]

A.6 Platinum Iridium

Platinum/Iridium 90/10 is the material of construction making up the tissue interface for the epimysial stimulating electrodes of the COSMIIC System.

Platinum, iridium, and other precious metals are routinely used in a variety of biomedical applications; the inert nature of platinum and iridium render the metals highly biocompatible.[77] These metals are typically added to the device in the form of a layer, coating, band, or powder depending on the intended use of the device. Platinum can be fabricated into very tiny components which do not corrode inside the body, even when in direct contact with the bloodstream. Wire electrodes manufactured with platinum/iridium (typically 90%/10%) are currently used in many implant procedures to provide muscular or neural stimulation from high amplitude electronic devices to assist mobilization of paraplegics, phrenic pacing, or cardiac function.[78] Pacemakers, used to treat heart disorders, which result in slow or irregular heartbeat, usually contain at least two platinum/iridium electrodes, through which pulses of electricity are transmitted to stabilize the heartbeat. Platinum electrodes are also found in pacemaker-like devices which are used to help people at risk of fatal arrhythmia. Pacemaker electrodes manufactured with titanium have also been used to deliver the electrical energy from the pacemaker to the heart. These electrodes may be coated with iridium oxide to prevent nonconductive layers from forming. Platinum marker bands and guide wires are also often incorporated into catheters which Interventional Cardiologists use to guide the device to a specific treatment site.

The biocompatibility of platinum/iridium wire has been well characterized over the last decade. One study examined the tissue reaction of platinum-iridium wire electrodes implanted in the cochlear nucleus of the guinea pig.[79] Histopathological examinations demonstrated a glial cell proliferation that never exceeded 15 microns in width,

confined to the area of the electrode. No neuronal loss or significant effect on cell morphology was observed, and reactive cells were absent. Another study in an adult human male used intramuscular platinum/iridium wire electrodes to contract the buttock muscles and improve hybrid locomotion of the legs. The permanently implanted system was reported at 7 months to be satisfactorily working. Dymond *et al*., implanted 90% platinum/10% iridium wire into cat brains and histopathologically evaluated the material effects after 2 months.[80] The tissue reactions were noted to be minimal, with the material ranked highly among several metallic materials.

Another study set out to determine the decomposition of various metal wires used as stimulator electrodes in saline.[81] This study has important consequences regarding carcinogenicity, since most of this type of activity is caused by corrosion of the metal and release of ions (e.g., nickel ions are suspected carcinogens, while nitinol is practically inert). They employed a 0.5 ms bidirectional wave with a frequency of 50 Hz delivered from a constant current stimulator. Platinum and iridium electrodes were submerged in saline, and current was passed for 24 hours/day for periods up to 9 months. The authors concluded that iridium and platinum (along with rhodium and palladium) were very resistant to corrosion.

Platinum/iridium alloys have been used in many FDA-approved medical device applications, a number of which are summarized in the table below.

Table 15. Examples of Devices Manufactured with Platinum/Iridium Alloys

Description of Device	Device Category	Manufacturer	Approval
VENTAK PRIZM AVT Automatic Implantable Cardiac Defibrillator (AICD) - specifies that Pt/Ir is in long term direct contact with blood or tissue	Implant	Guidant	P960040
Revo MRI Surescan IPG and Pacing System	Implant	Medtronic	P090013
St. Jude Frontier™ Biventricular Cardiac Pacing System	Implant	St. Jude Medical	P030035
Drug eluting permanent right ventricular or right atrial pacemaker electrodes	Implant	ELA Medical, S.A.	P020030
Endocardial pacing lead	Implant	ELA Medical, S.A.	K993448
ACUITY™ Steerable Lead Models 4554, 4555, and 4556 (drug eluting permanent left ventricular pacemaker electrode)	Implant	Guidant CRM	P050046
Freehand System® (upper extremity neuroprosthesis)	Implant	NeuroControl Corp.	P950035
Kurz Upper Eyelid Implant	Implant	Heinz Kurz GmbH	K011115
AZUR CX Peripheral Coil System (vascular embolization device)	Implant	MicroVention, Inc.	K151358

A.7 EPO-TEK 301

EPO-TEK® 301 is used as the header adhesive to the metal capsule and as a back-fill used to seal weld access points after assembly on the RM.

EPO-TEK 301 is a two-component, room temperature curing epoxy (65ºC / 2 hours), featuring very low viscosity, and excellent optical-mechanical properties.[82] It is transparent and suggested for medical devices such ultrasonic applications, flex circuit assembly, electrical contacts and acoustic matching, as well as biometric and biosensor applications.[83] Other common applications for EPO-TEK 301 include imaging systems, diagnostics, surgical tools, endoscopes, and implantable devices (cardiac defibrillators, pacemakers, ophthalmic and neurostimulators), and non-implantable devices (insulin pumps, cochlear, hearing aids, skeletal/spinal /ortho).[84] All EPO-TEK adhesives are medical device grade, and ISO 10993 tested for biocompatibility, passing ISO 10993-4, 5, 6, 10, 11.[84]

EPO-TEK 301 adhesive has been subjected to biocompatibility testing by the manufacturer.[85] The results of this testing are summarized in Table 16.

Table 16. Summary of Biocompatibility Testing Conducted on EPO-TEK 301 Epoxy Adhesive

Standard	Test	Results	Study Number
ISO 10993-5:2009	Cytotoxicity Study Using the ISO Elution Method	Non-cytotoxic	Toxikon 11-5535-G1
ISO 10993-10:2002	ISO Kligman Maximization Study	Non-sensitizer	Toxikon 12-1481-G1
ISO 10993-10 :2002	ISO Intracutaneous Reactivity Test	Non-irritant	Toxikon 12-1481-G2
ISO 10993-11:2006	ISO Systemic Toxicity Study	Non-toxic	Toxikon 12-1481-G3
ISO 10993-4:2002 ; ASTM F756-08	Hemolysis (ASTM)	Non-hemolytic	Toxikon 12-1481-G4
ISO 10993-6:2007	Muscle Implantation Test (2 week)	No local effects, Non-irritant	Toxikon 12-1481-G5

The successful completion of the tests listed above indicates that EPO-TEK 301 complies with USP class VI biocompatibility standards.[86] However, all adhesives are considered toxic prior to cure and complete cure is required to achieve Class VI certification status. Provided that the adhesives are properly cured per the manufacturer's instructions for use, no obvious risks are identified with the use of this biocompatible epoxy in the manufacture of the COSMIIC System.

Appendix B Risk Analysis of Manufacturing Processes

Alongside raw materials, another key parameter to consider when establishing the biocompatibility of a medical device is the manufacturing processes, which may introduce manufacturing residues. These residues, if present, could cause biological effects once the medical device comes into contact with the patient.

B.1 Manufacturing Flowchart

The manufacturing operation/steps are presented in Figure 9 below for the RM component and Figure 10 below for the RM. Related manufacturing agents used in the construction of the COSMIIC System are presented in Table 17.

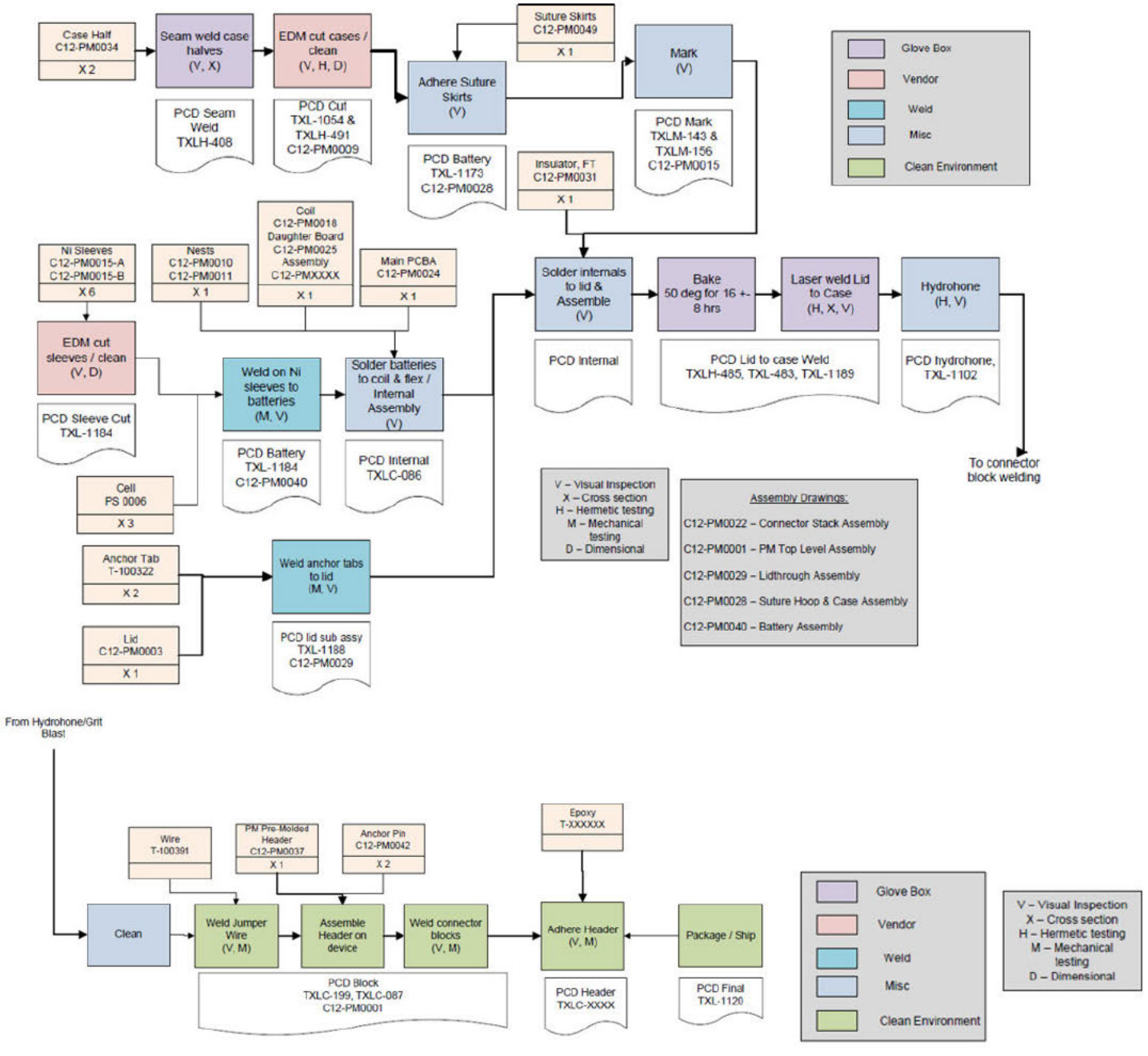


Figure 9. Process Flow Chart for COSMIIC System Power Module

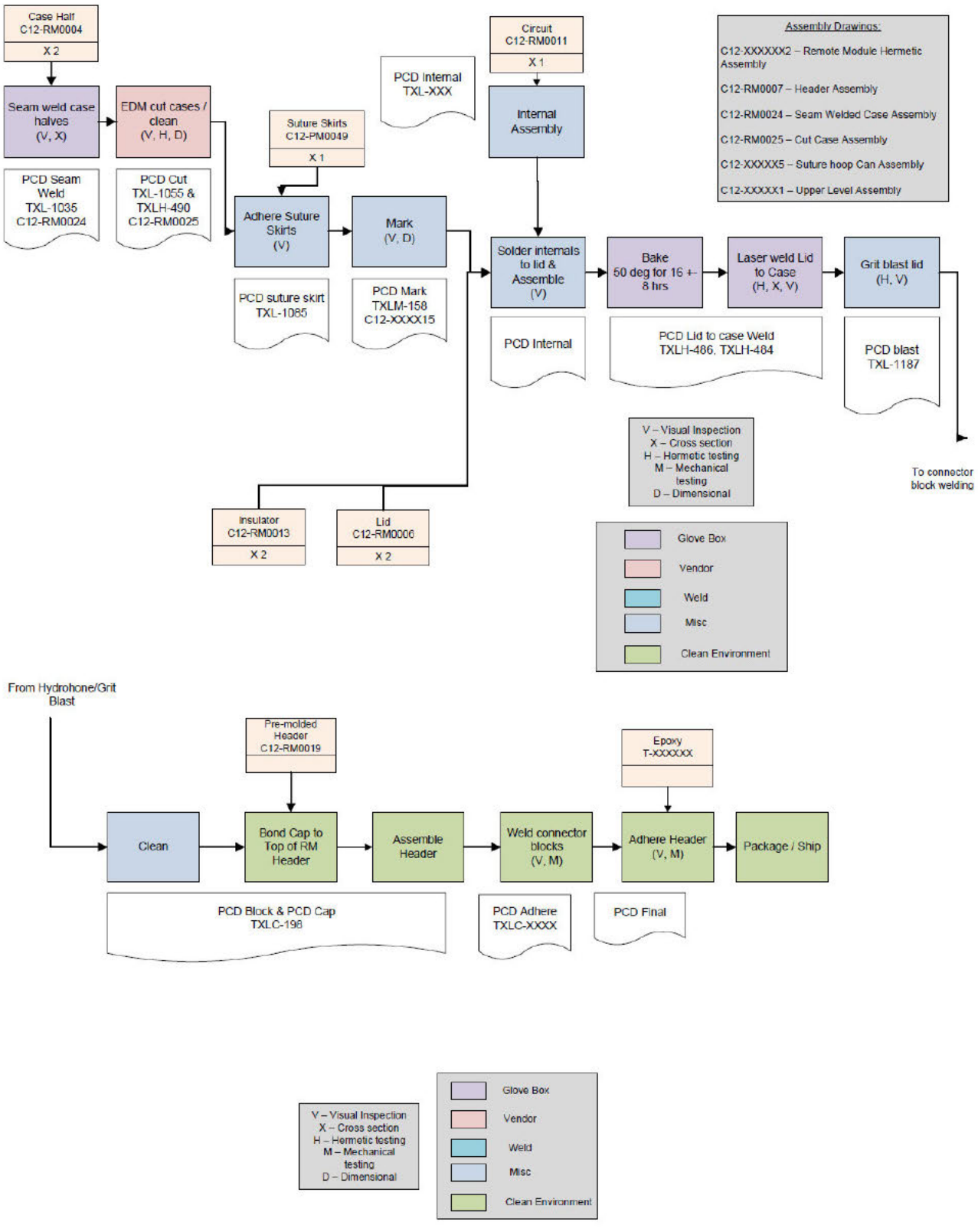


Figure 10. Flow Chart for COSMIIC System Remote Module

B.2 Evaluation of Manufacturing and Processing Agents including CMR and ED Properties

The manufacturing agents used in the construction of the COSMIIC System are presented in Table 17.

For each of the manufacturing/processing agents used in the manufacture of the COSMIIC System, the hazard code(s), inclusion (or not) as a Substance of Very High Concern (SVHC), carcinogenic, mutagenic or reproductive toxin (CMR), or whether the substance is an endocrine disruptor, are indicated in Table 17. The health hazard statement codes for the manufacturing agents were reviewed and also listed in Table 17 to identify potential hazards to the patient.

Table 17: Manufacturing/Processing Agents: CMR and ED Assessment

Manufacturing Agent	Chemical of Concern	CAS Number	Concentration	Health Hazard Statement Code§	CMR Category 1A or 1B¥	Human ED¥
PM and RM						
Cleaning agent	Isopropyl alcohol	67-63-0	--	H319, H336	No	No
Network Cables and Electrodes						
Cleaning agent	**Liquinox[87]**					
Cleaning agent	Sodium alkylbenzene sulfonate	68081-81-2 or 68411-30-3	10-25%	H303, H315, H318**	No	No
Cleaning agent	Sodium Xylenesulphonate	1300-72-7	2.5-10%	H319**	No	No
Cleaning agent	Alcohol ethoxylate	84133-50-6	2.5-10%	H315, H318**	No	No
Cleaning agent	Lauramine oxide	1643-20-5	1-2%	H315, H318**	No	No
At use dilution: 1% in water						
Cleaning agent	Sodium alkylbenzene sulfonate	68081-81-2 or 68411-30-3	0.1-0.25%	H319**	No	No
Cleaning agent	Deionized water*	7732-18-5	--	Not listed	No	No
Cleaning agent	Acetone*	67-64-1	--	H319, H336	No	No
Cleaning agent	Distilled water*	7732-18-5	--	Not listed	No	No
Cleaning agent	Isopropyl alcohol*	67-63-0	--	H319, H336	No	No
Connector Assembly						
Cleaning agent	Acetone*	67-64-1	--	H319, H336	No	No
Cleaning agent	Isopropyl alcohol*	67-63-0	--	H319, H336	No	No
Cleaning agent	2-propanol*	67-63-0	--	H319, H336	No	No
Release agent: 7th Generation[88]						
Diluent	Water	7732-18-5	30-100%	Not listed	No	No
Cleaning agent	Sodium lauryl sulfate	68585-47-7	10-30%	Not listed	No	No
Foam stabilizer	Glycerin	56-81-5	1-3%	Not listed	No	No
Cleaning agent	Lauramine oxide	70592-80-2	1-3%	Not listed	No	No
Cleaning agent	Decyl glucoside	68515-73-1 110615-47-9	≤1%	Not listed	No	No
Viscosity modifier	Magnesium chloride	7786-30-3 7791-18-6	≤1%	Not listed	No	No
pH adjuster	Citric acid	77-92-9	≤1%	H319, H335	No	No
Preservative	Benzisothiazolinone	2634-33-5	≤0.1%	H302, H315, H317, H318	No	No
Preservative	Methylisothiazolinone	2682-20-4	≤0.1%	H301, H311, H314, H317, H318, H330	No	No

Manufacturing Agent	Chemical of Concern	CAS Number	Concentration	Health Hazard Statement Code§	CMR Category 1A or 1B¥	Human ED¥
Packaging						
Tyvek	High density polyethylene fibers*	9002-88-4	--	Not listed	No	No

(§): Health hazard statement code either as reported in the Safety Data Sheets (SDS) provided by the manufacturer *or* in the European Regulation (EC) No. 1272/2008 (CLP Regulation) as amended:
(¥): Annex VI of CLP Regulation (substances with harmonized classification and labelling up until the 20th Adaptation to Technical Progress), as well as the Candidate List of Substances of Very High Concern (SVHC) for Authorisation and the Endocrine Disruptor (ED) assessment list, were searched using chemical CAS No. August 2024.
*CAS numbers not provided, so CAS number for general material evaluated.
**Hazard codes based off provided safety data sheet.

Applicable CLP Hazard Code Key:
H301: Toxic if swallowed.
H303: May be harmful if swallowed.
H302: Harmful if swallowed.
H311: Toxic in contact with skin.
H314: Causes severe skin burns and eye damage.
H315: Causes skin irritation.
H317: May cause an allergic skin reaction.
H318: Causes serious eye damage.
H319: Causes serious eye irritation.
H330: Fatal if inhaled.
H335: May cause respiratory irritation.
H336: May cause drowsiness or dizziness.

Based on information presented in Table 17, the processing agents used in the manufacture of the COSMIIC System are not classified as CMR substances or substances with endocrine-disrupting properties. Some processing agents are significantly hazardous if swallowed, inhaled; or severely hazardous if in contact with the skin or eye. Several are volatile agents, likely evaporated after application. However, these hazards are applicable to chemicals in their neat state, and represent a higher risk to workers exposed to these chemicals in the manufacturing environment, but not clinically relevant when the device is used as intended. See further discussion in Section 9.2.

13 CVs of Author/Reviewer

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