Date: February 20, 2024

To: Food and Drug Administration, Center for Devices and Radiological Health (WO66-G609)
ATTN: OHT 5/ DHT 5B Neuromodulation and Rehabilitation Devices

Q-Sub Type: Presubmission request for feedback on a proposed Master File

Method of Feedback: Written and meeting.

Meeting Information: See **Appendix A** for meeting request details.

Device Information:

Device Name: COSMIIC NNP System
Intended Use: The COSMIIC NNP System is an open-source, implantable neuromodulation system that is intended as a research platform for preclinical and Early Feasibility clinical evaluation.

Sponsor Contact Information:

Applicant:
Kevin Kilgore, Ph.D., Principal Investigator

Sponsoring Institution:
Case Western Reserve University
10900 Euclid Avenue
Cleveland OH 44106

Primary Point of Contact for Correspondence:
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Manufacturer Information

Case Western Reserve University
10900 Euclid Avenue
Cleveland OH 44106

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1. Executive Summary

In 2015, our investigator team received FDA approval to begin an Early Feasibility IDE (**G140225**) of the Case Western Reserve University **Networked Neuroprosthesis (NNP)** to restore trunk stability and upper extremity function in people with cervical spinal cord injury. In that application, the NNP was described as a "platform technology" with a modular design that would allow investigators to explore its capabilities for neural activation, myoelectric signal processing, and other functions. With funding from NIH/NINDS's HORNET program, we now have the opportunity to make the NNP more widely available to researchers who want to study neurotechnology applications in bench, animal, and Early Feasibility human studies.

With NIH's funding, we have created the Cleveland Open-Source Modular Implant Innovators Community (COSMIIC), which intends to make the NNP system available for research purposes through an **open-source model**. The open-source model will allow investigators to have access to components of the "COSMIIC NNP System" to use in bench, animal, and Early Feasibility human studies. In addition, Case Western Reserve University, as a member of the COSMIIC Investigator Community, will also make freely available all the documentation necessary to allow investigators to design new modules and components that can connect to the NNP platform, in order to explore new functionality of the overall system.

As part of the project, a benefit corporation is being established: **COSMIIC, Inc.** While the complete range of functions of this company are still being established, we will attempt to highlight its role throughout this presubmission.

The novel idea of an open-source technology raises new regulatory questions. First, as multiple investigator teams begin working with the COSMIIC NNP System, they will require basic information about its functionality and performance. We are proposing to file a Master File with the FDA that contains all the information in our Original IDE (G140225) and to offer a blanket right-of-reference to that Master File as part of the open-source documentation. Second, investigators exploring clinical applications of the COSMIIC NPP will need up-to-date information about risks, and they will likewise need to share their risk experience with the COSMIIC community. We are proposing a novel use of the MAUDE database to serve as the repository of device-related adverse events for COSMIIC NNP. Finally, as investigators develop new functionality for the COSMIIC NNP, the role of Manufacturer of Record needs to be clear to the FDA.

To recap some of the terminology used in this presubmission:

- **COSMIIC NNP System** – refers to the technology itself. In its current form, it consists of the identical components reviewed under G140225, which is a combination of both implanted components and external accessories. Over time, additional functionality and components may be added to the COSMIIC NNP System.
- **COSMIIC, Inc.** – refers to a benefit corporation that has been created to serve as the corporate entity involved in the overall project. Over time, it will take on roles and responsibilities heretofore performed by Case Western Reserve University, for example, serving as the **manufacturer of record** for the COSMIIC NNP System, and serving as the **holder of the eventual Master File**.
- **COSMIIC Investigator Community** – refers to a virtual community of investigators interested in having access to the COSMIIC NNP for their research, in order to develop new compatible modules and potentially evaluating those features in Early Feasibility IDE studies. The Investigator Community will utilize the open-source model to both obtain existing information and share new information created in the course of their research.

2. Purpose

The main purposes of this presubmission are: 1) to start the conversation with FDA about COSMIIC; 2) to identify unique regulatory issues we believe the COSMIIC project raises, along with proposed solutions; and 3) provide examples of how we see the investigator community using the COSMIIC technology and interacting with the FDA.

3. COSMIIC Project

The overall goal of the Cleveland Open-Source Modular Implant Innovators Community (COSMIIC) is to establish an open source, modular network of active implantable devices for use in Early Feasibility human research and to provide ongoing support for this technology through a vibrant, sustainable community of active users. Our concept is based on our established platform ecosystem, the Networked Neuroprosthesis (NNP), which provides a solid technological platform with known regulatory status. Critically, all technology involved in the COSMIIC project was invented by the Case Western Reserve University investigative team and therefore we are able to fully embrace the open-source ideology for the end-to-end technology.

The proposed COSMIIC System, which will be established on the platform NNP System, is a system of interoperable and integrated modules that can simultaneously electrically activate, block, and sense throughout the body. The system can record and process electroneurogram (ENG), electromyogram (EMG), intracortical signals, electrocardiogram (EKG), kinematic variables, photoplethysmogram (PPG), and temperature. Each module can directly communicate with all other modules through an established network communication protocol. The system can process signals to implement complex closed-loop control without requiring non-implanted hardware. Importantly, the existing NNP platform components (power module, stimulator module, biopotential recording module, network cable, electrodes) are already the subject of an approved IDE (**G140225**) and have been successfully implanted and implemented in human research participants.

3.1. What is Meant by Open-Source?

The CWRU team intends to establish the COSMIIC community with full open-source access to the COSMIIC NNP System, a modular implantable device for use in the peripheral and central nervous system. Access will be given for all circuit designs and layouts; mechanical drawings for all enclosures, connectors, and cabling; the annotated code for all operating software, firmware, and bootloader; written instructions and videos of fabrication techniques; and all regulatory documents and test data, including our approved IDE document, G140225. We also propose an extensive educational component to increase expertise in the design and use of active implantable devices for bioelectronic, neuromodulation, and neuroprosthetic applications.

The COSMIIC Open-Source License will use the "Creative Commons maximally-permissive" license ("CC BY 4.0"), which features the following attributes:

- Available for any purpose, including commercialization
- Available for modification; modifications can be protected and sold
- License attribution must accompany any use of any aspect of COSMIIC
- Open-Source licenses applies specifically to the hardware/software
- Open-Source licenses will generally reference specific patents
- Open Source does not apply to the clinical applications of the technology or to the derivatives of the technology to be used in clinical applications.

The general expectation is that the COSMIIC open-source system can be used as-is for early feasibility human study to establish concepts and to refine device requirements. However, pivotal studies will need to use a proprietary system designed specifically for the clinical requirements (which may or may not be based directly on the open-source system). For FDA's purposes, this means that investigators may file presubmissions and Early Feasibility IDE's requesting to use the COSMIIC NNP system either as-is or with modifications. However, it is not expected that pivotal clinical trials will be conducted, or that marketing applications will be filed for the COSMIIC NNP system.

4. How COSMIIC Intends to Serve the Needs of Investigators

4.1. What is the COSMIIC Community?

Many research institutions have the necessary expertise to run first-in-human clinical trials using implantable devices, but only by repurposing existing commercial devices off-label, greatly limiting the technological features available. The primary goal of this COSMIIC project is to enable the research field to not only have access to new implantable technology, but also, where possible, to establish the ability to **modify and innovate** around that implantable technology. In order to achieve this goal, it is absolutely necessary that the COSMIIC project is directly applicable to the needs of the bioelectronic research community. To achieve this, we have formed a growing community of experts in neural interface technologies and applications, many with NIH SPARC funding. A key feature of this team of investigators is the broad representation across the spectrum of bioelectric clinical applications, featuring expertise across multiple organ systems, the autonomic nervous system, with synergistic applications in the brain and motor systems.

As researchers get underway, we anticipate the following kinds of interactions among investigators, the Case Western Reserve University team, and COSMIIC, Inc.

- Introductory meetings to discuss scope of the proposed project;
- A discussion of whether and how the COSMIIC NNP System could fit into the proposed project;
- A guide to the open source documents;
- Recommended practices for interacting with the FDA on clinical applications (e.g., IDEs and presubmission); and
- Access to a right-of-reference Letter of Authorization for the proposed COSMIIC Master File.

Importantly, all investigators will be strongly encouraged to adhere to the following expectations:

- Utilize relevant COSMIIC NNP components
- Perform "test runs" of open-source documents
- Present the open-source concept at national meetings
- Submit grants utilizing COSMIIC NNP system
- Attend COSMIIC Community project meetings
- Share documents and data on the NIH SPARC Portal
- **Other expectations or requirements identified by FDA as part of this presubmission (see Question 5)**.

The long-term objective is widespread use of the COSMIIC NNP modules to develop new medical treatments for a wide range of applications. The investigators will:

1. **Ensure the widespread utility of modifications to the NNP system**. The COSMIIC Investigator Community will provide feedback on novel designs early in the design process to ensure that the device specifications and modes of operation will serve a wide community of users.
2. **Evaluate the documentation resources for completeness and safe ethical use**. The COSMIIC modules will be designed for use by research teams with strong engineering expertise, who must have a thorough understanding of the devices they will use. Members of this investigator community will evaluate design and regulatory documentation prior to distribution to the public and oversee website content.
3. **Support the community of early adopters who can serve as a resource for others**. Each investigator has a personal interest in using this technology for their own research. They will lay the groundwork for that use through grant applications and interactions with FDA. Each of the applications represented by this initial group of investigators has a larger community of scientists who may benefit from using these devices.

4.2. Types of COSMIIC Investigators

For the purpose of our discussion, we acknowledge **two types of investigators** who could be interested in conducting research on the COSMIIC NNP. The **first type of investigator** is one who wants access to the identical NNP system components described in our IDE. If these investigators only wish to study the NNP in bench or animal research, there are no anticipated FDA interactions. If these investigators wish to explore *clinical* applications of the as-is COSMIIC NNP, the COSMIIC project encourages them to engage with the FDA by filing a presubmission

and targeting the Early Feasibility IDE program. To reduce the regulatory burden on these investigators, we propose to develop a Master File that contains all the documentation filed for G140225 and provide a blanket right-of-reference letter to investigators to that Master File (**see Section 5.1**). The expectation is that by referencing the "COSMIIC Master File", their burden of preclinical bench testing would be significantly reduced.

The **second type of investigator** is one who wishes to develop *new* modules that integrate with the COSMIIC NNP platform configuration. Again, if these investigators wish to study these modules in bench or animal research only, there are no anticipated FDA filings. However, if they want to explore clinical applications of these new modules, they would be required to file an IDE with the FDA, with a right-of-reference to G140225 serving as the bridge comparing the new technology to the original. Additional testing of components to validate performance would be expected, along with system testing to demonstrate compatibility with the COSMIIC NNP. However, for unchanged components, preclinical testing could be leveraged from the COSMIIC Master File.

4.3. Q232285 as an example of a COSMIIC investigator presubmission

An example of a COSMIIC investigator is Dr. Nathan Makowski, with his recent presubmission to study the NNP system in people with incomplete SCI to improve community ambulation (Q232285). The presubmission relied heavily on being able to reference the NNP IDE, G140225. It contained a comparison of the proposed NNP configuration for incomplete SCI compared to the original IDE; a description of the clinical use case; a Risk Analysis; a rationale for the pre-clinical test plan; and a proposed clinical trial design. We can use this presubmission as a preview of the likely regulatory challenges for other COSMIIC investigators. *NOTE: The following comments about Q232285 are not intended to influence the direction of that presubmission or reflect the investigator's response to it. Rather, we are citing this as illustrative of the types of FDA concerns that could be anticipated in future COSMIIC presubmissions*.

Through Q232285, we have the following observations about FDA's acceptance of the basic COSMIIC model:

1. The FDA appeared to accept broadly the reference to G140225 as an established baseline technology for comparison. For future COSMIIC investigators, it would be our intention to **provide a blanket right-of-reference to the COSMIIC Master File containing the entire G140225/Original submission (see Section 5.1.).**
2. The FDA requested that the Risk Analysis be updated to include a summary or discussion of the safety of the NNP system under G140225, including relevant adverse event data. **We believe this will be a common request of COSMIIC investigators going forward, and propose using the MAUDE database as the repository for device-related adverse events (see Section 5.2).**
3. The FDA identified specific tests that were conducted under G140225 that have been supplanted by later requirements. Specifically, FDA acknowledged that G140225 cited the IEC 60601-1 series for electrical safety, but stated that ISO 14708-1 and -3 are more appropriate, and acknowledged that this standard has become an FDA-recognized standard since the prior IDE approval for G140225. **We believe it will be common for the FDA to recognize new standards over time, and that the original test reports under G140225 may become outdated.**
    a. In Q232285, FDA appeared open to Dr. Makowski providing either additional testing or a rationale for why no new testing would be necessary, stating, "…we recommend that your future EFS-IDE application include further electrical safety testing and/or rationale, as necessary to demonstrate that essential electrical safety requirements…have been addressed." To facilitate future COSMIIC investigators, we are proposing to allow updates to the COSMIIC Master File to incorporate both new test reports and examples of successful rationales that can be referenced by other investigators. **We have a question about how best to amend a Master File with new information (e.g., test reports and rationales) over time (see Question 2).**

5. Regulatory Strategy for COSMIIC

At its core, COSMIIC represents an investigational technology that is targeted to investigators exploring bench, animal, and Early-Feasibility human research studies. To facilitate COSMIIC investigators through the EFS-IDE regulatory requirements, we propose several concepts: 1) COSMIIC investigators will be offered access to an FDA Master File that they can leverage to reduce their burden of preclinical testing; 2) we propose using the MAUDE database to collate risk information about the COSMIIC NNP that is viewable by FDA, searched, and added to by different investigators; and 3) we propose guidelines for investigators in identifying their EFS-IDE as being part of the COSMIIC community. Each of these is described in more detail below.

5.1. The COSMIIC NNP Master File

The COSMIIC NNP Master File would contain the complete contents of G140225 Original application (**see Appendix A** for the Table of Contents of the Master File). Over time, COSMIIC Inc. may amend the Master File to include updated device descriptions to account for new components being developed, their accompanying test reports and rationales, and other documentation from investigators' EFS-IDEs. The amended information would be identical to information FDA would have reviewed under those EFS-IDEs. The main purpose of the Master File is to give FDA access to *collated* information related to the COSMIIC project in one location. The Master File will be a subset of the publicly available, open-source information provided through the COSMIIC website and community portal. We have a question about the adequacy of this approach (**see Question 1**).

5.2. Maintaining an Updated Risk Profile Using the MAUDE Database

FDA raised a specific concern in Dr. Makowski's presubmission that would require him to have access to adverse event information from G140225. While we can provide that information to Dr. Makowski, having to continuously provide updates to investigators on the changing landscape of adverse events could pose challenges, particularly as new investigators identify new events. One thought was to make EFS-IDE annual reports part of the open documentation expectation for COSMIIC investigators. However, there are several downsides to this approach. First, this raises concerns about investigators' ability to appropriate de-identify cases for the public, compared to sharing with the FDA where confidentiality is assured. Second, since IDE reports are only submitted annually, it will be difficult to see the changing landscape of adverse events as they happen. Third, IDE annual reports also include medical but non-device related reports. What is needed is a way for investigators to submit de-identified information about device-related adverse events in a consistent way that is viewable and searchable by other investigators.

We propose encouraging COSMIIC investigators to submit their adverse events through MAUDE so that these events become available to both the larger community and the FDA. It would be the responsibility of new investigators to submit individual reports of device-related adverse events to the MAUDE database, and also to search the MAUDE database in order to collate and summarize known device-related events as part of their Risk Analysis. We have a question to FDA whether it is possible to use MAUDE for an *investigational device* in this way, and whether this could satisfy FDA's expectations for the COSMIIC community to stay on top of new risk information (**see Question 3**). Note that the use of the MAUDE database is not proposed as a substitute for having each investigator also file an annual report to their EFS-IDE.

5.3. Other Regulatory Guidelines for the COSMIIC Investigator Community

The lead COSMIIC team from Case Western Reserve University will share information on best practices to interact with the FDA, and in general one purpose of the COSMIIC Investigator Community is to share regulatory experiences so that the entire community can learn from real case examples. Some specific recommendations are listed below; we have included a question about the adequacy of this approach (see **Question 4**):

1. **Clear identification of the EFS-IDE as being derived from the COSMIIC NNP System.** Investigators will be encouraged to identify whether their EFS-IDE references the COSMIIC NNP System, and to use the blanket right-of-reference document, which will feature standard language.

2. **Clear identification of the Manufacturer of Record for new system components**. For investigators that are working with the current COSMIIC NNP system, the Manufacturer of Record will be listed as COSMIIC, Inc. However, if an investigator wishes to develop a *new* module that works with the COSMIIC NNP platform configuration, they are responsible for managing the design control, risk analysis, and V&V activities, and overseeing manufacturing of that module. If these investigators want to explore clinical applications of these new modules, they would be required to file an EFS-IDE with the FDA, and clearly describe their manufacturing processes and oversight activities. As members of the COSMIIC Community, they will be encouraged to make their documentation part of the open-source marketplace. Following a process of review by the COSMIIC Community, these new documents will be filed by COSMIIC, Inc., as amendments to the Master File.
3. **Clear guidelines for how to approach establishing biocompatibility for new modules**. Recall that our original IDE included some biocompatibility testing as well as rationales for similarity of some components to those used in earlier IDEs. As a baseline, we wish to provide more comprehensive information about the current NNP biocompatibility in support of the COSMIIC NNP System that can be leveraged by members of the COSMIIC Investigator Community. We appreciate that FDA's requirements around biocompatibility have changed since we filed the IDE in 2014. **Please see Question 6**.

6. Anticipated Regulatory Filings

Following FDA feedback on this presubmission a Master File, consisting of the entire contents of the original filing for G140225, will be submitted by COSMIIC, Inc.

7. Questions for the FDA

QUESTION 1.
Through COSMIIC Inc., we propose to file a Master File containing the contents of the original filing for G140225 for use by investigators. Furthermore, we intend to provide a blanket right-of-reference to investigators wishing to cite the Master File in the EFS-IDE applications. Does FDA have any concerns about this approach? Are there other content elements that should be included in either the Master File or the right-of-reference letter to facilitate FDA's review?

QUESTION 2.
Through COSMIIC, Inc., the Master File will be amended with new information about the COSMIIC NNP System as it becomes available, including descriptions of new NNP-compatible components, the results of preclinical testing for new components, preclinical rationales, and accompanying risk analyses. We have questions about how the Master File program works. If the Master File is amended with new information and an investigator then makes reference to it, would FDA's questions be directed to the Master File holder, or to the investigator? If amendments to the Master File are *identical* to material reviewed under an EFS-IDE, and the EFS-IDE is reviewed and approved, does that change FDA's view of the material? We appreciate that these reflect generic questions; we are interested in learning more about how the Master File system can be used as a repository for FDA-reviewed information about the COSMIIC NNP System.

QUESTION 3.
In Section 5.2, we propose using the MAUDE database as a way of collating device-related adverse events across multiple investigators and multiple use-cases for the COSMIIC NNP System. We would appreciate FDA's guidance on the feasibility of this approach. Since the COSMIIC NNP will be an *investigational* device, is it even possible to include it in the MAUDE database?

QUESTION 4.
In Section 5.3, we identify other regulatory considerations we believe would be important to address in terms of guiding the COSMIIC community in their regulatory applications. Does FDA have any concerns about these items? Are there any other high-level regulatory issues that should be considered?

QUESTION 5.
In Section 4.1, we describe expectations that will be strongly encouraged of the members of the COSMIIC Investigator Community. Are there other specific requirements (apart from the standard regulatory requirements for filing IDEs and presubmission) that FDA would like investigators to follow? Given that some of the COSMIIC Community's educational materials will relate to regulatory filings and best practices, does the FDA see a role for the Agency as an informal member of the COSMIIC Community?

QUESTION 6.
We intend to provide more comprehensive information about NNP biocompatibility in support of the COSMIIC NNP System that can be leveraged by members of the COSMIIC Investigator Community. We understand that FDA's requirements around biocompatibility have changed since we filed the IDE in 2014. However, since 2014, we also have had many years of experience with the NNP system safely implanted in our study participants. Is there a method by which human experience can satisfy the requirements of the "implantation test", particularly considering our experience with revision surgeries, in which components were removed and evaluated, and in which re-implantation offered an assessment of the *in vivo* site?

8. Appendices

Appendix A. Meeting Information
Appendix B. COSMIIC NNP Master File Table of Contents
Appendix C. Right-of-Reference Letter Template

Appendix A. Meeting Information

Draft Agenda

Topic	Approximate Time
Introductions and opening remarks	5 minutes
Overview of COSMIIC Project	10 minutes
Review of FDA feedback and requests for clarification	40 minutes
Wrap-up and next steps	5 minutes

Meeting Format

We request a 1-hour Zoom meeting with the ability to do screen sharing.

Preferred Dates and Times

We have flexibility as to the date and time. The following are offered as placeholders:

- April 30, 2024, 9am-12pm ET, or 2-4pm ET
- May 2, 2024, 9-11am ET
- May 3, 2024, 9:30am – 12:00pm ET

Meeting Attendees

Name	**Title / Role on Project**	**Institutional Affiliation(s)**
Kevin Kilgore, PhD	Principal Investigator	Case Western Reserve University
Brian Smith, BSc (Hons)	Co-Investigator	Case Western Reserve University
Cindy Chestek, PhD	Co-Investigator	University of Michigan
Jim Coburn	CEO	COSMIIC, Inc.
Megan Moynahan, MS	Executive Director, Institute for Functional Restoration Regulatory point of contact for COSMIIC.	Case Western Reserve University

Requested FDA Attendees

We request attendance by an FDA member who can represent the MAUDE database.

Appendix C
Blanket Right-of-Reference Letter – Proposed Language

NOTE: The following contents are based on FDA recommendations, "Device Master Files" https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/device-master-files, accessed 2/19/2024.

[COSMIIC letterhead, including name, address, telephone number]

[Date]

To Whom it May Concern:

This letter authorizes the Food and Drug Administration to include by reference information in the COSMIIC, Inc., device master file, MAF xxxxxx for the IDE, G140225, for the COSMIIC Networked Neuroprosthesis (NNP) System in any Investigational Device Exemption (IDE) or presubmission submitted by any investigator.

Investigators using this blanket right-of-reference letter are strongly encouraged to:

1. Interact with COSMIIC, Inc., and the COSMIIC Investigator Community to develop modifications to the COSMIIC NNP System;
2. Share their documents and data on the NIH SPARC Portal; and
3. Work with COSMIIC, Inc., to enable new device descriptions and test reports to be formally added to this Master File.

[COSMIIC, Inc., signature block]