Q240410
Case Western Reserve University
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Re: Written Feedback for COSMIIC NNP System

This document is being communicated via e-mail as an attachment. The date on which the Food and Drug Administration (FDA) sent this e-mail is the official date of this correspondence.

This document contains the FDA's written feedback to your Pre-Submission request. This feedback represents our best advice based on the information provided in the Pre-Submission and other information currently known. While our review of your Pre-Submission does not imply that your future submission will necessarily be approved or cleared, FDA intends that this feedback will not change, provided that the information submitted in a future IDE or marketing application is consistent with that provided in this current Pre-Submission and that the data in the future submission do not raise any important new issues materially affecting safety or effectiveness.

If you requested a meeting and this feedback satisfies your needs, you may cancel our upcoming meeting by contacting the lead reviewer. If you still wish to meet, please provide us with your agenda of items and any slides you wish to present no later than two business days prior to the scheduled meeting date per the Pre-Submission Guidance https://www.fda.gov/media/114034/download. If that agenda or presentation contains significant new information, FDA may not be prepared to discuss it. As a reminder, you are expected to submit draft meeting minutes as an amendment to this pre-submission within 15 days of the meeting.

Our feedback to your pre-submission questions is provided below.

Sponsor Question 1 - Master File + Blanket Right-of-Reference Approach

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?

Official FDA Response

1. Your current Pre-Submission proposed to make information about your investigational Networked NeuroProsthesis (NNP) System available for reference in FDA submissions by the broader scientific community through the use of FDA's Master File (MAF) Program, while simultaneously sharing this information publicly with your Cleveland Open Source Modular Implant Innovators Community (COSMIIC). While this proposed use of the MAF Program as an administrative mechanism to reference "open-source" information is unconventional and contrary to the original intended use of this program

to maintain the confidentiality of proprietary device design and testing information (as described on FDA's "Device Master Files" web page, https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/device-master-files), we agree that the Master File Program can also be used as you have proposed, to streamline the submission and review of NNP device-specific information across multiple Investigational Device Exemptions (IDEs). However, we would like to stipulate the following limiting considerations:

a. Your proposed issuance of a "blanket" Right of Reference (RoR) letter that would give unconditional authorization for any future investigators to leverage the Master File contents in their own IDE submissions does not ensure COSMIIC Inc.'s visibility or ability to monitor the intended uses or modifications to your COSMIIC NNP system by future IDE sponsors. While FDA maintains the ultimate authority and responsibility to determine whether the proposed investigational uses and/or modifications of the NNP system in future IDEs are appropriate and justified by adequate supporting evidence, we recognize that your knowledge and experience as developers and investigators of the NNP system give you additional insight into potential safety or use issues with your system that may or may not be obvious to future FDA review teams. Therefore, to help ensure that the COSMIIC NNP system is used and modified in a safe and appropriate manner, it is important that COSMIIC Inc. maintain visibility over which investigators are using the NNP Master File, and in what ways.

   Furthermore, because it remains the ultimate responsibility of IDE (or premarket) sponsors to furnish adequate documentation to meet all regulatory requirements for their submission type and intended use, and because the Master File is reviewed only in the context of their IDE (or premarket) submissions that reference the MAF, it is important that IDE sponsors be made aware of any updates to the MAF (including those stemming from separate IDEs) that may affect the safety or effective use of the COSMIIC NNP in their investigations. To this end, we believe it is important for COSMIIC to maintain traceability of which investigators are using the NNP Master File and in what ways, and to notify all IDE sponsors of any relevant changes or updates to the MAF – as well as any new information about the NNP's safety or performance – that affect the design or manufacturing of the NNP system or its safe and effective use in their clinical investigations.

   For the above reasons, we recommend that the right to reference the COSMIIC NNP Master File in future IDE (or premarket) submissions be granted not by a "blanket" (unconditional) RoR letter, but by individual RoR Letters to each individual IDE sponsor or investigator who references the MAF. To promote adoption of the NNP system by the scientific community, you may include a statement (or sample letter) on your COSMIIC website indicating your general intent to allow use of the NNP System and Master File within an acceptable range of investigational uses, provided it is sufficiently clear that final permission to do so requires a RoR letter from COSMIIC Inc.

b. FDA will not share the contents of a Master File with the applicant(s) who are referencing its contents, as such sharing is not part of FDA's role under MAF Program policy (per the Device MAF Website). Thus, we remind you that any information to which IDE sponsors may need direct access should be provided to them by another means, such as via the COSMIIC website. Likewise, to enable effective use of the MAF in IDE submissions, future IDE sponsors will need to know the scope of the MAF's contents and the location of relevant contents (e.g. detailed device description,

biocompatibility testing, electromagnetic compatibility testing (EMC)) within the Master File. Accordingly, we recommend that you provide a detailed outline of the MAF's contents (such as the Table of Contents in Appendix B) through the COSMIIC forum, along with the detailed contents of the MAF as may be needed by the IDE sponsors.

c. With further regard to the appropriate use of the MAF, your intended use statement for the COSMIIC NNP System specifies that it is intended to be used for preclinical or Early Feasibility clinical studies. On this point, please note that FDA does not have any *a priori* requirement that Master Files be limited to the use of certain application types. Therefore, we foresee that the referencing of your MAF may eventually be of interest to sponsors pursuing later-stage (e.g. pivotal) clinical trials or premarket authorization. While such use of the MAF would be acceptable from a regulatory perspective, the regulatory requirements and necessary levels of supporting evidence will vary by application type (e.g. Early Feasibility Study vs. pivotal trial vs. premarket application). Therefore, we recommend that you consider whether your MAF may eventually be made available for use in later-stage IDE and premarket submissions. If so, to ensure the effective and appropriate use of the MAF to support later-stage clinical trials and premarket submissions, we recommend that you specify to the COSMIIC community the terms under which such use of the MAF is acceptable, and what additional information (including preclinical and clinical testing data) will be needed to support such submissions.

Sponsor Question 2 – Updates to Master File

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. **[For example:]**

- ***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.

Official FDA Response

2. In the event that the Master File is amended with new information and an IDE investigator then references the updated MAF in a subsequent IDE submission or supplement, questions may be directed either to you (the MAF holder), to the IDE sponsor, or to both, depending on the scope of the questions. Typically, questions related to the amendment (e.g. device modification) itself or the supporting information (e.g. lab bench or biocompatibility testing) would be directed to Master File holder, while questions concerning in the intended use of the device in the investigational study would be directed to the investigator. However, if the Master File contains no confidential or proprietary information that you wish to protect, then we can direct our questions to whomever you authorize, as appropriate based on the nature of the questions

relative to the scope of your and the investigator's respective expertise. Therefore, if you have any preferences with regard to the routing of questions during interactive review, we recommend that you specify these preferences both in the Master File and in your Right of Reference letters. For example, we recommend explicitly stating in both places (e.g.) that all information in the Master File can be shared with any sponsor that has a Right of Reference letter and that questions may be directed to those sponsors in addition to or instead of the master file holder, as applicable.

If the MAF holder (COSMIIC Inc.) wants questions directed to the IDE sponsors instead of the MAF holder, these questions, discussion, and responses will all be part of the IDE review documentation and actions, and will not be part of the Master File. Additionally, if the MAF is intended to be used to support multiple IDE applications, there may be some benefit to having the MAF holder submit a MAFamendment responding to all questions that would apply broadly to all IDEs that would be referencing it (as applicable). Otherwise, these same questions would likely need to be answered by each sponsor who references the master file, since there may not permissions to reference between IDEs.

With regard to your second question concerning the scenario in which amendments to the Master File are identical to material reviewed under an EFS-IDE, which is then reviewed and approved, the approval of the IDE would not change our view of the Master File material. It may, however, streamline our review of this material when the MAF is referenced in the future. Note, however, that Master Files are *only* ever reviewed in the context of an IDE (or premarket) submission that references the MAF, and that no action is taken on amendments to the MAF itself in the absensce of a referencing submission. Accordingly, amendments to the MAF would not automatically grant approval for IDE sponsors who have previously referenced the MAF to make use of the amended information – e.g. if the amendment were to consist of updates to the device design. To the contrary, IDE sponsors who wish to make use of updated information in the MAF would need to file an IDE supplement that encompasses the relevant changes.

Sponsor Question 3 - Use of MAUDE Database for Adverse Event Reporting

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?

Official FDA Response

3. Your submission proposes to use FDA's Manufacturer and User Facility Device Experience (MAUDE) database to report and track device-related adverse events across multiple IDE investigations and multiple use-cases for the COSMIIC NNP System. However, we have determined that the MAUDE database is not fit for this purpose because (as you have alluded in your question) the NNP System is an investigational device without market authorization – and thus, without a product code, which is required information for MAUDE entries. Moreover, FDA does not have any existing public database that tracks adverse events across multiple IDEs using the same investigational device in the manner that you propose. Accordingly, if COSMIIC wishes to aggregate and publicly share adverse event data across multiple IDEs that use the NNP System, we encourage you to aggregate and share such information through your own COSMIIC platform (website).

In any event, we remind you that all IDE investigators who use the COSMIIC NNP system will remain subject to all standard adverse event reporting requirements in accordance with 21 CFR 812.150.

Sponsor Question 4 – Additional Regulatory Guidelines

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* [including expectations for IDE investigators to clearly identify their use of the COSMIIC NNP System in their IDE submissions and to specify the manufacturer of record, plus biocompatibility considerations for new components]. *Does FDA have any concerns about these items? Are there any other high-level regulatory issues that should be considered?

Official FDA Response

After review of your additional proposed regulatory guidelines for the COSMIIC community in Section 5.3 of your submission, we agree that clear identification of the use of the COSMIIC NNP system (including specific reference to the Master File number) as well as detailed manufacturing information will both be essential to the review of future IDEs that reference your Master File. Accordingly, we recommend that you include these expectations as required conditions of use of the MAF and state these conditions both in the MAF itself and the Right of Reference letters to IDE investigators. Furthermore, we note that irrespective of the manufacturer of record (whether COSMIIC, Inc. or otherwise), *any* changes in device materials or manufacturing processes (including the use of additives, surface treatments, cleaning agents, mold release agents, etc.) relative to the device information in the Master File should be clearly identified in all original IDE submissions that reference the MAF. Likewise, any and all such changes in manufacturing to the NNP System (investigational device) following original IDE approval must be reported to FDA in an IDE supplement, pursuant to 21 CFR 812.35. Finally, we recommend that you remind all COSMIIC investigators that per FDA's 2013 Guidance on Early Feasibility Studies (full text at https://www.fda.gov/media/81784/download), investigational devices with approved IDEs, while exempt from the complete good manufacturing practice (GMP) requirements of 21 CFR Part 820, remain subject to the Design Control requirements specified in 21 CFR 820.30.

With regard to biocompatibility information, please see our response to your Question 6, below.

In addition to the above considerations, we also remind you and the COSMIIC community (including manufacturers) that pursuant to 21 CFR 812.20(b)(8), the NNP System and any component(s) thereof may not be sold in a manner that constitutes commercialization of the device.

Sponsor Question 5 – Specific Requirements for COSMIIC IDE Investigators

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?

Official FDA Response

Your proposed list of expectations for COSMIIC investigators (i.e. those who reference the COSMIIC NNP Master File in their IDE submissions) in Section 4.1 of your submission appears appropriate and aligned with the COSMIIC project's objectives. In addition to these expectations, we recommend the following additional guidelines for COSMIIC investigators:

- As noted above in our response to Question 1, we recommend that all COSMIIC investigators obtain a specific Right of Reference letter from COSMIIC Inc. to support their use of the Master File in FDA submissions.
- To maximize the safety and effectiveness of the COSMIIC NNP and all future investigational systems derived there-from, we recommend that COSMIIC investigators be encouraged to authorize the addition of any updates or modifications to the NNP System architecture and supporting information provided for IDE approval (e.g. including lab bench performance testing, electrical safety and EMC testing, and biocompatibility testing) to the Master File upon IDE approval. (Note: the formal amendment of the MAF remains the sole responsibility of the MAF holder.)
- As noted above in our response to your Question 3, apart from whatever adverse event reporting guidelines you may wish to establish amongst your community, we recommend that your remind all investigators who use the COSMIIC NNP System that they will remain subject to all adverse event reporting requirements pursuant to 21 CFR 812.150.
- In response to your question about FDA's potential role as an informal member of the COSMIIC community, we support the stated aims of your project and will be happy to continue providing feedback to you and other COSMIIC investigators through the Q-Submission Program. With regard to direct participation in the COSMIIC community, we are open to learning more about what such participation would entail and considering whether such participation would be appropriate within the bounds of our existing policies and programs governing our external stakeholder engagement.

Sponsor Question 6 - Biocompatibility

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?

Official FDA Response

In general, per Section III.C.2 of FDA's 2023 Biocompatibility Guidance (full text at https://www.fda.gov/media/142959/download), clinical data is generally not sufficiently sensitive to identify biocompatibility concerns. This limitation arises because clinical history of use information is typically not collected in a manner or as part of a study designed to evaluate biocompatibility endpoints with adequate sensitivity and specificity. Although adverse event data from clinical studies are informative, this data may be of limited utility from a biocompatibility perspective if specific biocompatibility assessments are not included in the monitoring plan or if such assessment is not technically possible in human subjects. Additionally, any definitive determinations about the biocompatibility-related adverse events can be

challenging due the presence of many confounding variables, such as the patients's clinical status, co-mobidities, and concomittant medications.

Based on the information provided in your current pre-submission, it is unclear what "human experience" data you intend to provide regarding the NNP's biocompatibility in your future Master File. This information is needed for FDA to evaluate the adequacy of the data to support the biocompatibility of the NNP System for future EFS IDE submissions. Therefore, to assess the adequacy of supplemental clinical data to further support the biocompatibility of the NNP System, we recommend that you specify in greater detail what additional information you propose to add to the Master File that was not included in the referenced IDE G140225. To thoroughly evaluate local tissue responses after implantation for biocompatibility purposes, we recommend that you consult ISO 10993-6, which describes test methods for implantation in clinically relevant sites and evaluation at short-term and long-term timepoints using macroscopic and histopathological evaluation with comparison to an appropriate negative control.

Typically, histopathology and information on tissue-device interactions is not available from human data; however, you have indicated that your human data may include an assessment of the in vivo site during re-implantation in revision surgeries. This data may be informative; however, it is unclear what types of assessments were conducted, how local tissue responses to the device would be distinguished from the surgical procedures (e.g., removal, re-implantation), and/or if other confounding factors may interfere with interpretation of the results (e.g., cause of the revision).

For the reasons identified above, previous human clinical experience alone is difficult to use to address local tissue responses upon implantation; however, information on clinical observations, imaging or other tissue evaluation, and adverse event data may be helpful to support biocompatibility for an Early Feasibility Study if other device-related information is available (e.g., materials and manufacturing information, use in U.S. marketed devices with similar tissue-contact, animal safety study data). An adequate implantation assessment is important because exposure to the device (if it includes even a small amount of chemical toxicant or has physical characteristics that might contribute to an unwanted tissue response) can lead to inflammation, scar tissue formation, pain, or other medical complications. Therefore, if you intend to leverage clinical data to support the biocompatibility of the NNP System (and any future variants), we recommend that you and/or future IDE investigators provide the following information, as applicable to your investigational device:

a. Confirmation that the device used in the G140225 clinical study is identical to the final finished device proposed for the EFS IDE with regards to materials, formulation, suppliers, processing, packaging, sterilization (including dose and duration), geometry, and no other chemicals (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents, etc.) have been added (per Attachment F of the FDA's 2023 Biocompatibility Guidance). If there are any differences in the aforementioned attributes between the proposed finished, sterilized device and the device used in the clinical studies, please describe each difference and provide appropriate rationale for why it will not affect the biocompatibility of the device.
b. Per Section III.B of FDA's 2023 Biocompatibility Guidance, the local tissue response to an implant depends not only on the chemical leachables and manufacturing residuals but also on the physical properties (e.g., geometry and surface properties) of the device. Therefore, please provide surface characterization (e.g., 40X scanning electron microscopy or optical microscopy) of the device and rationale for why the surface properties are not expected to result in adverse local tissue responses.

c. A complete description of all clinical study and/or post-market adverse events.

d. Detailed information on the clinical study procedures, including information related to monitoring and reporting of adverse events.

e. Detailed information on the clinical study procedures related to revision surgeries, including the timepoint when revision surgery was conducted, and evaluation of the device-tissue interactions and in vivo site if this data is being leveraged.

f. Justification for the number of patients from whom you intend to leverage data.

g. Rationale for why the procedure(s), treatment, medication, and/or medical conditions do not confound interpretation of the data.

h. Per Clause 5.1.1 of ISO 10993-6 "Biological evaluation of medical devices—Part 6: Tests for local effects after implantation", the test sample shall be implanted into the tissues most relevant to the intended clinical use of the device and justification for the implantation site shall be documented. If leveraging clinical data to assess local tissue responses, please provide information on the implantation site(s) and rationale for why the implantation data is relevant to the proposed indications for use for the EFS IDE.

Although our review focused on addressing the questions you asked, in the course of reviewing your pre-submission, we also noted the following. This is not intended to be an exhaustive list of issues.

Additional Biocompatibility Considerations

1. For a list of information that should be included in device Master Files to support biocompatibility evaluations in future IDE and premarket submissions, we recommend that you refer to Attachment B of FDA's 2023 Biocompatibility Guidance (full text at https://www.fda.gov/media/142959/download). Although your approach for the use of a master file is unique, the recommended list of information in Attachment B ("Device Master Files for Biocompatibility Evaluations") may nevertheless be helpful as you consider what biocompatibility-related information to include in your Master File.

2. Section 5.3 of your submission states that you intend to provide clear guidelines for how to establish biocompatibility for new modules and notes that your original IDE (G140225) included some biocompatibility testing as well as rationales, including reference to previous IDEs and master file data. However, your proposed Right of Reference letter language in Appendix C only authorizes reference to G140225, but not to the preceding IDEs and Master Files that were referenced therein. Therefore, if you intend to leverage information from prior IDEs and/or other MAFs that was not directly contained in your IDE submission no. G140225, then to uphold the confidentiality of the information contained in those prior IDEs and MAFs, we recommend that your future right of reference documentation include RoR letters from the original IDE and/or MAF holders, as applicable. If COSMIIC investigators need to leverage information in the original MAFs about the raw materials or supporting data to support biocompatibility, they will need to provide adequate RoR from the original master file holder for use of any proprietary data from the original Master File.

3. To leverage previous biocompatibility data, future IDE investigators should specify whether the device proposed for their EFS IDE is identical to the device used in the testing. We recommend sponsors provide a statement per Attachment F of the FDA's 2023 Biocompatibility Guidance confirming the device is identical in important attributes:

"The test article is identical to the medical device in its final finished form in formulation, processing, sterilization, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents)."

Future investigators may provide a statement confirming the EFS IDE device is being used as received from the manufacturer (with no additional downstream manufacturing/processing/sterilization) as well as a statement from the manufacturer confirming the device is identical (example statement per Attachment F of FDA's 2023 Biocompatibility Guidance) to support leveraging previous data.

If there are any differences in the device proposed for the future EFS and the test article used in the previous biocompatibility testing, FDA will request a detailed description of any differences in the aforementioned attributes and rationale for why these changes will not impact biocompatibility. In order for future sponsors to provide an adequate comparison of their device and the test article used in the biocompatibility testing, we recommend you consider providing a detailed description of the test article used for the biocompatibility testing, including but not limited to information on the device design/geometry specifications, materials of construction (e.g., formulation, product name, supplier), manufacturing and processing (e.g., manufacturing steps, process parameters, manufacturing materials), and sterilization (dose, parameters). If the device is manufactured by one or more different manufacturer than the original investigational device for which biocompatibility data was previously provided, additional information may be needed to demonstrate that the differences will not impact biocompatibility, such as information on the equipment in contact with the tissue-contacting components, environmental conditions, water sources, etc. Your justification should address the impact of the difference(s) on each of the recommended biocompatibility endpoints (per Attachment A of the FDA's 2023 Biocompatibility Guidance) for your device.

4. It appears there is potential for there to be increased number of devices and/or increased size in devices of the NNP that would result in increased material and extractables and leachables in a future IDE submission. Per Clause 4.8.3 of ISO 10993-11, for systemic toxicity the dose should be based on clinical relevance and the dose shall be specified and justified. FDA recommends systemic toxicity evaluation using the worst-case dose per clinical use, with consideration of the maximum volume of device, maximum number of devices (e.g., number of levels), as well as a safety factor. Similarly, ISO 10993-17 recommends toxicological risk assessment of the worst-case estimated exposure dose (Clause 3.32). Accordingly, we recommend that you clearly describe and justify the worst-case clinical use supported by your biocompatibility evaluation.

5. It appears there is potential for future IDE sponsors to implant components of the NNP system into different tissues and/or for different durations than in G140225. As recommended biocompatibility endpoints are based on the type and duration of tissue contact (per Attachment A of the FDA's 2023 Biocompatibility Guidance), differences in the type and duration of tissue contact may require additional biocompatibility evaluation. We therefore recommend that you clearly describe the nature of tissue contact and duration of the NNP tissue-contacting components for G140225 and that any future IDE sponsor also provide a detailed description of the tissue contact to confirm the nature of tissue contact is the same and no additional biocompatibility evaluation is needed.

This notification is being sent in lieu of a formal written letter. If you have any questions, please contact Zach B McKinney, PhD at 301-796-4328 or Zachary.McKinney@fda.hhs.gov.