June 3, 2019

Bakul Patel
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U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback (FDA-2019-N-1185)

Submitted electronically

Mr. Patel,

Biocom appreciates the opportunity to offer comments on the Food and Drug Administration (FDA) discussion paper *Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)* ("AI framework").

Biocom is the largest, most experienced leader and advocate for California's life science sector, which includes biotechnology, pharmaceutical, medical device, genomics and diagnostics companies of all sizes, as well as research universities and institutes, clinical research organizations, investors and service providers. With more than 1,200 members dedicated to improving health and quality of life, Biocom drives public policy initiatives to positively influence the state's life science community in the research, development, and delivery of innovative products. California's life sciences industry generates nearly $317 billion in annual economic output, boosts the state's total gross product by $171.4 billion, supports more than 1.1 million jobs, and increases labor income by $92 billion per year[1].

Biocom applauds the agency's efforts to develop a framework for regulating artificial intelligence (AI) products used in medicine that continually adapt based on new data. AI and machine-learning (ML)-based technologies have great potential to improve patient care by making quality healthcare affordable and more accessible to everyone. The discussion paper demonstrates careful forethought about the field of AI in medicine and acknowledges the challenges with regulating a continuously learning device.

[1] *Biocom 2017 Economic Impact Report Databook*. 2017, issuu.com/biocom0/docs/biocom-2017-economic-impact-report-_9995632bde2e0c?e=30611789/53618285.

FDA's AI Framework defines AI and ML as "techniques used to design and train software algorithms to learn from and act on data." A key challenge for the FDA is how to apply the agency's traditional framework for assessing changes and modifications to devices to AI/ML technologies. The framework proposes to use the International Medical Device Regulators Forum ("IMDRF") risk categorization principles, FDA's benefit-risk framework, risk management principles in FDA's software modification guidance[2], and builds on FDA's Software Pre-Certification (Pre-Cert) Program's[3] organizational-based total product lifecycle regulatory (TPLC) approach.

Biocom respectfully offers the comments and recommendations below.

Discussion Questions

Types of AI/ML-based Software as a Medical Device (SaMD) Modification

1. *Do these categories of AI/ML-SaMD modifications align with the modifications that would typically be encountered in software development that could require premarket submission?*

   Biocom agrees that the categories of AI/ML-SaMD modifications generally align with the modifications that would typically be encountered in software development that could require premarket submissions. However, there is some overlap. For example, if a modification is made related to inputs, it most likely will result in a change to the underlying ML-algorithms architecture. New inputs require additional neural network input layer nodes.

2. *What additional categories, if any, of AI/ML-SaMD modifications should be considered in this proposed approach?*

   Biocom suggests that the FDA consider modifications related to outputs with or without change to the intended use, for example, the ML algorithm could be modified to provide additional information for the same set of inputs/architecture.

3. *Would the proposed framework for addressing modifications and modification types assist the development AI/ML software?*

   Biocom agrees that the proposed framework for addressing modifications and modification types assist the development AI/ML software. It provides a framework on how to classify the changes being made to the SaMD and thereby helps in assessing the type of risk. Biocom requests that the FDA develop clear and easily-understood resources for its framework and clarify this guidance's relationship to existing guidance documents and the Software Precertification Program.

Quality Systems and Good Machine Learning Practices (GMLP)

4. What additional considerations exist for GMLP?

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[2] Deciding When to Submit a 510(k) for a Change to an Existing Device https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device

[3] Digital Health Software Precertification (Pre-Cert) Program https://www.fda.gov/medical-devices/digital-health/digital-health-software-precertification-pre-cert-program

Biocom requests clarity on the following: does the FDA include scenarios where a medical device cognitive network (CN) update its own ML architecture? If so, how does FDA foresee monitoring real world performance when each implanted device of the same model could possibly be operating very differently (because it is being trained on data from different patients)? Does the FDA foresee enforcing additional monitoring to ensure the ML algorithm is 'behaving' correctly when it's deployed live in the body? This process should be aligned with overall software development, verification and validation process.

5. *How can FDA support development of GMLP?*

Biocom recommends that FDA provide clarification on how a manufacturer should apply existing design controls and lifecycle management principles (which are general and intended to apply to all devices) to AI/ML SaMD. In addition, FDA should communicate through guidance any expectations for premarket review. Biocom encourages FDA to develop detailed examples to support the development of GLMP. For example, disclosing the best software practices that the FDA has seen in submissions involving readily available and standardized algorithms would be helpful.

6. *How do manufacturers and software developers incorporate GMLP in their organization?*

AI practitioners are knowledgeable of good mathematical methods, for example, splitting test/training data sets, ensuring training on data that represents the same distribution function of the target population, and making sure that there is enough training examples used based on the complexity of the ML architecture. These methods need to be formalized and match companies' need to demonstrate that these methods were followed.

Initial Premarket Assurance of Safety and Effectiveness

7. *What are the appropriate elements for the SaMD Pre-Specifications (SPS)?*

An important element to SPS would be user requirement/needs. The manufacturer would need to specify which parts of the architecture can change. Also, the manufacturer would specify what optimization function is being used to provide better performance.

Additional SPS elements could include:

- Initial risk classification and expected new or modified risks as the algorithm learns.
- Initial intended use claim and anticipated changes to intended use.
- Algorithmic boundaries for which the SaMD remains the same device because it maintains the same safety and efficacy. To address the safety element, the boundaries of the device should be those for which risk management indicates that the SaMD maintains the same safety profile (and same indication for use) as the original device. For efficacy, the boundaries are those for which the SaMD continues to have the same function: the output continues to provide the same type of information.

8. *What are the appropriate elements for the Algorithm Change Protocol (ACP) to support the SPS?*

   Biocom recommends that the FDA consider the following elements for the ACP: change identification, evaluation, risk assessment, execution plan, qualification plan and documentation. Additionally, we think it is important to specify how the manufacturer intends to avoid adverse events during the implementation of ACP and what mechanisms in the device design are being deployed to ensure the adaptive algorithm is not harmful.

9. *What potential formats do you suggest for appropriately describing a SPS and an ACP in the premarket review submission or application?*

Approach for modifications after initial review with an established SPS and ACP

10. *How should FDA handle changes outside of the "agreed upon SPS and ACP"?*

    Biocom recommends that changes made outside of the agreed upon SPS and ACP should go through a new approval process because the manufacturer deviated from their initial stated design intent.

11. *What additional mechanisms could achieve a "focused review" of an SPS and ACP?*

12. *What content should be included in a "focused review"?*

    A focused review should include: modifications; data to support the changes; risk documentation; data demonstrating that the device still performs within the same safety limits for an old data set; known anomalies; and labeling updates.

Transparency and real-work performance monitoring of AI/ML-based SaMD

13. *In what ways can a manufacturer demonstrate transparency about AI/ML-SaMD algorithm updates, performance improvements, or labeling changes, to name a few?*

    To demonstrate transparency, Biocom recommends that manufacturers provide the following: provide results of regression tests; show how the algorithm performs on large public datasets; provide statistics about the data used to retrain the models, for example, how many examples were used for each age group/disease condition etc.; provide example of cases where they did not have adequate data for training.

14. *What role can real-world evidence play in supporting transparency for AI/ML-SaMD?*

    Training data needs to be logged and reported to a repository for review. Most of these ML algorithms are not about code (i.e. if-then-else). These algorithms work on static architectures and it's the data that modifies the algorithm. Therefore, some mechanism needs to be incorporated to be able to log the data that is causing the underlying ML algorithm to change in the real word.

15. *What additional mechanisms exist for real-world performance monitoring of AI/ML-SaMD?*

16. *What additional mechanisms might be needed for real-world performance monitoring of AI/ML-SaMD?*

    As mentioned above, an ability to log data from the device for further evaluation later.

Proposed Content for Algorithm Change Protocol

17. Are there additional components for inclusion in the ACP that should be specified?

18. What additional level of detail would you add for the described components of an ACP?

Biocom believes that this list is fairly comprehensive.

Other Considerations

Biocom recommends that the agency provide clarity on how the AI Framework would apply to AI/ML-based software associated with a drug or biologic. There is no mention of this in the framework and the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) did not join the discussion draft. CDER and CBER published a framework for prescription drug-use-related software[4] in December 2018, which takes a different approach to digital health as compared to the policies of the Center for Devices and Radiological Health (CDRH). Differences between the centers' approaches for AI/ML-based software could lead to similar software being subject to different regulatory requirements depending on which Center has the lead role in regulating the product.

Biocom is dedicated to improving patient access to innovative therapies and thanks you again for the opportunity to provide these comments. We commend you for your leadership and commitment to developing this important regulatory framework, and look forward to a continued dialogue with CDRH. If you have any questions about these comments, please contact Brittany Blocker, Manager of Regulatory Affairs at bblocker@biocom.org.

Sincerely,

Joe Panetta
President and CEO
Biocom

[4] Prescription Drug-Use-Related Software https://www.federalregister.gov/documents/2018/11/20/2018-25206/prescription-drug-use-related-software-establishment-of-a-public-docket-request-for-comments