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December 6, 2023

Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane, Room 1061, (HFA-305)
Rockville, MD 20852-1740

RE: Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions; Draft Guidance for Industry and Food and Drug Administration Staff

File code: FDA-2023-D-3133, Via Docket Submission

Dear FDA Review Team:

The Digital Medicine Society (DiMe) is a global non-profit dedicated to advancing the ethical, effective, equitable, and safe use of digital technologies to redefine healthcare and improve lives. DiMe appreciates the opportunity to respond to the Food and Drug Administration's (FDA) *Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions* draft guidance.

FDA developed this guidance to improve the predictability, consistency, and transparency of the 510(k) premarket review process. While the four scenarios presented in the guidance provide greater insight into the FDA's approach to 510(k) evidence determinations, this draft guidance does not fully satisfy product manufacturers' need for transparency and predictability. DiMe's comment primarily focuses on the additional resources that manufacturers need to efficiently bring new digital health technologies (DHTs) to market through the 510(k) pathway.

DiMe encourages the FDA to achieve full transparency, consistency, and predictability by pairing the methodology presented in this draft guidance with open access to 510(k) case-specific clinical evidence determinations. Industry stakeholder access to a repository of real-world Center for Devices and Radiological Health (CDRH) decisions will provide complete transparency into FDA's 510(k) clinical evidence determination process. This level of predictability and consistency will ultimately benefit timely and continued patient access to safe, effective, and high-quality medical devices by removing unnecessary regulatory barriers, lowering evidence generation uncertainty, and reducing product time to market.

Manufacturers Require Proactive Transparency
Q-submission (Q-sub) and pre-submission (pre-sub) programs provide manufacturers with the opportunity to collaborate with CDRH review teams in advance of a formal

submission to identify optimal methods to demonstrate products' safety and effectiveness.

DiMe appreciates the FDA's openness and willingness to engage with manufacturers prior to product submissions. Manufacturers, however, need greater transparency about the specific elements they will be required to complete as part of the 510(k) submission process, such as clinical evidence requirements, before individualized meetings with the FDA.

Given the significant time, financial, and clinical resources that go into conducting clinical studies for regulatory and downstream decision-makers, it is important for manufacturers to clearly understand what will be required of them prior to embarking on the 510(k) submission process. Manufacturers also face high opportunity costs if regulatory clinical evidence requirements are added onto baseline requirements once the 510(k) process starts, thereby reducing their ability to conduct studies for downstream decision-makers efficiently and on time.

Manufacturers applying through the 510(k) program will therefore continue to face low levels of regulatory predictability if they cannot determine the specific application requirements that are necessary to demonstrate Substantial Equivalence (SE) to a predicate device based on publicly available guidances and resources. Manufacturers, downstream decision-makers, and patients will greatly benefit from access to routinely captured data that is made available from the FDA and other agencies to industry decision-making and evidence-generation.

Impact of Case-by-Case Determinations

While pre-sub meetings aim to apply a consistent methodology to SE determinations, they introduce the ability for review teams to make product-specific case-by-case determinations. The *Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions* draft guidance, for example, presents a large number of variables for manufacturers to navigate in determining when clinical evidence requirements may be necessary to demonstrate SE. Manufacturers therefore currently rely on pre-sub meetings to determine how the methodology in this and other guidances will be applied to their product on a case-by-case basis.

DiMe is concerned that greater case-by-case determinations could:

- Discriminate against small businesses that do not have the same level of upfront resources (i.e., financial, legal, regulatory strategy) by benefiting larger, well-resourced companies.
- Create greater business risk for companies until the agency provides greater transparency on how case-by-case determinations are consistently made.
- Drive innovations into the wellness space if they cannot tolerate current regulatory risk (i.e., unpredictable evidence requirements that could impact submission timelines).
- Divert company resources from downstream evidence generation requirements toward 510(k) submission regulatory evidence requirements.

- Limit transferability of clinical data outcomes generated for regulatory purposes to downstream payers or for usability across other regulatory jurisdictions.

To reach greater efficiency and scalability in the regulatory review process, particularly as the DHT ecosystem continues to expand, DiMe supports reducing manufacturer reliance on case-by-case determinations. It is critical for the FDA to provide industry stakeholders with resources to independently understand and predict which elements they need to demonstrate SE to a predicate device.

Ongoing Variability Enabled
This draft guidance provides three previously discussed scenarios for which clinical evidence may be required to demonstrate SE to a predicate device: 1. Differences in the indications for use; 2. Differences in the technological characteristics; and 3. SE cannot be determined by nonclinical testing. Even though these three scenarios are already addressed in the 510(k) Program Guidance, Section IV.F, "Requests for Performance Data," manufacturers continue to face uncertainty in how these principles will be applied to their specific product(s) despite the additional examples provided in this draft guidance.

Specifically acknowledged in the draft guidance, "the applicability of these scenarios *may be determined based upon current knowledge, understanding, evidence, and experience available for the new device*. Following the least burdensome provisions, the need for clinical data *may also change as information on the device type is accrued*. FDA acknowledges that there may be situations *where one or more of these scenarios exist, but clinical data may not be needed* depending on the specific circumstances surrounding the particular new device." (emphasis added)

Based on this draft guidance alone, manufacturers cannot definitively determine whether they will be required to develop additional clinical evidence – nor the level or type of evidence – necessary to demonstrate SE. This guidance should be supplemented with real-world case-specific 510(k) clinical evidence determinations that manufacturers can use as precedent for future product submissions.

Increased Burden on Manufacturers
This draft guidance introduces a new fourth scenario in which product manufacturers are responsible for producing clinical evidence to demonstrate SE if their chosen predicate device has "a newly identified or increased risk."

Since predicate device makers do not provide external companies with access to their products or subsequent safety data, manufacturers are unable to independently determine when a predicate may have a newly identified or increased risk. The point at which new risks in a predicate device require manufacturers to take action with their own device is also impossible to determine independently. While public bulletins may be a helpful tool, they typically focus on products with long-standing or firmly established risks, as opposed to products with new or increased risks.

Without direct access to predicate products or relevant safety and outcomes data, manufacturers will:

- Be unaware of the types and quantity of adverse events (AEs) that a predicate device or candidate predicate devices accrue over a certain period of time.
- Require additional insights on what level, severity, or frequency of AEs trigger additional clinical research requirements.
- Need to understand at what point into their regulatory submission and review process additional clinical evidence may still be required (i.e., final dossier under formal review when additional risks for a predicate are identified by the FDA).
- Bear financial implications of conducting additional studies and opportunity cost of potentially delaying market access if additional clinical evidence requirements are added following conclusion of clinical studies.

In August 2023, DiMe published the Digital Health Industry Regulatory Needs Assessment, which identified ten opportunities for the FDA to advance regulatory science and policy to support the product, portfolio, and organizational goals of the digital health industry. Industry experts ranked these opportunities in order of urgency, impact, and relevance to advancing the field of digital health, identifying the top industry needs as FDA alignment with downstream payer decision-makers.

One of the proposed approaches to address this is the categorization and availability of routinely captured data from the FDA and other agencies to support staff education, industry decision-making, and evidence-generation.

Unless manufacturers have access to predicate safety data and clear guidance on when to act, manufacturers will not be able to consistently achieve the scenarios in this draft guidance independently. The only possible way to derive this information will be through increased engagement with the agency, which will become increasingly inefficient and unscalable as the DHT ecosystem grows.

FDA Determination Repository

When consistent and predictable requirements exist, DHT manufacturers welcome the opportunity to demonstrate product outcomes, impact, and SE to predicate devices. While draft guidances such as *Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions*, provide more insight on the FDA's methodology and approach, it does not go far enough to enable full consistency and predictability.

To enable true transparency, the FDA should provide industry stakeholders – including manufacturers, investors, purchasers, clinicians, and end users – with open access to a repository of real-world CDRH 510(k) case-specific clinical evidence determination decisions. Recommended resource elements could include:

- Product class, intended use, and description
- Target predicate device

- Whether clinical evidence was submitted as part of the 510(k) process
- The level and type of clinical evidence that was required
- Whether data from non-US jurisdictions was accepted as part of the clinical evidence dossier

With access to this type of resource, manufacturers can better independently understand the specific reasons of why and when additional clinical evidence data is required in the 510(k) process to demonstrate SE. Case-specific determinations will serve as precedent for future 510(k) device applications, demonstrating how the FDA consistently applies this methodology to product reviews.

Over time, this repository will reduce manufacturers' reliance on individualized pre-submission meetings and case-by-case determinations. This will lead to less regulatory uncertainty. Increased transparency will directly improve the predictability, consistency, and viability of the 510(k) process.

Supporting Work and Resources
In January 2024, DiMe will launch a project to improve coordination and alignment with downstream payer decision-makers, which ranked as the top industry need in the Digital Health Industry Regulatory Needs Assessment report. This Integrated Evidence Plans (IEPs) project aims to better position DHTs for broad adoption, commercial success, and improved health and economics outcomes across U.S. patient care settings.

When pairing IEP project outcomes with insights from this draft guidance and precedent-setting case-specific 510(k) evidence determinations, manufacturers will be able to consistently understand the collective regulatory and downstream expectations they are responsible for in advance of developing an efficient evidence generation strategy, engaging with the FDA for pre-sub meetings, compiling their regulatory submission dossier, and meeting the evidence requirements of downstream payers.

Conclusion
To directly support CDRH's mission of providing patients and providers with timely and continued access to safe, effective, and high-quality medical devices, manufacturers should have full clarity on the clinical evidence that may be required to demonstrate SE to a predicate device.

Based on this draft guidance alone, manufacturers cannot definitively determine whether they will be required to develop additional clinical evidence – nor the level or type of evidence – necessary to demonstrate SE. This draft guidance should be supplemented with real-world case-specific 510(k) clinical evidence determinations that manufacturers can rely on as precedent for future product submissions. Ideally in the future, case-by-case determinations will be the exception, not the rule.

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These actions will ultimately benefit patient access by removing unnecessary regulatory barriers, lowering evidence generation uncertainty, and reducing product time to market. The FDA has shown great leadership and willingness to engage with industry on mapping forthcoming steps to ensure greater clarity and transparency across the regulatory process. Thank you for taking patient care seriously and we look forward to partnering with CDRH to further develop these critical resources.

Sincerely,

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CEO

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