May 21, 2023

Robert M. Califf M.D.
Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Submitted electronically via www.regulations.gov

Re: Framework for the Use of Digital Health Technologies in Drug and Biological Product Development [Docket Number: FDA-2022-N-3319]

Dear Dr., Califf:

Premier Inc. appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) in response to the *Framework for the Use of Digital Health Technologies in Drug and Biological Product Development*. *[Docket Number FDA-2022-N-3319].* The Framework provides FDA's current thinking on the use of digital health technologies (DHTs) to support a multifaceted program for drug development and review.

Premier recognizes this framework will guide activities such as (1) defining objectives for workshops and demonstration projects; (2) developing methodologies for evaluating DHTs proposed as measuring key endpoints or other important in clinical trials; (3) managing submissions with extensive and continuous data; and (4) developing a standardized process for data management and analysis of large datasets from DHTs.

In our comments, Premier urges the FDA to:

- develop data standards for DHTs, in conjunction with the private sector, to minimize confusion around the quality of DHT data that can or cannot be leveraged as part of a clinical trial submission;
- create consistent approaches to the review and evaluation of study submissions;
- work with multiple external stakeholders, including companies such as Premier, to ensure that the Framework incorporates real world knowledge and experience;
- remain nimble and flexible to regularly update the Framework as DHTs continue to evolve and transform.

I. BACKGOUND ON PREMIER INC.

Premier Inc. is a leading healthcare improvement company and national supply chain leader uniting an alliance of 4,400 hospitals and approximately 250,000 continuum of care providers to transform healthcare. With integrated data and analytics, collaboratives, supply chain solutions, consulting and other services, Premier enables better care and outcomes at a lower cost. Premier's sophisticated technology systems contain robust standardized data gleaned from nearly half of U.S. hospital discharges, 812 million hospital outpatient and clinic encounters and 131 million physician office visits. Premier is a data-driven organization with a 360-degree view of the supply chain, working with more than 1,300 manufacturers to source the highest quality and most cost-effective products and services. Premier's work is closely aligned with healthcare providers, who drive the product and service contracting decisions using a data driven approach to remove biases in product sourcing and contracting and assure access to the highest quality products.

A 2006 Malcolm Baldrige National Quality Award recipient, Premier plays a critical role in the rapidly evolving healthcare industry, collaborating with healthcare providers, manufacturers, distributors, government, and other entities to co-develop long-term innovations that reinvent and improve the way care

is delivered to patients nationwide. Headquartered in Charlotte, North Carolina, Premier is passionate about transforming American healthcare by accelerating care alignment with evidence-based guidelines and best practices to enhance clinical performance, identify effective interventions and help improve patient outcomes.

II. ADDRESSING CHALLENGES RELATED TO THE USE OF DHTs IN REGULATORY DECISION-MAKING FOR DRUGS

Advances in DHTs (e.g., electronic sensors, computing platforms and information technology) may provide new opportunities to obtain clinical trial data directly from patients. Portable DHTs that may be worn, implanted, ingested, or placed in the environment allow real-time collection of data from trial participants in their homes or at locations remote from clinical trial sites. While the emergence of DHTs can provide some efficiencies in clinical trial design, however, Premier encourages the FDA to consider the following when leveraging and using data collected from DHTs in regulatory decision-making for drugs and for clinical trial analysis.

Data collected from DHTs must be properly cleaned and validated to be leveraged as part of clinical trials. While it is convenient to collect data from DHTs, there is also a risk that DHTs may collect a lot of unnecessary data that is subject to potential patient manipulation of the data collection process (e.g., patients turning off the devices during certain activities, mis-logging activities, etc). Before using DHT data for clinical trials, data must be cleaned and validated in a way that meets the traditional clinical trial data standards, such as inclusion of predefined data ranges, consistent formats, appropriate data validation, logic checks, and adherence to international standards such as the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). ***Premier urges FDA to develop data standards for DHTs, in conjunction with the private sector, to minimize confusion around the quality of DHT data that can or cannot be leveraged as part of a clinical trial submission.***

III. INTERNAL PROGRAMS

Premier agrees with FDA's statement that the successful utilization of DHTs to support drug development and review will depend on FDA and other stakeholders addressing the challenges discussed throughout the Framework together. The Framework includes programs to support DHT-related activities within FDA (internal programs) and programs to engage industry and other stakeholders (external programs) in the development and use of DHTs.

Technical Expertise and Training

The Framework defines artificial intelligence (AI) as a branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions, and making predictions. The subset of AI known as machine learning (ML) allows models to be developed by training algorithms through analysis of data, without models being explicitly programmed. The Framework also states that DHTs may incorporate the use of AI algorithms that have the potential to transform healthcare by deriving new and important insights from the vast amount of data generated by DHTs.

Premier supports the use of AI and ML and believes there are numerous opportunities to use these technologies to transform healthcare, including:

- Predictive modeling: AI and ML can be used to develop predictive models that can identify patients at high risk of developing certain conditions or diseases, allowing for early intervention and treatment.

- Diagnostic support: AI and ML can also be used to assist in the diagnosis of conditions, by analyzing DHT-derived data and providing automated interpretations or decision support tools for clinicians.
- Personalized medicine: AI and ML can help to tailor treatment plans to individual patients, by analyzing DHT-derived data to identify patient-specific risk factors or treatment responses.
- Real-time monitoring: AI and ML can facilitate real-time monitoring of patients, by analyzing DHT-derived data and identifying patterns or trends that may indicate a change in health status, allowing for timely intervention.
- Disease surveillance: AI and ML can be used to monitor disease outbreaks and track the spread of infectious diseases, by analyzing DHT-derived data from a variety of sources such as social media, internet search data, and electronic health records.

If the FDA intends to build on its domain-specific expertise in data science, informatics, statistics, and mathematics to help ensure the appropriate application of AI technology in the context of DHTs used for drug development, Premier has the following comments:

- When appropriate, ***Premier suggests a requirement for structured communication layers such as Predictive Model Markup Language (PMML)*** This would allow for system interoperability in a fashion similar to FHIR.
- ***The FDA should provide open-source client libraries in Python, R, or other important languages***. Python and R are important data science tools, and a client library would allow researchers to interact directly with the data elements in the fashion the FDA intends them to be used rather than each vendor making their own access decisions. In addition, it is essential for FDA to provide support (ideally financial and at a minimum technical) to vendors who create these libraries.
- ***The FDA should consider a federally hosted private cloud for communicating with clinical trial sponsors.*** This would facilitate health information exchange (HIE) activity and can be used to train and evaluate the data.

The Framework also states that the FDA intends to enhance their relevant expertise through hiring new staff, training existing staff, and consulting with internal and external experts, as appropriate. ***Premier encourages the FDA to subcontract the knowledge transfer work to a single source as currently there are challenges in getting clear, comprehensive answers***. This kind of documentation requires both technical skill and marketing knowledge to ensure effective communication and compliance.

Consistency of Evaluations Across Review Divisions

The Framework asserts that a single DHT measurement may be used for studies of different diseases and different drugs and that the DHT Steering Committee will help facilitate consistent approaches to the review and evaluation of such submissions. Although Premier supports this statement***, Premier recommends the Committee incorporate the following elements to create consistent approaches to the review and evaluation of study submissions.***

- ***Consider integrating the derived metrics into the Unified Medical Language System (UMLS) for standardization***. The UMLS is used widely in digital health to normalize the language and coding systems of health providers and is used extensively in research and the analytics of research publications.
- ***Provide training***: Consistent training can help ensure that all evaluators have a shared understanding of the evaluation process and criteria. Providing training on standard operating procedures and evaluation methods can help to promote consistency across review divisions.
- ***Establish quality control measures***: Quality control measures can help to ensure that evaluations are conducted consistently and accurately. These measures may include peer review, expert panel review, or independent verification of data.

- ***Use standardized templates and tools***: Standardized templates and tools can help ensure that evaluations are conducted consistently across review divisions. These may include standardized data collection forms, scoring rubrics, or decision trees.
- ***Encourage collaboration and communication***: Collaboration and communication across review divisions can help to promote consistency by sharing best practices, discussing challenging cases, and providing feedback on the evaluation process.
- ***Conduct regular audits***: Regular audits of the evaluation process can help to identify inconsistencies and areas for improvement. These audits can be conducted by internal or external auditors and can provide valuable feedback to improve the consistency of evaluations across review divisions.

Statistical Considerations in the Analysis of DHT-Derived Data

The Framework sets out that although use of DHTs in clinical investigations has increased, few clinical investigations have used sensor based DHTs to support primary or secondary endpoints. The FDA plans on leveraging its statistical expertise to address novel analytical considerations for endpoints derived from DHT data and will consider developing technical data specifications to facilitate submission of readily analyzable DHT-derived data supporting drug development.

Premier encourages the FDA to adopt the following approaches as it develops technical data specifications:

- ***A focus on longitudinal data and techniques including mixed-effects models or generalized estimating equations (GEE)***. These are statistical methods allowing for analysis of repeated measurements or other correlated data like those from DHT. It is important to consider this type of data modeling to create more effective studies.
- ***Adding in data normalization to account for differences in measurement scale or baseline characteristics***. For example, normalization involving dividing values by a reference value or using z-scores to account for differences in baseline values. This allows for interoperability among different types of DHT systems/devices, helps to streamline data, simplifies a database and makes it more concise, and prevents data from being replicated in two tables at the same time or unrelated product data being gathered in the same table.
- ***Selection and measurement bias that will need to be adjusted for in the analysis to avoid inaccurate or skewed results***.
- ***Using various data visualizations techniques and methods which can be used to facilitate understanding of the data*** and to identify patterns or trends that may not be apparent from summary statistics alone.

IV. EXTERNAL PROGRAMS

The Framework describes a range of activities for FDA to engage with external stakeholders, such as sponsors, patient advocacy groups, DHT companies, clinical investigators, international regulatory bodies, and professional societies. Premier agrees that such activities can help FDA better understand the challenges and opportunities associated with DHTs and looks forward to participating in various manners outlined in the Framework. ***Premier urges the FDA to work with multiple external stakeholders, including companies such as Premier, to ensure that the Framework incorporates real world knowledge and experience. In addition, it critical for FDA to remain nimble and flexible to regularly update the Framework as DHTs continue to evolve and transform.***

V. CONCLUSION

In closing, Premier appreciates the opportunity to submit comments regarding the "*Framework for the Use of Digital Health Technologies in Drug and Biological Product Development*." Premier looks forward to working with the FDA to support and advance the use of DHT-derived data in regulatory decision-making for drug and biological products.

If you have any questions regarding our comments or need more information, please feel free to contact me at soumi_saha@premierinc.com or 732-266-5472.

Sincerely,

Soumi Saha, PharmD, JD
Senior Vice President of Government Affairs
Premier Inc.