Click Therapeutics

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Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Docket No. FDA-2025-N-2338 for "Digital Health Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments"

Re: Request for Comments - Generative Artificial Intelligence-Enabled Digital Mental Health Medical Devices

To the Digital Health Advisory Committee,

Enclosed are comments from Click Therapeutics ("Click") in response to the Digital Health Advisory Committee request for comments on the topic of *Generative Artificial Intelligence-Enabled Digital Mental Health Medical Devices*.

Click is a software-as-a-medical-device (SaMD) manufacturer that is committed to developing clinically validated, FDA-regulated digital therapeutics (DTx) mobile applications that deliver evidence-based interventions intended to treat medical conditions. Click is also developing software-enhanced drug™ (SE™) treatments; these treatments combine software with pharmacotherapy for an integrated therapeutic approach, offering additional clinical benefits to patients through software as compared to drug alone.

We appreciate the Committee's continued focus on this critical topic and are grateful for the opportunity to provide further perspective. As detailed in our previous correspondence to Docket No. FDA-2024-N-3924, we believe Generative Artificial Intelligence (Gen AI) offers significant positive potential to improve therapeutics effectiveness, sustain long-term patient engagement, and extend the reach of these therapies when developed responsibly in order to ensure ongoing safety and effectiveness.

Gen AI can be leveraged in a variety of ways in mental healthcare. Gen AI could be used as a tool for diagnosis and assessment to detect, classify, and evaluate mental health conditions as well as a therapeutic intervention to deliver mental health support, therapy or interventions to patients [1].

Benefits of Gen AI-enabled Device Software Functions (Gen AI-DSFs)

Responsibly developed Gen AI-DSFs have the potential to deliver hyper-personalized therapeutic interventions that augment and parallel the skills of human mental health professionals.

One of the most compelling advantages of integrating Gen AI into regulated DTx and SE™ drugs is the ability to achieve profound personalization at scale and thus individual precision in treatment delivery. Mental health conditions often present with significant cross-subject variability, making traditional, generalized therapeutic models difficult to generalize effectively across diverse patient populations. This capacity for personalization is central to the mechanism of digital therapeutics, offering the potential for the DTx to dynamically adjust and optimize engagement and adherence, and when paired with a drug as an SE drug, enhance overall clinical outcomes beyond what the drug alone can achieve.

Additionally, Gen AI-DSFs enable an unprecedented degree of on-demand interactivity (e.g., via simulated chat or phone call) that can engage the patient at a time of need, likely when they are most receptive to care. This eliminates existing access barriers where patients may need to wait or must travel before being able to consult a healthcare professional.

Gen AI models have already demonstrated strengths in both psychoeducation and emotional awareness and have been shown to be able to assist patients with evidence based techniques such as cognitive restructuring, goal setting, and motivational support [2].

When developed responsibly, these software functions can help reduce burden on clinicians and enhance the efficiency and reach of mental health treatment options.

Risks to Health of Gen AI-DSFs

While the potential benefits are significant, the implementation of Gen AI in digital mental health applications introduces novel and potentially serious risks to patient health and safety. These risks necessitate a rigorous risk management approach as per *ISO 14971:2019 Risk Management* and its companion consensus report *AAMI CR34971 Guidance on the Application of ISO 14971 to Artificial Intelligence and Machine Learning*. These risks are no longer theoretical, they are emerging in real-world use cases and require proactive mitigation through both technical controls and systematic post-market monitoring.

1. Risk of "AI-Induced Psychosis”

There is growing concern that interaction with Gen AI chatbots may generate delusions in individuals prone to psychosis. Emerging and rapidly accumulating reports describe individuals experiencing an onset or exacerbation of psychosis symptoms after intense engagement with AI. Additionally, a new preprint study highlights a trend of AI appearing to reinforce and elaborate on users’ delusions creating dangerous negative feedback loops [3]. While further research is necessary, the anecdotal evidence provides compelling evidence of a novel risk of Gen AI that should be considered and mitigated for in Gen AI-DSFs.

To mitigate this risk, manufacturers should implement appropriate risk controls, such as comprehensive interaction monitoring using model management platforms that are able to track conversation patterns, session duration, and semantic drift. These systems can automatically detect when interactions become repetitive or focus on potentially delusional themes, triggering safety protocols (e.g., escalation to human oversight).

2. **Risk of Harmful Hallucinations**

Gen AI models are non-deterministic and can "hallucinate" outputs, generating content that may be factually incorrect, clinically inappropriate, or even directly harmful. In a mental health context, this could manifest as providing unsafe advice, using stigmatizing language, or misinterpreting a user's input in a way that causes psychological distress.

Manufacturers can address hallucination risks through systematic evaluation frameworks that assess model outputs for faithfulness and correctness. While manual human review of outputs (human-in-the-loop) may be appropriate when feasible or for spot auditing purposes, automated approaches such as multi-agent review and LLM-as-a-Judge enable large-scale evaluations against faithfulness metrics (how well outputs align with expected output, e.g., pre-approved clinical content) as well as correctness versus a prespecified "ground truth."

3. **Failures in Crisis Management**

There is also the potential for the Gen AI to fail to recognize a user in crisis (e.g., expressing suicidal ideation) and may respond inadequately or harmfully.

To mitigate this risk, manufacturers should implement safety protocols, for example ones that leverage machine learning models specifically trained to detect and classify user inputs that may indicate a user is in crisis.

4. **Risk of Inconsistent Performance**

If trained on non-representative data, a Gen AI model may perform poorly for certain demographics or patient groups [4]. This can lead to unpredictable outcomes and potentially erode trust in digital health solutions.

In addition to the already referenced evaluation framework with LLM-as-a-Judge for large scale evaluation, "red teaming" can help identify how a model performs to edge cases and challenging scenarios that may reveal biases. Red teaming has traditionally been used to describe a type of security testing but the terminology has now expanded to describe adversarial testing used to discover unsafe or undesirable behaviour of LLM [5]. For mental health application, this may involve crafting inputs from a wide variety of user personas and use contexts to test whether the model offers inequitable outputs across personas despite presenting with identical symptoms. These red teaming tests can be versioned, tracked, and run automatically thereby creating a

robust validation process to evaluate fit-for-context responses across different populations throughout the feature's lifecycle.

Use Case: Gen AI in PDURS, including Software-Enhanced Drugs

We would also like to offer a specific additional use case to highlight another area for Gen AI-DSF applicability. We hope this example assists the Digital Health Advisory Committee in developing recommendations for a right-sized regulatory solution that also applies to drug- and combination product-related use cases. This example of Gen AI in Prescription Drug Use-Related Software (PDURS) is intended to highlight the need for a clear and consistent regulatory framework across multiple regulated product types.

Frameworks for the regulation of Gen AI in therapeutic devices should also extend to PDURS, as described in FDA's draft guidance *Regulatory Considerations for Prescription Drug Use-Related Software*, published September 2023. PDURS is defined as software that is disseminated by or on behalf of a drug sponsor and generates an end-user output that supplements, explains, or is otherwise textually related to one or more of the sponsor's prescription drug products. The end-user output, which includes screen displays, sounds, and other content presented to the patient or practitioner, is regulated by the FDA as prescription drug labeling, either promotional or FDA-required:

1. **Promotional Labeling (General Support)**

   Most PDURS outputs, such as general patient support, adherence reminders, or educational information, are promotional labeling. These outputs, which are *not essential* to the drug's safe use and provide *no documented clinical benefit* beyond the drug itself (e.g., personalized adherence schedules, FAQ responses), are typically submitted to the FDA's Office of Prescription Drug Promotion (OPDP) via Form 2253 upon initial dissemination.

2. **FDA-Required Labeling (Clinical Benefit)**

   When a PDURS software function demonstrably provides a clinically meaningful benefit to a prescription drug, its output may be incorporated into the FDA-Required Labeling. This necessitates submitting clinical evidence from one or more adequate and well-controlled clinical studies to the FDA to support its inclusion in the official Prescribing Information (PI).

One potential PDURS Gen AI use case could involve a co-packaged combination product comprised of (1) an approved drug for a mental health condition (e.g., antidepressant or antipsychotic) and (2) a Gen AI device software function that regularly interacts with the patient via interactive chat or phone call check-ins for the purposes of symptom monitoring, crisis prediction and crisis detection. In this case, the Gen AI-DSF works hand-in-hand with the medication to provide the added clinical benefit of reduced risk of crisis or hospitalization.

Incorporating appropriate details on the Gen AI-DSF digital component into the drug Prescribing Information (PI) is crucial for prescribers to make an informed decision about the benefits, risks and applicability of the Gen AI-DSF for their patient on the related medication. Clear, consistent AI-related labeling guidelines for Gen AI-enabled PDURS can thus facilitate appropriate prescription, thereby ensuring this added clinical benefit can reach patients.

The PDURS framework augments the Center for Devices and Radiological Health's (CDRH) existing regulatory oversight concerning the software's device functions. It is important to recognize that while PDURS specifically pertains to the labeling requirements for the drug component and does not supersede or replace device regulations, frameworks for the regulation of Gen AI in device software functions should consider labeling scenarios of PDURS Gen AI functions ranging from general disease awareness (unregulated) to basic adherence support (promotional labeling), and finally, to added clinical benefit (required labeling).

Comments Re: Generative Artificial Intelligence-Enabled Digital Mental Health Medical Devices

Click presents the following key requests for the Digital Health Advisory Committee's consideration and subsequent FDA action in Table 1 below. These requests, in addition to the comments and examples provided above, aim to foster Gen AI innovations across a broad spectrum of mental health applications, including general disease awareness, DTx, SE drugs, and other PDURS applications.

Click Therapeutics

Table 1. Key Requests for DHAC Consideration and Subsequent FDA Action

Consideration	Challenge / Rationale	Request to FDA
Clarify which Gen AI-enabled software functions are subject to enforcement discretion in the upcoming draft of the *Policy for Device Software Functions*	The FDA's current policy denotes that the FDA will exercise enforcement discretion for low-risk software that is intended to help patients "self-manage their disease or conditions without providing specific treatment or treatment suggestions." The American Psychological Association (APA) provided testimony to Congress highlighting the potential risks without regulation on some of these software functions. For example, AI chatbots are able to present themselves as "therapists" or claim to offer "psychotherapy" as these terms are unregulated in many states. The general public may not be aware that these terms are not protected like "psychologist" or "licensed professional counselor" and this misrepresentation and potential for unqualified, unvalidated, and potential harmful advice should not be under enforcement discretion [6]. Additionally, recent state laws (e.g., in Illinois, Nevada, and Utah) have started to address this risk by prohibiting unlicensed therapy services and requiring clear disclosure of AI identity.	We request that in the upcoming draft of *Policy for Device Software Functions* (formerly titled *Policy for Device Software Functions and Mobile Medical Applications*) be updated to consider Gen AI-specific examples of software functions. Examples that do or do not fall under enforcement discretion will explicitly confirm that software functions meeting the definition of a device are subject to regulatory oversight, even when the software functions use Gen AI. Please see the following for potential examples that could be included in the Appendices of the updated policy. **Proposed "Example of Software Functions for which FDA intends to exercise enforcement discretion"** ● Software functions that use Gen AI to provide users general education on behavioral coping skills and wellness techniques for the self-management of diagnosed psychiatric conditions (e.g., post-traumatic stress disorder (PTSD), depression, anxiety, obsessive compulsive disorder (OCD)) without providing specific treatment or treatment suggestions. ○ These functions are intended to help a patient *learn about* available coping skills and techniques but do not provide specific skill acquisition, treatment or treatment suggestions. These functions are not intended to be used for crisis management or as a substitute for professional medical care from a licensed provider or from an authorized medical device software function. **Proposed "Example of Software Functions that are the focus of FDA's regulatory oversight (Device Software Functions and Mobile Medical Apps)"** ● A software function that uses Gen AI to engage in personalized dialogue to diagnose, assess, or create/manage individualized mental health treatment, or representing itself as a licensed professional or "therapist." ○ These functions have a device intended use by nature, whether by directly providing diagnosis or treatment, or implying it by presenting in dialogue as a therapist or healthcare agent (virtual or otherwise).

Consideration	Challenge / Rationale	Request to FDA
Gen AI-Enabled Wellness Products - Risk Considerations & Communication to End Users	As discussed in the Executive Summary for the 2024 Digital Health Advisory Committee, it can be challenging to determine how a product's intended use may align within the scope of FDA's current digital health policies due to the evolving nature of many Gen AI-enabled products. There is a risk that new, emergent intended uses can appear in the real world setting without proper controls, e.g., a chatbot that claims to only help users with behavior coping skills and wellness information offering therapeutic treatment to a patient with severe mental illness.	Establish clear risk-based requirements for the information that shall be provided in transparent labeling of Gen AI-enabled products, including those under enforcement discretion. Requirements for transparent labeling could include description of where Gen AI is used in the product, how the model was tested, guardrails implemented to constrain its intended use, etc. Further, establish clear guidance regarding actions that should be taken when a Gen AI-enabled wellness product, due to data drift or occurrence of real world medical use cases, has an emergent intended use that meets the definition of a medical device. This could include establishing expectations for postmarket controls and postmarket surveillance, even for products that may be medical devices but under enforcement discretion for certain premarket requirements.
Establish Considerations for Gen AI-enabled Software in PDURS Guidance	FDA's draft guidance *Regulatory Considerations for Prescription Drug Use-Related Software*, published September 2023 does not mention Gen-AI. However, the PDURS may include Gen-AI that produces outputs that are promotional or FDA-required labeling of a drug, and the regulatory oversight and risk-based requirements for such Gen-AI PDURS functions are not clearly established.	We request that FDA include information on the regulatory oversight and risk-based requirements for Gen-AI PDURS in the forthcoming final guidance *Regulatory Considerations for Prescription Drug Use-Related Software*, published September 2023. This information is requested to explicitly address the complexity of PDURS with multiple functions and varying intended use (e.g., Gen-AI PDURS outputs that are promotional or required labeling, PDURS outputs that are generative artificial intelligence device software functions (AI-DSF), PDURS outputs that are Gen-AI general wellness tools) while facilitating a risk-based, right-sized regulatory approach that enables innovation within the combination product framework. Additionally we request that FDA expedite the finalization of the PDURS guidance, including guidelines on the clinical data considerations and combination product compliance requirements applicable to Gen AI and Gen AI-DSF PDURS.

Consideration	Challenge / Rationale	Request to FDA
Configuration Management	As with off-the-shelf software (OTS) in SaMD/SiMD, version control and configuration management of third-party softwares, including third party LLM (“foundation models”) presents challenges due to general lack of visibility that manufacturers may have about how the OTS was developed, and also information about changes to the OTS (e.g., notification of changes, detailed scope of changes).	Establish clear requirements regarding the level of information and controls (e.g., versioning, automatic regression testing) that the Agency would like to see in a pre-market review as well as inspection when a LLM (“foundation model”) is used within a Gen AI-enabled device. Where applicable, expand the scope of existing guidance and frameworks for risk management of OTS, such as the FDA Guidance on *Off-The-Shelf Software Use in Medical Devices*, published August 2023.

Click Therapeutics appreciates the opportunity to provide feedback and support the Digital Health Advisory Committee's efforts. Please contact Austin C. Speier, Chief Strategy Officer at Click Therapeutics, with any questions or requests for further information.

Sincerely,

Signed by:
Austin Speier
Signer Name: Austin Speier
Signing Reason: I am the author of this document
Signing Time: 10/17/2025 | 3:22:30 PM EDT
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