Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

March 22, 2022

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

Re: Docket No. FDA-2021-D-1128; Digital Health Technologies for Remote Data Acquisition in Clinical Investigations; Draft Guidance for Industry, Investigators, and Other Stakeholders

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to provide comments on FDA's "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations; Draft Guidance for Industry, Investigators, and Other Stakeholders" dated December 23, 2021 (the "Draft Guidance").

The CPC greatly appreciates FDA's efforts to provide this draft guidance which helps to establish Agency expectations for the types of evidence required to support use of digital health technologies ("DHTs") for remote data acquisition in clinical investigations. Our coalition represents members developing a range of products including combination products with embedded software and software as a medical device ("SaMD") applications which may be labelled for use with drug or biological products.

The CPC's comments on the Draft Guidance are captured below. The comments are organized by page number, reference content, and proposed revision or addition, with a discussion and rationale for our proposed change (if applicable) appearing below each portion of the table. Where multiple comments are related, the discussion and rationale for their conclusion have been combined.

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products and digital products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad, and unique perspective to these issues.

I. Comments Regarding Prior CPC Requests Regarding Medical Device DHTs Used in Investigational New Drug Studies

Upon reviewing the Draft Guidance, the CPC member companies were disappointed that the Draft Guidance did not address any of the requests made by our coalition as communicated in an August 3, 2021 letter regarding use of medical device digital health technologies in medicine investigations. Specifically, we requested that the Agency develop policy which relaxes obligations for manufacturers to fulfil 21 CFR 820.30, Design Controls, for certain low risk but unapproved medical devices used within medicine studies. We respectfully request that the Agency consider the CPC's requests whilst composing the final version of the subject guidance and implement policy which allows manufacturers to demonstrate compliance with Section IV.C of the Draft Guidance for low risk medical device digital health technologies in medicine investigations rather than comply with the full breadth of Design Controls.

For convenience, the CPC's August 3, 2021 communication is attached to this letter and can also be found at : https://combinationproducts.com/wp-content/uploads/2021/09/CPC-Letter-Re-Use-of-Investigational-Digital-Medical-Devices-in-Clinical-Studies-3Aug2021.pdf.

II. Comments Regarding Scope of Guidance

As authored by the Agency, the Draft Guidance is focused only on DHT systems which accomplish remote data acquisition from participants in clinical investigations evaluating medical products. However, upon review of the document, CPC member companies find that the central tenants of the Draft Guidance apply to other types of DHT systems beyond those that accomplish remote monitoring. For example, the Agency's guidance on selection, verification, and validation of DHT systems used in medicine studies should apply equally to medication clinical decision support systems or medication dose calculators. Therefore, we recommend that the scope of the final guidance be expanded to cover all DHT systems used in medicine studies that are provided by the study sponsor or required by the sponsor in the study protocol.

III. Comments Regarding Investigational Device Submission Pathways

The Draft Guidance suggests that unapproved medical devices used within Investigational New Drug ("IND") studies should be approved via an Investigational Device Exemption ("IDE") submission. This suggestion runs counter to the historical experience of CPC member companies where both medical device digital health technologies and investigational drug or biological products may be administratively submitted in a single application (i.e., the investigational application associated with the primary mode of action of the product that is the object of the clinical investigation).

The CPC appreciates that there may be occasions where separate IDE and IND applications are desired, for example where an in-vitro diagnostic companion is co-investigated with a medicine. In that situation, each have unique study endpoints and the study will be used to establish the safety/efficacy of both products and support separate marketing applications for the products. However, in the majority of cases, the number of investigational applications should be left to the discretion of the study sponsor and the Agency should accept a single investigational application

for a study of investigational drug or biological products that incorporates digital health technologies. This approach is consistent with "least burdensome" principles outlined in existing FDA guidance ("The Least Burdensome Provisions: Concept and Principles" (February 2019)) and help support efficient use of both FDA and industry resources.

Additionally, some portions of the Draft Guidance may inadvertently imply that an IDE application is required for any digital health technology used within an investigational drug or biological product study, rather than exclusively applying to digital health technologies that meet the statutory definition of a medical device.

Page	FDA Guidance Reference Text	CPC Proposed Revisions / Additions
4	Footnote 14 It is possible that a DHT, as proposed for use in a clinical investigation of a drug or biological product under an IND, may meet the definition of a significant risk device under 21 CFR 812.3(m) and require submission of an IDE application to FDA under part 812 for the same clinical investigation. In these cases, when information required under 21 CFR 812.20 is also contained in the IND, sponsors should consult with CDRH regarding ways to streamline the IDE application submission process for the particular clinical investigation. See, e.g., 21 CFR 812.20(d).	Footnote 14 It is possible that a DHT, as proposed for use in a clinical investigation of a drug or biological product under an IND, may meet the definition of a significant risk device under 21 CFR 812.3(m) and require submission of an **investigational** ~~**IDE**~~ application to FDA ~~**under part 812 for the same clinical investigation**~~. **Investigational device application information commensurate with 21 CFR 812 may be provided under an IDE application to CDRH, or, where appropriate may be provided within the IND application.** ~~**In these cases**~~, When information required under 21 CFR 812.20 is ~~**also**~~ contained in the IND**, the Agency intends to consult CDRH for review of applicable sections of the IND through the inter-Center consultation process.** ~~**sponsors should consult with CDRH regarding ways to streamline the IDE application submission process for the particular clinical investigation. See, e.g., 21 CFR 812.20(d).**~~
4	Devices—intended for use in clinical investigations are exempt from most requirements applicable to devices, including premarket clearance or approval, as long as the investigation complies with applicable requirements under 21 CFR part 812.14. Therefore, DHTs used in clinical investigations of medical products typically would be exempt from applicable requirements to	Devices-intended **only** for use in clinical investigations are exempt from most requirements applicable to devices, including premarket clearance or approval, as long as the investigation complies with applicable requirements under 21 CFR part 812.14. Therefore, DHTs **that meet the definition of an investigational device and are** used in clinical investigations of medical products

Page	FDA Guidance Reference Text	CPC Proposed Revisions / Additions
	obtain marketing authorization and other device requirements, as long as the clinical investigation is compliant with part 812.	typically would be exempt from applicable requirements to obtain marketing authorization and other device requirements, as long as the clinical investigation is compliant with part 812.
5	Sponsors should engage early with the appropriate Center responsible for the medical product under investigation to discuss use of DHTs in a specific clinical investigation.[17]	Sponsors should engage early with the ~~appropriate~~ **lead** Center responsible for the medical product under investigation to discuss use of DHTs in a specific clinical investigation.[17] **The lead Center will consult other centers as appropriate regarding the use of the DHT in the trial.**

IV. Comments Regarding Usability Studies for Non-Medical Device DHTs

The Draft Guidance contains a section describing the importance of conducting usability evaluations for DHTs. This section includes a reference to FDA's guidance "Applying Human Factors and Usability Engineering to Medical Devices" (February 2016) via footnote 35 and implies that usability/human factors principles for medical devices also apply to DHTs used in clinical investigations, irrespective of whether the use of the DHT meets the definition of a medical device.

As stated in the cited human factors guidance, the goal of human factors/usability engineering is "to ensure that the device user interface has been designed such that use errors that occur during use of the device that could cause harm or degrade medical treatment are either eliminated or reduced to the extent possible." As such, for non-device DHTs, the CPC requests that within the final guidance the Agency clarifies the regulatory basis for requiring usability validation for non-medical device DHTs. Additionally, usability validation, either for medical device or non-medical device DHTs, should not be required by default and should be applied with discretion based on the risk that use-related errors may pose during the conduct of the study and the unique mitigations available within clinical investigations.

Page	FDA Guidance Reference Text	CPC Proposed Revisions / Additions
12	Usability studies are a critical component in confirming the suitability of the DHT and/or general-purpose computing platform for the proposed clinical investigation. These studies are considered part of the validation process and should enroll a cohort that is similar to intended trial participants. Usability studies should test the ability of future participants to use the DHT as directed in the trial protocol.	Replace Reference Text with: While usability studies are always considered as best practice in confirming the suitability of the DHT and/or general-purpose computing platform for the proposed clinical investigation, such usability evaluations may be conducted in various ways. More rigorous human factors engineering and usability evaluations may be required where use-

Page	FDA Guidance Reference Text	CPC Proposed Revisions / Additions
	• Usability testing should assess whether users are able to enter all data before being logged out of a DHT. • When appropriate, sponsors can refer to published studies in similar populations or on early use of the DHT in exploratory studies to evaluate whether trial participants can appropriately use the DHT. • Findings from the usability studies can be used to improve the design and functionality of DHT, to improve user satisfaction, to inform the instructions for use provided to trial participants, and to improve ease of learning and training for trial participants and trial personnel.	related risks are associated with unacceptable patient risk (e.g., where improper data collection, display, or interpretation could lead to significant risk). Where the DHT meets the definition of a medical device, applicable medical device human factors engineering principles and guidance should be applied.[35]

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

Attachment: August 2021 CPC Letter to FDA Regarding the Use of Investigational Digital Medical Devices in Clinical Studies for Medicine

ATTACHMENT

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VIA ELECTRONIC SUBMISSION

August 3, 2021

FDA Digital Health Center of Excellence
c/o
Matthew Diamond, MD, PhD
Medical Officer
Division of Digital Health
Office of Strategic Partnerships and Technology Innovation
Center for Devices and Radiological Health

Cc:
Thinh Nguyen, Director, Office of Combination Products
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Leonard Sacks, Associate Director for Clinical Methodology, Office of Medical Policy, CDER
Elektra Papadopoulos, Acting Deputy Director Division of Clinical Outcome Assessment, Office of New Drugs, CDER
Chris Leptak, Co-Director, Biomarker Qualification Program. Office of New Drugs, CDER
Sheryl Lard-Whiteford, Associate Director for Quality Assurance, CBER

Subj: Use of Investigational Digital Medical Devices in Clinical Studies for Medicines

Dear Dr. Diamond:

I am writing on behalf of the Combination Products Coalition's (CPC) Digital Health Working Group in follow-up to our meeting with the Agency held on April 7, 2021. During our meeting, we had the pleasure of presenting on one of our Coalition's key priority areas related to the COVID-19 pandemic: easing access to digital medical devices and digital health technology tools within clinical studies for drugs and biologics. This letter follows the discussion and your invitation to provide additional information supporting our requests to the Agency's Digital Health Center of Excellence. Contained herein please find background information outlining our concerns and a proposal intended to facilitate greater patient and investigator access to digital medical devices and digital health technology tools (e.g., remote monitoring technologies). The CPC would welcome the opportunity to participate in a meeting with the Digital Health Center of Excellence to answer any questions the Agency may have or to assist in any way we can in advancing this proposal.

Introduction and Background

As the Agency is well aware, the use of digital technologies in pharmaceutical and combination product clinical investigations is expanding rapidly. The use of electronic patient reported outcomes, electronic clinical outcome assessments, and digital biomarkers are becoming the norm in our industry. While the COVID-19 pandemic has accelerated the uptake and utility of these technologies, it is clear that remote data collection and patient monitoring using medical devices will be a permanent component of medicine investigations in the future.

In parallel with the expansion of digital technologies within investigational new drug (IND) studies, the industry is learning more about the FDA's expectations for when medical device software and connected medical sensor technologies will be regulated as medical devices and cases where they may be unregulated or considered under enforcement discretion. New legislation such as the *21st Century Cures Act* and new guidance such as the Agency's *Policy for Device Software Functions and Mobile Medical Applications* offer greater detail as to how the Agency will regulate these technologies.

As the pharmaceutical and combination product industries look to develop and rapidly deploy digital technologies into IND studies, we often face a lack of clarity about whether such technologies will not only be regulated by the Agency under requirements such as 21 CFR Part 11, Good Clinical Practice and data integrity standards, but also if they will be subject to medical device design and development regulations.[1] For example, it is conceivable that a piece of digital health software used to perform clinical calculations or used to display medical sensor values might indeed be held to medical device quality expectations and require submission of design controls information under IND review. Set forth in Attachment 1 are more detailed examples of digital technologies commonly used within IND studies that the CPC believes would likely meet the definition of a medical device.

If the intended use of a digital technology used within an IND study is determined to meet the definition of a medical device (either by the Agency or the sponsor themselves) and that technology is not already legally marketed as a medical device in the United States, the CPC understands it is the Agency's position that such technology would need to be designed, developed, and manufactured according to 21 CFR § 820.30, *Design Controls*.[2] This position is clearly presented within 21 CFR § 812.1 as well as the Agency's *Current Good Manufacturing Practice Requirements for Combination Products*. Through recent member company experience, the CPC

[1] We appreciate the clarity provided in Dr. Sacks's presentation at the DIA Global Annual Meeting, which noted that 21 CFR Part 11 requirements become applicable when the data enter the trial data repository. We understand that FDA does not intend to inspect individual digital technologies for Part 11 compliance, nor does the Agency intend to enforce 21 CFR Part 11 compliance for telehealth visits or mobile phones. We further understand that the data captured from these tools and visits, however, should be maintained in repositories that are compliant with 21 CFR Part 11. We encourage the Agency to share this helpful insight further in guidance or other mechanisms.

[2] We also understand, however, that FDA does not expect digital health tools which are not considered medical devices to follow design controls.

further understands that the Agency expects design control source documents to be submitted to the IND for review consistent with the Agency's *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*.

The broad application of design controls to all investigational medical device technologies used within IND studies appears inconsistent with the Agency's position on application of current good manufacturing practices (cGMP) for pharmaceutical product development which are generally applied in a stepwise, phase-based manner. Moreover, it may be overly burdensome in situations where the device is not the object of the investigation and the manufacturer is not seeking to use the study to support a new marketing indication for the device. Additionally, the CPC believes that state-of-the-art software validation practices used in the development of robust clinical software systems meet the central tenants of design controls (e.g., requirements definition, detailed design practice, and quality testing approaches) and should be considered satisfactory for the Agency to make a determination that the medical device digital technology is sufficiently safe with minimal risk to patients and that study data integrity is maintained.

The use of medical device digital technologies within IND studies offers significant benefit to patients and investigators and additionally presents unique opportunities to mitigate patient risk not available in the commercial environment. We recognize that FDA regulation and policy do offer some existing benefits to industry and investigators, for example allowing for a single investigational application for investigational drugs and unapproved devices, however there is additional opportunity available to streamline Agency expectations in software quality management system expectations. Specifically, we propose that these technologies should be afforded discretion in the application of medical device design, development, and manufacturing regulations. By reducing the software validation documentation burdens applied to medical device software and digital sensors, the Agency will allow the pharmaceutical and combination product industries to develop and deploy safe digital technologies to improve the conduct and quality of IND studies. If the expectations to develop and validate the digital technology are overly burdensome and time consuming, in our experience, sponsors will decide not to use the device and avoid delay to the overall development program. This may result in continued use of less sensitive or less ideal, historical endpoints. It could also result in continued reliance on traditional "brick-and-mortar" study designs, rather than use of decentralized techniques that are less burdensome on patients.

Proposal

The CPC proposes that the Agency develop a new policy governing the medical device design and development practices required for medical device software and digital sensors used within IND studies, if there is not an existing legal marketing status available for the medical device technology. The policy should be risk-based and permit study sponsors to implement investigational medical devices within clinical studies if the sponsor has developed the systems in alignment with state-of-the-art software validation practices and has demonstrated patient risk is acceptable, but not necessarily medical device design controls according to 21 CFR § 820.30.

We propose the policy would be applicable if the following conditions are met:

- The medical device software/sensor system is only intended to support the clinical investigation of a medicine and is not intended for future commercialization as a marketed medical device (as best known to the sponsor and Agency at time of study approval)

- The intended use of the medical device software/sensor system within the IND study is sufficiently low risk (see proposed criteria below)

The CPC believes that there are several available and Agency-recognized medical device risk schema that could be applied to determine if alternative software development and validation strategies may be accepted, for example:

Risk Criteria Reference	Risk Categories Eligible for Alternative Development and Validation Approaches
ANSI AAMI IEC 62304:2006/A1:2016 - Medical device software - Software life cycle processes	Section 4.3 of the standard outlines a schema for "software safety class". The CPC proposes that Class A or Class B systems should be eligible for Alternative Development and Validation Approaches.
FDA Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices	Page 6 of the guidance document provides a risk-based schema for medical device software risk. The CPC proposes that systems with a Minor and Moderate level of concern should be eligible for Alternative Development and Validation Approaches. Note: For this guidance to be applied, the rule contained in Table 1 "Is the Software Device intended to be used in combination with a drug or biologic?" which automatically classifies the system as a "Major Level of Concern" should not be used.
IMDRF Document - Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations	Section 7.2 of the document outlines a schema for "SaMD Categories". The CPC proposes that systems with a Category of I, II, or III should be eligible for Alternative Development and Validation Approaches.

If the Agency agrees to establish the policy described above, the CPC proposes that the study sponsor may provide (if agreed or requested by the Agency) the following types of information concerning the medical device software/sensor development and validation process within IND eCTD Module 3.2.R – Regional, Medical Device:

- A description of the system including intended use, user population, user environment, relevant schematics, screenshots, and architectural diagrams

- A summary of:
    - the regulatory classification of the proposed system, and
    - an explanation for why the eligibility criteria for use of alternative development and validation approaches (i.e., low risk and investigational scope only) are met.

- A description of the development and validation methods applied to the system. Potential alternative development and validation strategies that may be cited include:
    - 21 CFR Part 4 and associated Agency guidance on developing and validating systems that use electronic records and electronic signatures
    - E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) and associated Agency guidance developing and validating electronic systems for use in clinical programs
    - ISO/IEC/IEEE 90003 Software engineering – Guidelines for the application of ISO 9001:2015 to computer software
    - Good Automated Manufacturing Practice (GAMP®)

- A summary of:
    - the risk management activities conducted for the system,
    - any residual risks, and
    - a justification for why any such residual risks are outweighed by benefit to patients, investigators, or the clinical program.

- A statement from the study sponsor that all referenced development and software validation activities have been conducted.

The CPC presumes that FDA will consult across centers as appropriate to facilitate the review of this information by Agency staff with applicable expertise. The CPC also does not intend any element of the above proposal to affect the applicable clinical team's (e.g., review division staff from CDER or CBER) discretion regarding the use of the digital technology as a drug study endpoint and/or the decision of whether the digital technology is safe to include within the clinical program.

Summary

The use of digital technologies within the IND studies offers significant benefit to patients and investigators and additionally presents unique opportunities to mitigate patient risk not available in the commercial environment. In cases where the study sponsor desires to use software or medical sensors that meet the definition of a medical device, the application of full medical device design, development, and manufacturing cGMP controls is burdensome and introduces undue delay in the deployment of such systems. By establishing a risk-based policy allowing study sponsors to apply state-of-the-art software development and validation approaches, the Agency will greatly improve the pace at which pharmaceutical and combination product sponsors can deploy these technologies to the benefit of patients and investigators.

The CPC respectfully requests that the Agency find a pathway to release the above policy quickly such that study sponsors can realize the benefits immediately. The Agency has been successful in releasing similar policy statements in connection to the COVID-19 pandemic and the CPC views the proposed policy as directly applicable to easing pandemic and post-pandemic care for patients enrolled in IND studies.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition