Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

February 1, 2022

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

Re: Docket No. FDA-2021-D-0775; Content of Premarket Submissions for Device Software Functions; Draft Guidance for Industry and Food and Drug Administration Staff

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to provide comments on FDA's "Content of Premarket Submissions for Device Software Functions: Draft Guidance for Industry and FDA Staff" dated November 4, 2021 (the "Draft Guidance").

The CPC greatly appreciates FDA's efforts to provide this Draft Guidance which updates Agency expectations regarding the content of premarket submissions for device software functions. 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The CPC's comments on the Draft Guidance are captured below.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.

1. Comments Regarding the Importance of Applying Consistent Medical Device Software Review Policies across all Medical Product Centers

Page	FDA Guidance Reference Text	CPC Proposed Revisions / Additions
1	Statement of authoring FDA medical product centers includes, "Center for Devices and Radiological Health" and "Center for Biologics Evaluation and Research".	Statement of authoring FDA Medical Product Centers should be amended to include, "Center for Drug Evaluation and Research."
4	The Scope section of the Draft Guidance states, "This guidance applies to all types of premarket submissions that include one or more device software function(s). Premarket submissions include: • Premarket Notification (510(k)); • De Novo Classification Request; • Premarket Approval Application (PMA); • Investigational Device Exemption (IDE); • Humanitarian Device Exemption (HDE); and • Biologics License Application (BLA)"	The list of applicable premarket submissions should be amended to include: • Investigational New Drug application (IND) • New Drug Application (NDA)

Upon reviewing the Draft Guidance, CPC member companies were disappointed that the Center for Drug Evaluation and Research (CDER) and the applications for which that medical product center maintains review authority were not represented in the document. Specifically, the preface of the Draft Guidance only lists the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) as the Agency centers that have endorsed the content of the document, and the list of applicable premarket submission types which the review policy covers does not include investigational or marketing applications for drugs.

The scope of the Draft Guidance notes that the document applies to FDA's review of the device constituent of a combination product (line 132). As the Agency is aware, drug-led combination products as defined in 21 CFR part 3 may have software medical device constituent parts that receive investigational or marketing applications which are reviewed by CDER.[2]

Therefore, it is critical that all three review centers – CBER and CDRH (authors of this Draft Guidance) as well as CDER – are aligned regarding expectations reflected in this Draft Guidance. CPC respectfully requests that all three Agency centers collaborate on the final version of the Draft Guidance to ensure that each of the three human medical product review Centers agree on policies

[2] For example, Abilify MyCite (aripiprazole tablets with sensor). Abilify MyCite (aripiprazole tablets with sensor) has an ingestible sensor embedded in the pill that records that the medication was taken. FDA, *FDA approves pill with sensor that digitally tracks if patients have ingested their medication* (Nov. 13, 2017), https://www.fda.gov/news-events/press-announcements/fda-approves-pill-sensor-digitally-tracks-if-patients-have-ingested-their-medication.

for the content of premarket submissions for device software functions such that industry can expect consistent treatment for the same underlying technologies regardless of application type. This will also help to avoid duplication of efforts and promote regulatory clarity from both an industry and Agency perspective.

2. Comments Regarding the Implementation of Software Submission Content Policies for Device Parts of Combination Products

Page	FDA Guidance Reference Text	CPC Proposed Revisions / Additions
7-8	Lines 236 – 239 of the Draft Guidance state, "Enhanced Documentation should be provided for any premarket submission that includes device software functions, where any of the following factors apply: 1) The device is a constituent part of a combination product."	Remove the status of the device as a constituent part of a combination product from the list of considerations for basic and enhanced documentation by striking, "1) The device is a constituent part of a combination product." and footnote 35 from the document.
27	Appendix A: Documentation Level Examples	At least one example within Appendix A should be provided for a combination product, preferably a drug-device or biologic-device combination product with a drug or biologic primary mode of action combination.

The CPC was initially pleased to find that the updated Draft Guidance removed the question found within the current final 2007 version of the guidance which asked "Is the Software Device intended to be used in combination with a drug or biologic?" in determining level of concern. However, upon analyzing the Draft Guidance, we noted that a similar concept has now been applied for "device constituent parts of combination products." We believe that this question, and the subsequent direction that any combination product software must automatically be considered as following the enhanced documentation pathway, is not appropriate.

The level of documentation required for submission (basic vs. enhanced) should be based on the intended use, classification, and risk to patients. Designation as a combination product should not automatically require enhanced documentation. The level of documentation should instead be based on a risk analysis of the particular function of the software in relation to the overall safety and efficacy of the combination product.

For example, software that drives the drug delivery components of the combination product would likely require enhanced documentation due to the risk of disabling the intended purpose of the system to deliver a drug. However, a software device constituent that registers activation/actuation of a drug delivery system and relays this information to patients and caregivers would likely be lower in risk and therefore basic documentation for such functions should suffice.

We believe that the illustration of how combination product software may be considered as lower or higher risk and therefore qualifying for Basic or Enhanced documentation should be further elucidated within the list of examples provided in Appendix A. We request that the examples

provided above (i.e., software driving drug delivery vs. data capture software) be considered by the Agency and placed in Appendix A.

3. Comments Regarding Approaches to the Preparation and Submission of Software Validation Documentation

Page	FDA Guidance Reference Text	CPC Proposed Revisions / Additions
8	Within Section V of the Draft Guidance, in describing criteria that would result in software being classed as requiring "Enhanced Documentation," the document states one criterion as: "A failure or latent flaw of the device software function(s) could present a probable risk of death or serious injury, either to a patient, user of the device, or others in the environment of use. These risk(s) should be assessed prior to implementation of risk control measures. You should consider the risk(s) in the context of the device's intended use; the direct and indirect impacts to safety, treatment, and/or diagnosis; and other relevant considerations."	For software embedded in medical devices, it is not clear whether the assessment considers risk mitigations implemented to reduce the probability or severity of software failures, in particular where those mitigations are enabled outside of the software itself, either through mitigations present in the hardware of the device or external to the device altogether.
9	Within Table 1, *System and Software Architecture Design Chart* (Section IV.C) both Basic and Enhanced Documentation Levels are required to show "Detailed diagrams of the modules, layers, and interfaces that comprise the device, their relationships, the data inputs/outputs and flow of data, and how users or external products (including IT infrastructure and peripherals) interact with the system and software."	IEC 62304 does not require creation of a Software Architecture Document or Software Detailed Design for Class A software. Hence, a Class A software program may not have flow charts or state diagrams as part of its documentation. Therefore, we recommend that the Agency consider the IEC 62304 software safety classification construct in requiring a System and Software Architecture Design Chart and specifically remove the need for it from Basic Documentation software.
10	Within Table 1, Section IV. J, *Unresolved Anomalies (e.g., Bugs, Defects, or Errors)*, the Draft Guidance states: "List of remaining software anomalies (e.g., bugs, defects) annotated with an explanation of the impact on safety or effectiveness, including operator usage	We recommend that this sentence be reworded to remove, "timeframe for correction." It is commonly accepted that not every bug needs to be fixed in each software version. Every new software release needs to assess past unresolved anomalies. This assessment must document the impact of fixing or not

	and human factors and work-arounds, and timeframe for correction."	fixing a bug or anomaly with an appropriate risk assessment to back up the justification. It may turn out that fixing a past defect may take longer depending upon the type of defect. Therefore, any timeframe provided could be inaccurate.
22	Within Section VI. H of the Draft Guidance, when describing Software Testing as part of Verification and Validation activities, the document states: "Any intentional changes made in response to failed tests and documentation of test results demonstrating that the intentional changes were implemented correctly."	We recommend that the excerpted statement be replaced with: "A root cause analysis and a justification is needed prior to either re-executing failed test cases or accepting the failure as an acceptable anomaly."
22	Within Section VI. H of the Draft Guidance, when describing Software Testing as part of Verification and Validation activities, the document states that Enhanced Level of Documentation would include: "Basic Documentation Level PLUS unit and integration level test protocols including expected results, observed results, pass/fail determination, and unit and integration level test reports."	Historically, for "Major Level of Concern" software, the Agency has accepted the submission of a few exemplary test protocols and individual test reports to demonstrate how the testing process is executed. Those examples, along with an overall test summary report, have been deemed acceptable. We recommend that the Agency clarify that this examples-based approach would still be an acceptable process for "Enhanced Documentation" under the new guidance.
23	Within Section VI. J of the Draft Guidance, when describing Unresolved Anomalies, the document states: "An anomaly is any condition that deviates from the expected behavior based on requirements specifications, design documents, standards, or from someone's perceptions or experiences." "Each item should be annotated with an explanation of the impact of the anomaly on device safety or effectiveness, including operator usage and human factors issues."	We recognize that accepted software industry definitions of "software anomalies" include considerations of user "perceptions and experiences," however, in the context of medical devices, and with more specific language available in the regulations and guidance associated with design controls, we recommend carefully distinguishing between a software anomaly where the performance of the software differs from documented requirements vs. when a use error or user confusion occurs which should be evaluated under use-risk management and human factors engineering. These two types of observed "anomalies" should be evaluated within their respective constructs and not conflated.

25	Within Section VII. B. of the Draft Guidance which describes Off the Shelf Software, the document states: "Multiple Function Device Product: Policy and Considerations. Therefore, please consider the impact of the OTS software on the device function-under-review and provide information (as recommend in the OTS guidance) about the impact on the device function from the OTS software in a manner consistent with the policy described in the Multiple Function Device Product: Policy and Considerations guidance."	We recommend that the Agency clarify if documentation required per the Multiple Function guidance needs to be provided for OTS software if the OTS software documentation is provided (e.g., Google libraries), given that the documentation to be provided per the Multiple Function guidance is similar to Software of Unknown Provenance documentation in IEC 62304.

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The CPC supports the further development of the Content of Premarket Submissions for Device Software Functions Draft Guidance. However, we would appreciate additional clarity in the final guidance regarding the comments provided in this document, with particular attention to the comments concerning cross-Center adoption of the software review policies on software documentation and application of this guidance to NDA and IND applications. We appreciate the opportunity to provide input on the Draft Guidance and welcome any questions or further discussion.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition