Combination Products Coalition

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FDA-2019-D-4258

VIA ELECTRONIC SUBMISSION

December 26, 2019

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

Re: Docket No. FDA-2019-D-4258: Type V DMFs for CDER-Led Combination Products Using Device Constituent Parts With Electronics or Software Guidance for Industry

Dear Sir or Madam:

The Combination Products Coalition ("CPC") [1] welcomes the opportunity to provide comments on FDA's "Type V DMFs for CDER-led Combination Products Using Device Constituent Parts With Electronics or Software Guidance for Industry" dated October 29, 2019 (the "Draft Guidance").

The CPC appreciates FDA's efforts to provide guidance that will help maximize efficiency and consistency in combination product reviews, using a drug master file approach. We believe regulatory efficiency and consistency can be improved by the approach proposed by the Agency, which can lead to timely access to new combination products for patients. To ensure utilization of this approach, however, the CPC strongly recommends that the Draft Guidance better clarify how the rapid, iterative nature of software updates are considered in the process, submissions and amendments for Type V DMFs that contain electronics or software. In addition, the CPC believes that the Draft Guidance should clarify that the proposed Type V DMF submission approach should be available to all types of platform device constituent parts, not just those containing electronics or software.

[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 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.

The CPC has carefully evaluated FDA's Draft Guidance and we ask that the Agency consider the following general comments, as well as our specific responses, which are provided below.

General comments:

1. The Draft Guidance should clarify that the proposed option to submit a Type V DMF is available to all types of platform device constituent parts, not just those containing electronics or software. While the Type III DMF for packaging materials is an available option for certain device constituent parts, delivery devices, even those without software or electronics, are often complex and have technological characteristics and performance attributes that go well beyond descriptions of packaging materials. Current review processes are duplicative and can result in divergent requirements for the same device. A single review for a platform device can allow FDA to allocate its resources more efficiently, rather than re-evaluating the same device constituent part across multiple CDER-led combination products. Use of one master file for the review of the platform device, which could be contained in an MAF, 510(k) or other file as provided in the proposed guidance, may simplify and expedite reviews of subsequent products, enhancing consistency in combination product reviews for both FDA and sponsors.

2. The frequency and nature of software changes could pose challenges with submitting amendments under the Draft Guidance. The CPC agrees that applicants are responsible for determining whether submissions to approved or pending applications are necessary. However, CPC members have frequently received requests to file a supplement to an approved application even with minor amendments to a Type V DMF. As such, it is sometimes unclear what changes trigger a DMF amendment compared to those that may warrant a postapproval report. This is particularly important given that software updates occur iteratively and frequently and documentation can be very detailed. We ask that FDA provide clarification on the types of changes to a CDER-led combination product that will trigger amendments to the DMF and those that may require submissions to approved or pending applications. In the final guidance, it would be helpful to include examples of each. Additionally, with respect to the timing of the submission of a DMF amendment, FDA should allow either of the following approaches:

    a. Updating the DMF prior to the modified sections being referenced in an application; or
    b. Updating the DMF as part of the routine annual DMF report.

    Note that changes made to software or electronics are also controlled under the provisions of 21 CFR Part 4 - Design Controls, a required cGMP component, which also ensures that changes made to these constituent parts are documented and appropriately specified, verified and validated.

3. The CPC agrees that one review of a Type V DMF or other file as provided in the proposed guidance may be applicable to later submissions and that FDA should use previously

completed scientific reviews to contribute to a consistent and efficient review of subsequent combination products using the same platform device. The ability to leverage prior scientific reviews can support a more efficient review process and help ensure consistency across CDER applications. The use of other files, such as the Type V DMF, can also help streamline submissions by sponsors. Once FDA has confirmed that providing the information in another file (not in the IND, NDA or BLA) is appropriate, the technical information applicable to the submission need not be duplicated in an individual CDER submission (IND, NDA or BLA). In the past, for other information now provided in Type V DMFs (e.g., sterilization process validation), sponsors have received requests from CDER reviewers to move the DMF content to the individual CDER submission. This has diminished the value of an efficient FDA review process to help ensure consistency across CDER applications referencing the same information. For this reason, the CPC supports the proposal to reference and rely upon the previously completed review of the DMF in subsequent reviews.

4. FDA should continue to ensure inter-center coordination and leverage existing expertise within FDA to review device constituent parts of CDER-led combination products, regardless of the location of the supporting documentation. The CPC recommends that the Draft Guidance provide clarity regarding review center policies and updates to any MAPPS or SOPs that provide transparency into how reviews or consulting reviews will be handled. This will help support better alignment and consistency across review centers and divisions.

5. The CPC appreciates FDA's recognition that the Type V DMF is one approach to submit supporting information for a platform device constituent of a CDER-led combination product with electronics or software. This provides sponsors with another tool that can be considered in addition to existing alternative submission types (e.g. device master file (MAF), premarket notification submission (510(k)), pre-market approval application (PMA), etc.). We agree with FDA that other master files (i.e., MAF and Type III DMF) may be appropriate for submitting platform device constituent part information to the FDA.

Specific comments:

Line	Section	Comment	Proposed Revision
25-28	Introduction	The Draft Guidance is limited to devices that incorporate software (i.e., electromechanical autoinjector or on-body device). The scope of the Draft Guidance should be expanded and the same type of submission structure should be allowed for platform mechanical autoinjectors as the submission content also needs to be reviewed by multiple centers, including CDRH, and may be platform based.	"This guidance explains when a Type V DMF may be used to submit information regarding a combination product for which the Center for Drug Evaluation and Research (CDER) has primary jurisdiction (i.e., CDER-led combination product) and which features a device constituent part ~~with electronics and/or software~~ that is planned to be used as a platform, that is, may be used in multiple CDER-led combination products."

Line	Section	Comment	Proposed Revision
			This change should be reflected throughout the Draft Guidance where "with electronics and/or software" is used.
64	Background	Please clarify when a BLA supplement/ notification is required in this process.	
194-198	IV.D. Administrative Procedures for a Type V DMF; Technical Review Process	Given that this option for Type V DMF for platform device data may be submitted by the marketing authorization holder (MAH) of the combination product(s) that will end up referencing the DMF, clarification should be provided if a separate Letter of Authorization is needed if the DMF holder and the MAH applicant for the combination product are the same and that confidentiality is not the only requirement for inclusion in the Master file.	
214-217	IV.D. Administrative Procedures for a Type V DMF; Technical Review Process	FDA notes that it will review amended DMF information and notify the applicant if it believes a submission is required. However, there is no timeframe given. If FDA disagrees with the sponsor's determination, please clarify that FDA will assess and notify the sponsor in the same way as would be done for any product change under FDA's existing regulatory authorities.	"If an amendment to a Type V DMF is submitted and no supplement or annual report to an approved application is received, FDA intends to evaluate the changes reported in the DMF amendment **as per existing processes for reviewing changes to a combination product** to determine whether a supplement to one or more approved applications is needed. If an applicant has determined that a supplement is not necessary and FDA does not agree with that decision (refer to 21 CFR 314.70 and 314.97), FDA will notify the affected applicant **as it would do under its existing regulatory authorities and timeframes**."
321-330	V.C. Content Recommendations for Type V DMF Submissions; Technical Information	The technical content listed here is not software validation or electronic testing specific and appears to contain almost all of the content required for approval of a drug delivery device. It is unclear if the DMF is replacing expectations from the BLA for non-software related information (i.e., biocompatibility, human factors, etc.). We assume FDA believes inclusion of this type of information is acceptable, and therefore proposes the scope of the Draft Guidance be expanded to mechanical autoinjectors or prefilled syringes as well.	Suggested change to footnote 18 or add new footnote 19: **The Type V DMF can replace most of the information that would typically be provided for a device constituent part in Module 3 of the marketing application. Therefore, it would be appropriate to simply reference the DMF in that section of the marketing application for platform-related data.**
330	V.C. Content Recommendations	The CPC recommends that FDA provide more context regarding what manufacturing	Replace last bullet with the following:

Line	Section	Comment	Proposed Revision
	for Type V DMF Submissions; Technical Information	information would be submitted in the DMF. We note that while the Draft Guidance covers a device and a biologic drug (BLA) combination, FDA's draft October 2019 "Drug Master Files (Revision 1)" draft guidance states (in FN 21) that applicants are "generally not permitted to incorporate information about drug substance, drug substance intermediate, or drug product by reference to a master file; rather, FDA generally expects such information to be submitted directly to the BLA." Therefore, we recommend that FDA clarify the extent of the manufacturing information expected from the device, drug product and/or the combination product that can be included in a DMF under the scope of this Draft Guidance.	**"**Manufacturing information **related to the device, drug product and/or of the combination product"**
336-339	V.C. Content Recommendations for Type V DMF Submissions; Technical Information	We recommend that FDA remove the words "scientifically valid" from line 337 as this does not add value to the intent of the statement and could lead to confusion on the part of the DMF submitter as to what is and isn't scientifically valid.	
339	V.C. Content Recommendations for Type V DMF Submissions; Technical Information	Please clarify that DMF content does not need to be included in an individual CDER submission, which diminishes the value of an efficient FDA review process, to help ensure consistency across CDER applications referencing the same information.	Add to end of paragraph: **"Once FDA has confirmed the submission is appropriate and has listed the Type V DMF number, the technical information applicable to the Type V DMF submission (or other file as provided in the proposed guidance) need not be duplicated in the individual CDER submission (IND, NDA, BLA)."**

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Overall, the CPC believes that the Draft Guidance represents a positive step forward in providing alternative options for sponsors that can help streamline the submission and review of information used in multiple CDER submissions. We appreciate the opportunity to provide input on the proposed Draft Guidance and are happy to meet with the Agency to clarify or discuss any of our suggested revisions.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition