Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

January 29, 2020

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

Re: Docket No. FDA-2013-S-0610: Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers Guidance for Industry. Document issued on October 22, 2019

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to offer comments on FDA's "Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers Guidance for Industry" dated October 22, 2019 (hereinafter the "Guidance"). We hope that FDA will consider our comments as the cumulative voice from the industry subject matter experts who develop and manufacture combination products with device constituent parts. We further hope these collaborative views will be leveraged to provide guidance that facilitates a least burdensome approach.

While the CPC appreciates the value of this Guidance in providing FDA's expectations for identification of manufacturing establishments to facilitate FDA's review and inspection activities, the CPC has some concerns and suggestions for improvement. The CPC recommends that FDA revise the Guidance by incorporating the following three areas for revision, which are discussed further below:

1. Limit the scope of sites listed on FDA Form 356h and in Module 3 to those involved in the disposition of commercial product.

[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.

2. Limit inclusion of FEI number, name and title of onsite contact person, contact details, and confirmation of inspection readiness to Form 356h in accordance with least burdensome approach.
3. Clarify that facilities manufacturing device components/sub-assemblies which are separately provided to combination product manufacturers for further modification/assembly/packaging with the drug constituent part are considered device component manufacturing facilities and should not be listed on Form 356h or in Module 3.

Below, we present our major observations, concerns, and recommendations surrounding the proposed areas for revision above.

1. Revise the Guidance to limit the scope of sites listed on FDA Form 356h and in Module 3 to those involved in the disposition of commercial product.

The scope of the Guidance includes not only manufacturing sites involved in drug substance or drug product manufacture and labeling/packaging, but also facilities used for storing or warehousing of drug substance, in-process material, quarantined material, stability samples, R&D manufacturing and testing, as well as device constituent part verification and validation testing facilities.

The CPC recommends facilities listed on Form 356h and in Module 3 should be limited to those facilities producing commercial drug substance/drug product/combination product, including: production/manufacture of drug substance/product or device assembly (exclusive of components) final finished good assembly, performing commercial product release or stability testing activities, or performing primary/secondary labeling and packaging. Under 21 CFR 314.50(d)(1), only the name and address of each manufacturer of the drug substance and drug product is required. Similarly, under 21 CFR 601.2, only the address of each manufacturer of the biological product is required. ICH M4Q(R1) specifies that the name, address and responsibilities of each manufacturer and production facility involved in manufacturing and testing be provided (in sections 3.2.S.2.1 and 3.2.P.3.1), but does not include research and development (R&D) manufacturing and testing site facilities. R&D manufacturing and testing sites, including those developing testing methods but not performing testing on commercial product, are not relevant to registration, validation, or commercial production and therefore should not be included in Module 3 of the commercial product filing.

The CPC also notes inclusion of facilities responsible for development activities in Module 3 in sections 3.2.S.2.1 and 3.2.P.3.1 creates additional confusion, as these sections are CTD sections that contain established conditions (per ICH Q12 and FDA "Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products" draft guidance) and established conditions require reporting to the Agency if changed, but the identity and responsibilities facilities responsible for the initial development activities is historical information, which will not change during the lifecycle of the product. An additional consideration is the complexities related to facilities which performed initial development activities in addition to the commercial manufacturing or testing responsibilities. If the commercial manufacturing or testing

responsibilities are withdrawn, it is not clear how the applicant would be expected to document these changes in responsibilities in the dossier.

Inclusion of other facilities, such as those performing device design control activities, including design verification or validation, is not aligned with device regulatory requirements for either Class II or Class III medical devices. Under 21 CFR 814.20(4)(v), only those facilities used for manufacture, processing, packing, storage, and, where appropriate, installation of the device" are required to be listed. For example, a laboratory performing electrical safety design verification testing for medical devices is not required to be listed as part of a 510(k) or PMA. According to 21 CFR Part 4 and in the corresponding final guidance "Current Good Manufacturing Practice Requirements for Combination Products" issued 10 January 2017, constituent parts of combination products retain their regulatory status. Therefore, the facility content requirements for device constituent parts of combination products should not exceed the requirements of comparable medical devices. The CPC accordingly also recommends that Class I and Class I-exempt medical devices should be exempt from the requirements laid out in this Guidance.

The CPC is also concerned that the facility listing requirements for combination products with device constituent parts as laid out in the current Guidance represent a regulatory paradigm that contradicts the least burdensome principles laid out in "The Least Burdensome Provisions: Concept and Principles Guidance for Industry and Food and Drug Administration Staff" issued 5 February 2019. All design verification and validation test reports, including facility information, are available to FDA upon Prior Approval Inspection of the sponsor's facility. Additionally, in the case of co-packaged or cross-labeled combination products, the manufacturing facility information should be managed in the regulatory filing of the device constituent part as required under the relevant regulatory classification rather than via duplicative effort that places additional administrative burden on the sponsor. For single-entity combination products referencing a Master Access File (MAF), the CPC recommends manufacturing facility information for finished device constituent parts be located in the MAF and not duplicated in the sponsor's filing.

Aligned with the above comments and recommendations, the CPC recommends that the facility listing content of Module 3 correspond directly with that in Form 356h and references to "inform control strategy" and "generating data in support of the application" be removed from the Guidance.

2. Limit inclusion of facility identifiers, name and title of onsite contact person, contact details, and confirmation of inspection readiness to Form 356h.

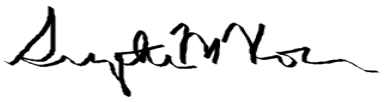
Form 356h is the repository of manufacturing site information which facilitates site inspection planning, and its content should not be duplicated in Modules 2 and 3 of the filing. Maintaining accuracy of this information within the filing content places unnecessary administrative burden on the sponsor. Inclusion of the facility identifier (e.g., FEI/DUNS number) in Modules 2 and 3 is duplicative to the inclusion in the 356h form. Additionally, onsite contacts, titles, and contact information are information which may change frequently. The CPC recommends that this information be confined only to Form 356h.

3. **Clarify that facilities manufacturing device components/sub-assemblies which are separately provided to combination product manufacturers for further modification/assembly/packaging with the drug constituent part are considered device component manufacturing facilities and should not be listed on Form 356h or in Module 3.**

The CPC recommends that FDA clarify that device component/sub-assembly manufacturers which provide components separately to combination product manufacturers for further modification which are not finished device constituent part manufacturers continue to be considered device component manufacturing facilities as clarified in the combination product GMP guidance referenced in Recommendation 1 above and should neither be listed on Form 356h or in Module 3 nor require FEI numbers.

We appreciate the opportunity to provide input on this Guidance and are happy to meet with the Agency to clarify or discuss any of our suggestions.

Yours truly,



Suzette Roan
CPC Submissions Working Group Chair
On behalf of the Combination Products Coalition