February 18, 2020

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

**Re: Requesting Food and Drug Administration Feedback on Combination Products (FDA-2019-D-4739)**

*Submitted electronically*

Dear Sir/Madam,

Biocom is the largest, most experienced leader and advocate for California's life science sector, which includes biotechnology, pharmaceutical, medical device, genomics and diagnostics companies of all sizes, as well as research universities and institutes, clinical research organizations, investors and service providers. With more than 1,300 members dedicated to improving health and quality of life, Biocom drives public policy initiatives to positively influence the state's life science community in the research, development, and delivery of innovative products. California's life sciences industry generates nearly $346 billion in annual economic output, boosts the state's total gross product by $195.8 billion, supports almost 1.3 million jobs, and increases labor income by more than $104 billion per year[1].

Biocom appreciates the opportunity to offer comments on the Food and Drug Administration (FDA) draft guidance *Requesting Food and Drug Administration Feedback on Combination Products* ("draft guidance") and thanks the agency for fulfilling its obligation under the 21st Century Cures Act to issue guidance on best practices when seeking feedback on combination products and how combination product agreement meetings (CPAMs) work.

We respectfully offer the comments and recommendations below.

Clarification on "Lead Center" Assignment for Co-packaged Convenience Kits

Section II. B covers how FDA reviews and regulates combination products based on the primary mode of action (PMOA). However, it is not clear which Center takes the lead for regulating co-packaged convenience kits. Kit regulation and jurisdiction can be confusing and is further complicated when additional processing, such as sterilization, is done to the constituent parts contained in a kit. Because a

[1] *Biocom 2019 Economic Impact Report Databook*

constituent part may be affected by a sterilization process not suitable for it, evaluation of the impact of the sterilization process on constituent parts in a kit may be necessary. To aid in providing clarity on which Center would have the jurisdiction on reviewing verification data for the different constituent parts in the convenience kit in the case of additional processing, it would be best if some examples could be included in this section.

Clarification on Device Constituent Manufacturers Feedback

Section IV discusses the feedback mechanisms available for combination products. However, this section, and the overall guidance in general, appear to be only focused on the owner of the NDA or BLA and does not provide enough assurance that feedback given to the device constituent manufacturer will be honored and transferred to the final product manufacturer. Device constituent manufacturers often request feedback about the testing needed and the information that needs to be made available through Master Files and in some cases 510(k) clearances for drug/biologic manufacturers seeking an NDA or BLA. However, this guidance appears to only be addressing the owners of the future combination product application and does not appear to include interactions that occur for device constituent manufacturers for these products. As such, we recommend adding such language to ensure that these interactions also maintain their value and that decisions made during these meetings will be honored for future customer applications.

IV Request for clarity on use of a Combination Product Agreement Meeting (CPAM) versus an application-based meeting, particularly with respect to Human Factors Studies

For application-based mechanisms, the guidance recommends that sponsors refer to applicable guidance as referenced in Appendices 1 and 2. However, the guidance does not include a reference to FDA Guidance Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (Feb 2016) which specifically recommends submission of information via the IND for FDA feedback on Human Factors Studies.

As such, we recommend adding language and examples to ensure sponsors leverage the appropriate mechanism to request feedback, particularly with respect to Human Factors Studies.

Thank you again for the opportunity to provide these comments. We look forward to a continued dialogue with the FDA on improving the regulatory framework for combination products. If you have any questions about these comments, please contact Brittany Blocker, Manager of Regulatory Affairs at bblocker@biocom.org.

Sincerely,

Joe Panetta
President and CEO
Biocom

| # | Line # | Proposed Change | Comment: Rationale/Justification for Change |
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| **1** | **4/II/B/line 88** | … combination product. Another example is for convenience kits containing drug and device components where the PMOA is the drug, the lead Center would be CDER. Convenience kit combination product manufacturers should check with the lead Center if their particular convenience kit is exempt from submission of marketing authorization. For instances where additional processing, such as sterilization, is done on the constituent parts contained in the convenience kits, convenience kit combination product manufacturers should also check with the lead Center to ensure no additional premarket submission is needed before marketing the kit. | Section II. B covers how FDA reviews and regulates combination products based on the primary mode of action (PMOA). However, it is not clear which Center takes the lead for regulating co-packaged convenience kits. Kit regulation and jurisdiction has always been confusing and is further complicated when additional processing, such as sterilization, is done to the constituent parts contained in a kit. Because a constituent part may be affected by a sterilization process not suitable for that constituent part, evaluation of the impact of the sterilization process on constituent parts in a kit may be necessary. To aid in providing clarity on which Center would have the jurisdiction on reviewing verification data for the different constituent parts in the convenience kit in the case of additional processing, it would be best if some examples could be included in this section. |

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| **2** | **9/IV/Line 241** | We recommend adding language that also speaks to device constituent part manufacturers that wish to obtain feedback about their device constituent parts that may be used by multiple drug or biologic product manufacturers.<br>For example, line 242: The sections below discuss the various ways sponsors, including device constituent part manufacturers, can interact with FDA via application-based mechanisms or CPAMs to discuss combination product issues or Master Files (MAF) used by NDA and BLA manufacturers.<br><br>Line 245: … sponsor can rely. Additionally, sponsors that manufacture a constituent parts that is not the PMOA, may also use application-based mechanisms to obtain feedback about the performance data that should be made available in a Master file (MAF) to help streamline review of NDA/BLA combination products that will utilize those specific constituent parts in the final combination product. | Section IV discusses the feedback mechanisms available for combination products. However, this section and the overall guidance in general, appear to be only focused on the owner of the NDA or BLA and does not provide enough assurance that feedback given to the device constituent manufacturer will be honored and transferred to the final product manufacturer. Device constituent manufacturers often request feedback about the testing needed and the information that needs to be made available through Master Files and in some cases 510(k) clearances for drug/biologic manufacturers seeking an NDA or BLA. However, this guidance appears to only be addressing the owners of the future combination product application and does not appear to include interactions that occur for device constituent manufacturers for these products. As such, we recommend adding such language to ensure that these interactions also maintain their value and that decisions made during these meetings will be honored for future customer applications. |

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| **3** | **IV/B Lines 280-282** | To enhance the clarity and utility of the guidance, we recommend that the guidance include specific examples to differentiate when a sponsor might request a CPAM or leverage an application-based meeting, particularly with respect to feedback regarding Human Factor Studies. These examples should be included within the body of the guidance and guidance referenced in Appendix 1 and/or 2 as appropriate. | Section III. D. includes recommendations of information to include for specific proposals grouped by discipline (e.g., Pharmacology/Toxicology, Pharmaceutical Quality/Chemistry and Manufacturing Controls (CMC), Engineering, Human Factors)...<br><br>Section IV. B "Feedback Mechanisms Available for Combination Products" refers to the use of a CPAM as a means for sponsors to obtain clarity and certainty for combination products for which the lead Center assignment is clear.<br><br>For application-based mechanisms, the guidance recommends that sponsors refer to applicable guidance as referenced in Appendices 1 and 2. However, the guidance does not include a reference to FDA Guidance Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (Feb 2016) which specifically recommends submission of information via the IND for FDA feedback on Human Factors Studies.<br>As such, we recommend adding language and examples to ensure sponsors leverage the appropriate mechanism to request feedback, particularly with respect to Human Factors Studies. |