April 13, 2017

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

Re: Docket No. FDA–2017-N-0086: Suggestions, Recommendations and Comments for Topics That May be Considered by the Food and Drug Administration Combination Product Policy Council

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding FDA's request for "Suggestions, Recommendations and Comments for Topics That May be Considered by the Food and Drug Administration Combination Product Policy Council."

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

We are generally supportive of the criteria listed to determine what topics the Council will consider. In addition to those criteria, we request that the Council develop recommendations for implementation of provisions introduced in the 21st Century Cures Act. In particular, recommendations to account for prior findings of safety and effectiveness or substantial equivalence for an approved constituent part, such as using a platform technology (e.g., same device constituent part approved with one drug used with a new drug) will be helpful. We also request more information about how the Council will address product specific inter-Center disagreements during a product's review cycle as Sponsor requests for input must come through the Office of Combination Products. Additionally, we request that the Agency provide a common lexicon to be used across Centers.

We have also provided the below detailed topic recommendations for the Council to consider:

- The Council should consider aligning recognized standards with pharmacopeia or guidances as a number of internationally recognized standards are not aligned with pharmacopeia or guidances. For example, according to pharmacopeia, applicable for drugs in syringes, Ph.Eur. 2.9.17 (Extractable volume), only 5 samples should be tested independently of the batch size (the USP has a similar requirement). For devices, when ISO 11608-1 is applied, a statistical sample size is required. Therefore, it is possible to fulfill one requirement but still fail the other. It may also be possible that if mixing syringe batches into a single combination product batch

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(i.e., into an autoinjector), the combination product may fail to comply with one or the other of the requirements because of the inter-batch variability even if the individual syringe batches fulfill both requirements.

Another example of misalignment includes the requirement for devices, if they are either packaging or a delivery package for a drug (e.g., inhalation products, prefilled syringes), to be tested to ISO standards (ISO 10993 for biocompatibility) as well as to USP standards (87 & 88 biocompatibility for packaging). This misalignment creates an unnecessary double testing requirement for devices.

- The Council should consider the issue of how misaligned communication pathways for drug-led[1] and device-led[2] reviews limit the ability to interact directly with reviewers. For example, when a Sponsor has a device under review, there is opportunity for direct dialogue with the device reviewer which fosters faster clarification and understanding of the product being reviewed and streamlines the deficiency process. Depending on the types of communications needed, the process for devices can be informal and oftentimes the CDRH reviewer will call the Sponsor directly to ask clarifying questions which facilitates the overall review process. An Interactive Review process has been adopted for device reviews which allows for multiple communication approaches based on the types of discussion needed, including one-on-one teleconferences.

  In contrast, with a drug-primary mode of action (PMOA) combination product, the communications go through the Regulatory Project Manager and follow the CDER processes. The CDER processes limit the opportunity for the Sponsor and the reviewer to ask clarifying questions because the process is much more formal. For drugs, the teleconference is coordinated by the Project Manager, requires the Branch Chief or Biopharmaceutics Team Leader approval, an agenda is prepared, required and optional attendees are identified, all attendees need clearance from their management to attend, and the Project Manager attends and takes minutes.

- The Council should consider the issue of pediatric development (e.g., age and technical differences)[3]. For example, in a single submission the rules of submission

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[1] Clarification Teleconferences Between Sponsors, Applicants, or Master File Holders on the ONDQA Review Team https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407749.pdf

[2] Types of Communication During the Review of Medical Device Submissions https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM341948.pdf
and Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements https://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0492-gdl0001.pdf

[3] For devices (includes both age and birthweight – ends at age 21): https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089742.pdf

for drug versus device are followed, but the drug review could treat 18 year olds as adults, while review of a device could consider 18 year olds as adolescents.

On the technical side, the CDER process for pediatrics is very formal, whereas on the device side there is a regulatory requirement[4] for inclusion of use in pediatrics in the submission. We recommend the Council consider developing guidance that addresses how to manage these differences for submission and post-market activities for pediatric drug-PMOA combination products.

BIO appreciates this opportunity to submit comments regarding FDA's request for "Suggestions, Recommendations and Comments for Topics That May be Considered by the Food and Drug Administration Combination Product Policy Council." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Cartier Esham, Ph.D.
Executive Vice President, Emerging Companies Section &
Vice President, Science & Regulatory Affairs
Biotechnology Innovation Organization

For Drugs (no birthweight and ends at age 16):
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071754.htm

[4] https://www.federalregister.gov/documents/2014/01/10/2014-00267/medical-devices-pediatric-uses-of-devices-requirement-for-submission-of-information-on-pediatric