April 12, 2020

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

Re: Docket No. FDA–2019-D-5585: FDA Draft Guidance, Bridging for Drug-Device and Biologic-Device Combination Products.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance, Bridging for Drug-Device and Biologic-Device Combination Products.

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's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO commends FDA for the development of the Draft Guidance on Bridging for Drug-Device and Biologic-Device Combination Products. Developers continue to face challenges with combination product development and review and guidance such as this provides important information for developers and helps alleviate challenges. BIO believes that the Draft Guidance presents a reasonable approach to bridging for combination products. The Draft Guidance appropriately provides a framework for sponsors to use in assessing what data are required for bridging and BIO believes that the approach taken in this Draft Guidance is more appropriate and flexible than outlining specific requirements for every bridging study. BIO has outlined in this letter suggestions for FDA's consideration as the FDA is finalizing the Guidance.

BIO appreciates the opportunity to submit comments regarding FDA's Draft Guidance, Bridging for Drug-Device and Biologic-Device Combination Products. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 24-30	In this Section FDA outlines the types of products that the FDA provides recommendations on in the Draft Guidance, including "*Bridging of information related to a combination product that employs a different device constituent part or parts with the same drug constituent part or parts as the proposed combination product.*" However, it would be helpful to include in the scope of the Draft Guidance bridging of information related to a combination product that employs the same device and drug product with a different clinical indication for use.	BIO requests that the FDA consider including in the Draft Guidance and the scope of the document, bridging of information related to combination products that employ the same device and drug product with a different clinical indication for use, along with an example.
II. STANDARDS		
III. DEVELOPING AN ANALYTICAL FRAMEWORK FOR IDENTIFYING INFORAMTION GAPS TO INFORM A BRIDGING AND LEVERAGING APPROCH		
Lines 167-170	In the guidance, Step 2 for bridging requires knowledge of the safety and effectiveness submission requirements. However, since the approach for the Draft Guidance takes the perspective of the manufacturer to assess whether bridging is possible, it is not uncommon for manufacturer bridging assessments to be less conservative than the Agency's bridging assessment. Therefore, it would be helpful if there were additional details in the Draft Guidance on safety and effectiveness requirements for combination products. Furthermore, the guidance does not provide clarification of the Agency's clinical data requirements	BIO requests that the FDA include considerations sponsors may want to assess when seeking to demonstrate clinical safety and effectiveness requirements for combination products. In particular, it would be helpful to include examples of what might merit real-life patient handling studies, and device robustness studies. Furthermore, options for study design (e.g., number of patients, types of data needed to be collected, how the data should be collected, etc.) would be also helpful.

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	or bridging opportunities related to 'real-life patient handling experience' or 'device robustness' (terms initially introduced in the FDA guidance for *Rheumatoid Arthritis: Developing Drug Products for Treatment*).	
IV. BRIDGING AND LEVERAGING EXAMPLES		
Entire Section	It would be helpful to include an example to address how data from a platform device should be bridged or leveraged across multiple drug products, and how sponsors could assess this prospectively. As many companies are moving toward a platform approach for the device constituent part, it would be helpful to have a forward-looking example about how data for the platform device can be leveraged in future submissions. BIO appreciates the bridging and leveraging examples discussed in the draft in section IV; specifically on bridging within an IND from a drug developed in a prefilled syringe to a drug developed in an autoinjector, and bridging from one autoinjector (prototype 1) to another autoinjector (prototype 2) for the same drug after phase 3 studies have been completed but before NDA submission, but it would be helpful to provide examples and considerations for marketed products on using bridging when changing the delivery device post-approval. To this end, BIO request that FDA provide an example, for instance, on bridging from a drug in a prefilled syringe to the drug/biologic in an autoinjector, or from one autoinjector (prototype 1) to another autoinjector (prototype 2) for the same drug/biologic after	BIO requests that FDA provide an example in the Guidance that addresses bridging in the context of a platform product.

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	NDA/BLA has been submitted or approved (i.e. considerations for marketed products on using bridging when changing the delivery device post-approval).	
Lines 212-214	FDA notes in this section that sponsors should use the final finished combination product in the drug clinical studies wherever possible, so there is no need for bridging. This may be necessary for some combination products (e.g. drug-eluting stents or implantables) but should not necessarily be required for all combination products. In some cases, such as drug delivery devices and autoinjectors, something as close as possible in functionality and usability to the final product may be appropriate.	BIO requests that FDA indicate in this section of the Draft Guidance that for some combination products it may not be necessary for the Sponsors to use the final finished combination product in the drug clinical studies. It would also be helpful for the FDA to indicate in the Guidance a few examples to demonstrate this point.
Lines 298-309	In this section FDA provides an example to illustrate Step 4, "The Applicant considers whether other existing information may be leveraged to support the items in Step 4." The text indicates that it will be challenging to bridge the human factors validation study for the autoinjector and indicates that the prior human factors study was conducted with a different disease state, indication, and is used in a different patient population with differing injection sites. However, it is unclear why specifically these differences would necessitate a new human factors study. It would be helpful if the Draft Guidance identified the specific patients risks that exist and gaps in the existing human factors study/methodology that would need to be evaluated and why. Similarly, it would be helpful to understand the Agency's views on bridging prior real-life patient	BIO requests that the Draft Guidance address the specific patients risks that exist and gaps in the existing human factors study/methodology that would need to be evaluated in a new human factors study and why. To this end, BIO requests the following edit: "The applicant recognizes, however, that since the product was developed for another population and indication, it will be challenging to bridge the applications. **Specifically, the applicant has identified new patient risks (e.g., reduced dexterity and/or reduced cognitive ability) with the new patient population. As such, the applicant ~~and~~** intends to conduct a HF validation study and prepare a HF validation study report to be submitted as part of the marketing application."

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	handling studies following the same types of changes.	For similar examples, BIO requests that the Daft Guidance also address the specific patients risks that exist and gaps in existing real-life patient handling study/methodology that would need to be evaluated in a new real-life patient handling study and why.
Lines 325-332	This section indicates that additional clinical information to assess local adverse events may be required as the new drug may impact injection time/rate which may impact pain of delivery. It would be helpful if the guidance explicitly includes examples for when/why the Agency would consider a difference in injection time to necessitate new local adverse event data as a justification could likely address whether the injection site pain risk necessitates clinical data.	BIO requests that the Draft Guidance provide examples for when/why the Agency would consider a difference in injection time to necessitate new local adverse event data as a justification could likely address whether the injection site pain risk necessitates clinical data.
Line 341-345	The text indicates that the applicant intends to provide "*a copy of design control documentation for the delivery system and combination product*". It is unclear what is meant by "a copy."	To clarify this section, BIO requests the following edit: "*The applicant also intends to provide* ~~***a copy of***~~ *design control documentation for the delivery system and combination product as a whole, . . .*"
Lines 353-359	The text indicates that additional clinical data may be necessary if PK differences are observed in the PK profile between the two presentations (e.g., in maximum concentration, in area under the curve, in shape of the concentration-time profile). Reference is also made to the FDA draft guidance for industry on Bioavailability Studies Submitted in NDAs or INDs-	BIO requests that the Draft Guidance note that sponsors still have the option to scientifically justify that any differences observed in PK do not impact safety or effectiveness.

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	General Considerations[1] which states "*When similarity in bioavailability is not demonstrated, the sponsor should demonstrate that the differences in the rate and extent of absorption do not meaningfully affect the safety and efficacy of the drug product based on the available dose-response or concentration-response data.*"	
Lines 393-394	In this section FDA provides an example where the drug is the same, but design changes are made to an autoinjector, that "*differences in functional performance of the device constituent part, if any, may affect the drug constituent part.*" The reference to the "drug constituent part" is unclear especially because quality of the drug constituent part is referenced in previous sentences in this bullet point.	For clarity, BIO requests the following edit: "*However, differences in functional performance of the device constituent part, if any, may affect the drug* ***delivery***."
Lines 411-416	In this section the text notes that combination product characteristics such as dose accuracy, injection depth, injection time, and activation force are examples of factors that could affect the drug delivery and *should* be assessed over combination product shelf life. However, it is possible that these characteristics have alternate controls in place that ensure the combination product meets its predefined specifications. As such, it should not be implied that these characteristics *should* be assessed over the combination product shelf life as other controls may be in place to ensure product quality.	BIO requests the Following edit: "The applicant is aware that the above are examples of factors that could affect the drug delivery and should be assessed over combination product shelf life **unless other controls are in place to ensure product quality that preclude an assessment over the product's shelf life.**"

[1] FDA Draft Guidance on Bioavailability Studies Submitted in NDAs or INDs-General Considerations

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Lines 529-532	For this example, the Draft Guidance indicates that "*because of these differences between Combination Products A and B that could affect device design and performance, the applicant determined that phase 3 clinical studies of Combination Product B, including the TBM device, are needed as well as other design verification testing for Combination Product B.*" It is understood that because an NME is being incorporated with an existing device that phase 3 data may be required to determine safety and effectiveness of Combination Product B. However, it is unclear why phase 3 clinical studies would be needed to address differences that could affect device design and performance.	BIO requests that the FDA provide additional detail and or examples to clarify what device design and performance differences could not be addressed by design verification testing and would additionally require phase 3 clinical studies as cited in this example.
A. Bridging Withing an IND from a Drug Developed in a Prefilled Syringe to a Drug Developed in an Autoinjector		
B. Bridging from One Autoinjector (Prototype 1) to Another Autoinjector (Prototype 2) for the Same Drug; After Phase 3 Studies have Been Completed but Before NDA		
C. Bridging of Data from Combination Product That Employs the same Device Combined with a Different Drug		