Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

April 6, 2021

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

Re: Docket No. FDA-2020-D-2101; Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to provide comments on FDA's "Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry," dated January 11, 2021 (the "Draft Guidance").

We greatly appreciate FDA's efforts to provide guidance for delivery devices used with human gene therapy products, which are important in ensuring these products can achieve their full life-saving benefit in treating patients. Detailed below are three CPC comments related to the delivery device expectations described within the Draft Guidance, followed by additional discussion (and examples) supporting our general recommendation that FDA allow additional flexibility in sponsors' use of delivery devices.

Comment #1: Use of "Representative" Delivery Devices

Page	FDA Guidance Text	CPC Proposed Revisions
4	When a device is used to deliver the investigational product, compatibility of the product with the delivery device should be demonstrated prior to initiating Phase 1 safety studies (21 CFR 312.23(a)(10)(iv) and 21 CFR 312.23(a)(11)). Such studies should be carried out with the final formulated product that is intended to be used in the	When a device or devices is/are used to deliver the investigational product according to the device's cleared or approved indications for use, compatibility of the drug product with the drug product contacting delivery device(s) should be demonstrated prior to initiating Phase 1 safety studies (21 CFR 312.23(a)(10)(iv) and 21 CFR

[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.

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	clinic, under conditions that would mimic those planned in the clinic. Specifically, the delivery device, product concentration (tested over the planned dose-range), drug product formulation, final infusion volume, duration and rate of infusion, and temperature should be the same for the device compatibility studies as they will be in the clinic.	312.23(a)(11)). Such studies should be carried out with the final formulated drug product (e.g., including the range of product concentrations or dose volumes) that is intended to be used in the clinic, under conditions that would mimic those planned in the clinic (e.g., temperature, hold times, or light exposure). For non-drug product contacting devices that may be used to deliver the investigational product, sponsors should consider appropriate performance requirements that adequately address the intended use of the delivery device in the clinical study, such as final delivery volume, duration and/or rate of delivery in conducting compatibility studies. When multiple equivalent devices are cleared or approved for delivery, sponsors may establish acceptability of representative devices through their established performance requirements.

The CPC agrees that the compatibility of the investigational product should be carried out with the final formulated product under conditions that mimic those of the clinic. However, the statement indicating that the device should be the "same" is overly restrictive; sponsors should be able to use "representative" cleared or approved devices for delivery when they are used according to their generally cleared or approved indications for use. As such, we recommend that FDA specifically allow "representative" delivery devices and clarify the requirements for drug contacting vs. non-drug contacting delivery devices, as further discussed below.

Product Contacting Devices

For product contacting devices, FDA should allow the sponsor's drug-device (or biologic-device) compatibility testing to be extrapolated to other devices that are constructed of the same materials, e.g., general types of delivery devices like syringes, needles, drug transfer devices, and infusion sets. This approach allows a sponsor to ***specify representative materials and relevant device characteristics*** (e.g., needle gauge, needle length, and small bore connector type) in clinical protocols, which subsequently allows the clinical site to select the appropriate device brand and model. If a range of device characteristics (e.g., needle length to accommodate differences in patient anatomy) is required, the sponsor could conduct compatibility testing with multiple device variants or by employing a bracketing approach.

Being able to specify by material type and device characteristics is important as it is not always practical or even possible to restrict clinical use to only one or a few specific brands of product

contacting delivery devices that comprise the delivery system. It is common practice for clinical institutions to restrict use to a specific device(s) based on specific policies and/or contracts at the institution as well as regional commercial availability. In addition, there is value in allowing use of devices available at the clinical site as these are associated with the greatest health care professional ("HCP") experience and training.

A sponsor may also choose to stipulate a device brand and model number in the IND and/or procure these for the clinical site to standardize delivery devices used in early clinical studies. In these cases, it is not appropriate to consider these cross-labeled combination products according to 21 CFR 3.2(e). The investigational drug or biologic is not intended for use only with an approved individually specified device; rather, the sponsor is merely attempting to ensure consistency of data generation during the study. Upon approval of the proposed product, the labeling of the approved product would not be intended to specify a particular device. It should still be appropriate to limit the evaluation of drug contacting devices to physical and chemical compatibility between the investigational product and device materials as outlined above.

The CPC believes that the Draft Guidance and FDA should re-evaluate the "combined use" (drug/biologic referencing a device) policies it is internally applying for investigational use and product approval of essential, selective delivery devices for human gene therapies for neurodegenerative (and other similar) diseases. The CPC does not consider these as cross-labeled combination products that require additional safety and effectiveness testing. Instead, the potential regulatory pathway for these delivery devices may result in "combined use" where an FDA-regulated product may reference another general class or specific product, but does not meet the definition of a combination product. The CPC authored a white paper in 2020, available on the CPC website,[2] which includes additional information and detail on challenges related to "combined use" of investigational products and cleared or approved devices.

Recent Agency feedback in applicants' IND submissions has included additional requirements for testing brand name devices (by model number) that have been 510(k)-cleared or approved and used by the sponsor within the cleared or approved indications for use. It should be sufficient to reference the delivery device and applicable 510(k) number for "combined use" scenarios. FDA should accept this as sufficient evidence that the legally marketed device meets the appropriate safety and effectiveness requirements, and its design has been sufficiently verified and validated to allow use in a clinical trial.

In recent IND applicants' submissions, the Agency has requested that the sponsor provide multiple Letters of Authorization ("LOAs") for devices specified in the IND even when they are to be used within the cleared or approved intended use of the device(s). However, this is inappropriate for the reasons stated above. The use of the device in this scenario is akin to an HCP procuring the cleared or approved device and using it off the shelf in the appropriate intended use population, in clinical practice. Additionally, this may limit sponsors to specific devices when other representative devices could be safely used or when a LOA cannot be obtained. It also opens a panoply of issues for other drug and biologic clinical trials, such that sponsors might be required to obtain LOAs

[2] CPC, *Proposed Cross-Labeling/Combined Use Guidance Considerations* (Aug. 2020), www.combinationproducts.com/wp-content/uploads/2020/09/CPC-CL-WG-Proposed-Cross-Labeling-Guidance-Considerations-Aug-2020.pdf.

every time a device is used on-label in their trial, which has not been the historical practice for drug studies. The CPC notes that sponsors may not have established a strategy for the marketing application at the time device(s) are introduced into clinical trial(s) and thus the data supporting device usage in this application will likely be collected during clinical development. In these instances, including the 510(k) number in the IND should be sufficient evidence that the device is sufficiently verified and validated and has met all FDA requirements for use in this population. We recommend that the Draft Guidance add recognition of these distinctions and provide additional guidance on this topic.

Non-Product Contacting Devices

For non-product contacting devices (e.g., infusion pumps, reusable injection pens, or cranial navigation systems), the CPC agrees that compatibility studies should be performed with delivery devices, though, similar to the points raised above, the device used in the clinical study may not need to be specifically identified. As described in FDA guidance,[3] the sponsor should perform in-device compatibility studies that support the recommended hold times and conditions outlined in the clinical protocol for patient administration. However, re-testing a cleared or approved device for accuracy parameters, for example, irrespective of its clinical use indication, should not be necessary as its performance is the same regardless of the indication: the clearance or approval of tested infusion performance specifications is evidence itself of this performance.

The devices to be used in a clinical trial, if identified, should be specified as meeting the required performance characteristics that "mimic" the studies planned for the clinic. The sponsor should be allowed to specify device ***performance characteristics*** (such as flow rate, injection/infusion time, etc.) that can be included in clinical protocols that would enable safe delivery. By determining the acceptable performance characteristics, a sponsor can allow multiple cleared or approved devices that meet the performance specifications.

Comment #2: A Risk-Based Approach for Sponsors' Use of a Delivery Device Falling Outside its Cleared or Approved Indications for Use

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4-5	If a sponsor plans to use a delivery device within the cleared or approved indications for use, compatibility of the investigational product with the delivery device should be demonstrated prior to initiating Phase 1 safety studies, as discussed above. If use of a delivery device falls outside the cleared or approved indications for use or if the delivery device has not been cleared or approved by the FDA for any indication, we recommend early discussion with	If a sponsor plans to use a delivery device within the cleared or approved indications for use, compatibility of the investigational product with the delivery device should be demonstrated prior to initiating Phase 1 safety studies, as discussed above. If use of a delivery device falls outside the cleared or approved indications for use, sponsors should conduct compatibility testing prior to Phase 1 safety studies and conduct a hazard analysis to determine the

[3] FDA, *Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs): Guidance for Industry* (2020), https://www.fda.gov/media/113760/download.

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	FDA (see section VI of this document) to determine the additional information that may be needed to inform FDA's safety evaluation of the delivery device when used with the investigational product for the proposed clinical use.	additional information that may be needed to inform FDA's safety evaluation of the delivery device when used with the investigational product for the proposed clinical use. If the delivery device has not been cleared or approved by the FDA for any indication, we recommend early discussion with FDA (see section VI of this document) to determine the additional information that may be needed to inform FDA's safety evaluation of the delivery device when used with the investigational product for the proposed clinical use.

The CPC agrees with the need to perform additional evaluations for delivery devices used outside the cleared or approved indications for use, or if the device has not been cleared or approved (i.e., is purely investigational). We also agree with the Draft Guidance recommendation for early discussion with FDA, but suggest that FDA also include specific language supporting a risk-based approach to inform such engagement and make the most efficient use of time for both the sponsor and FDA. Additional rationale is provided below and focuses on already cleared or approved devices that are being used outside their indications for use. In the CPC's view, the Draft Guidance would benefit from additional guidance (for industry and FDA) on delivery devices so that there is clarity on delivery device requirements throughout investigational phases and for commercial labeling.

For both product contacting as well as non-product contacting devices, a gap assessment between the cleared or approved indications for use and the clinical indications for use should be performed to identify additional materials testing in addition to drug-device compatibility. This is a risk-based assessment to identify whether any information, such as covering endotoxin, biocompatibility, or extractables/leachables, is required to meet materials requirements for the clinical indications for use for product contacting devices.

For non-product contacting devices, the labeled performance specifications should be the predominant factor in determining suitability for the clinic rather than the original cleared or approved indication. A gap assessment between the cleared or approved indications for use and the clinical indications for use is also appropriate to identify required safety and effectiveness data, if any, to support the clinical studies. Appropriate risk assessment would show that the specified devices or qualified alternates would not present significant new questions of safety and effectiveness even though the indications compared to their clearances are new. This approach allows the sponsor to specify an appropriate range of operating parameters, which supports allowing devices available at the clinical site rather than restricting to specific brands/models.

The CPC recognizes that, in many cases, target organs (e.g., intraventricular or intracerebral structures) for neurodegenerative therapies need specific operational procedures and specific administration devices to ensure the safety and effectiveness of the proposed gene therapy.

However, product-contacting cleared or approved devices with demonstrated compatibility, and non-product contacting devices (e.g., infusion pumps) that have been used for multiple routes of administration, generally do not present a substantial risk in their use in early phase clinical studies.

For delivery devices that are not approved or cleared (i.e., investigational), the CPC agrees that supplemental supporting information will be needed. The CPC recommends that the Draft Guidance include reference to FDA guidance for design and development of medical devices and required submission information to support clinical evaluation.

Comment #3: Flexibility in Specifying the Delivery Device and Procedure in Study Protocols

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10	To ensure consistency across study sites, sponsors should include in the study protocol a detailed description of both the product delivery procedure and the devices used for delivery.	To ensure consistency across study sites, sponsors should provide sites with a detailed description of both the product delivery procedure and the devices used for delivery. In situations in which more than one cleared or approved device may be suitable for delivery of the investigational product, sponsors should provide sites with adequate performance requirements that enables the study site to determine a compatible cleared or approved device suitable for delivery of the investigational product.

In line with the above comments, we do not believe that sponsors should be required to include a detailed description of both the product delivery procedure and the devices used for delivery in the study protocol, except when the device is investigational and not cleared or approved for any indications for use. This should be an option to ensure consistency across study sites, but not a requirement provided the sponsor specifies the device performance and material characteristics that can used to safely deliver the investigational product. As stated above, it may be impractical to restrict or specify the device and procedure used in the clinical study. Additionally, it is not the expectation in other drug or biologic trials, where a lyophilized product may need to be reconstituted by the site prior to delivery in the clinic or where an infused product may be administered in the clinic. In those cases, sponsors have historically provided information in the protocol such that the site can identify a compatible device. In addition, restricting delivery devices for investigational drugs in situations where the commercial use will likely be with multiple delivery system options, restricting the system used in the study may not be sufficiently representative of expected results.

The CPC agrees that the study protocols (or related documents, such as a surgical manual for the study) should specify appropriate devices needed to ensure the safety to patients and the collection of valid study data. This may involve use of specific target-tissue-specific cannulas/catheters as well as generic ancillary devices that could be specified and available to the investigator. However, the Draft Guidance should clarify when devices (not part of the fluid path or surgical delivery)

may be specified (e.g., infusion pumps meeting the infusion requirements) generally rather than by brand name and model.

Examples Supporting Flexibility in Sponsors' Use of Delivery Devices

To illustrate industry's concern with differences in device specificity required by FDA, we have provided below two examples based on final labeling of a gene therapy and biologic product. Although the CPC recognizes that these examples have limitations (i.e., they may not be the intended neuronal tissue, were approved by different Centers, and one was a biologic used for a neurodegenerative disease), we view these as generally useful examples that support flexibility in the use of delivery devices while accounting for the characteristics for those devices needed to assure safe and effective use.

- Regarding the devices used for subretinal delivery of the gene therapy LUXTURNA® (voretigene neparvovec-rzyl), as described in the US prescribing information ("USPI"), the devices listed for the required procedure are described generically in the USPI with their key characteristics specified. These include a 3-mL sterile syringe, a 20G 1-inch sterile needle, 1-mL sterile syringes, 27G ½-inch sterile needles, and specific to the product delivery to tissue, a "subretinal injection cannula with a polyamide micro tip with an inner diameter of 41gauge" and an "extension tube made of polyvinyl chloride no longer than 6" (15.2 cm) in length and with an inner diameter no greater than 1.4mm."[4] Only the vialed product and diluent is supplied.

- In contrast, the approved USPI for BRINEURA® (cerliponase alfa) injection, for intraventricular use, lists specific devices that must be used to perform the administration.[5] These include a branded intracerebral reservoir (three part numbers listed), a branded ventricular catheter (part number listed), and a branded syringe infusion pump (catalog product code listed, although alternative pumps may be used that meet listed rate and accuracy specifications, occlusion alarm specifications, and are cleared for intraventricular route of administration). The product is supplied with a convenience kit described as containing unbranded 20 mL syringes, 21 G, 25.4 mm syringe needles, an extension line, an infusion set with 0.2 micron filter, and a port needle.

These two examples demonstrate the issues that the combination products industry faces in defining a mix of devices that could be used in Phase 1, 2, and 3 studies, and eventually labeled for commercial use as ancillary delivery systems needed for a gene therapy product for neurodegenerative diseases (or any other gene therapy for administration to a target tissue). It is highly likely that devices specified for a Phase 1 study will be changed or refined for subsequent clinical trials or for commercial launch (with appropriate risk-based or test bridging) such that full approval-level characterization (e.g., fluid path biocompatibility, leachable/extractables, infusion rate/volume accuracy, ISO testing, etc.) is not needed whenever a minor change to the described infusion devices in clinical trial protocols is advanced. Many of these infusion devices have already

[4] https://sparktx.com/LUXTURNA_US_Prescribing_Information.pdf.
[5] https://www.brineura.com/wp-content/themes/jupiter-child/assets/pdfs/resources/Brineura-Prescribing-Information.pdf.

undergone drug contacting fluid-path testing using long-term extractions and elutions of the device materials satisfying their 510(k)-clearance requirements for cytotoxicity, sensitization, irritation, acute system toxicity, pyrogenicity, and hemolysis (and for implants, additional testing such as genotoxicity and implantations testing).[6]

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In addition to the comments provided above on the Draft Guidance, we also note that the absence of specific FDA guidance on how best to qualify cleared medical devices, or define specifications for them, is also a concern for these gene therapies. Further FDA guidance on "combined use" products would be valuable to standardize the requirements expected by industry to evaluate cleared and approved devices for "combined use" instead of requiring ad hoc requirements in each IND submission.

The potential for "combined use" strict interpretation by FDA, as a potential labeling expectation, and throughout development phases, remains a significant regulatory uncertainty. Highly specific labeling expectations for branded infusion devices are also likely to present lifecycle change and submission amendment and supplement change challenges as specific branded devices become obsolete and are replaced with improved devices. Such clarification in guidance would allow for more efficient and effective communication between industry and FDA, which would in turn facilitate faster initiation of clinical studies for these therapies and, ultimately, a more streamlined path to a commercial application.

The CPC supports the further development of the Draft Guidance and encourages FDA to incorporate additional clarity in the final guidance regarding the qualification of both routine infusion devices and specialized, surgical access delivery devices. We appreciate the opportunity to provide input on the Draft Guidance and welcome any questions or further discussion.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

[6] FDA, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process:" Guidance for Industry and FDA Staff* (2020), https://www.fda.gov/media/85865/download.