December 14, 2023

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

Re: Docket No. FDA-2023-D-2318 for *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*

Dear Sir/Madam:

The Alliance for Regenerative Medicine (ARM) is pleased to submit comments to the US Food and Drug Administration (FDA) in response to recently released draft guidance titled, *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence.*

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis.

We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

**General Comments**

ARM finds the issuance of this draft guidance document to be helpful to complement the draft guidance document, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) and the guidance document, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).

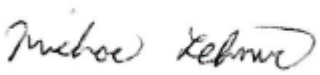
ARM appreciates the acknowledgment that disease-specific considerations, such as unmet need and size of the patient population, may be relevant to whether using one trial plus confirmatory evidence is appropriate (lines 150 – 152). We recommend restating from the 2019 Effectiveness draft guidance that a "second trial may be infeasible in certain rare disease settings where the limited patient populations preclude the conduct of a second trial," in which

case, "the substantial evidence of effectiveness would typically be provided by a single trial plus confirmatory evidence."

We also agree that under certain circumstances, a sponsor should be able to use evidence of effectiveness of a drug from a clinical investigation in a different, but closely related indication to provide confirmatory evidence of effectiveness. Doing so has the potential to enhance the efficiency of therapeutic development. In addition, ARM supports that mechanistic data may be appropriate for use as confirmatory evidence, such as when a disease is caused by a single gene and/or enzyme defect and the drug's mechanism of action corrects the enzymatic or genetic defect or its sequelae.

We identify below specific recommendations for changes and additions to the guidance document during finalization to be most beneficial to cell and gene therapy development. ARM appreciates your consideration of these comments.

Sincerely,



Michael Lehmicke
Vice President, Science and Industry Affairs

| **Specific Line-by Line Comments: Section/Line** | **Guidance Text** | **Rationale for Change or Comment** | **Proposed Change** |
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| II. Background and Scope | | | |
| Lines 101 – 109 | "The finding of substantial evidence of effectiveness is necessary but not sufficient for FDA approval. An approval decision, among other things, also requires a determination that a drug is safe for its intended use.[7] As all drugs can have adverse effects, evaluating whether a drug is "safe" involves weighing whether the benefits of the drug outweigh its risks. In some | ARM Comment: ARM believes the intent of this section is to indicate that additional safety data may be required if the original data insufficiently demonstrate safety, which is a potential in all clinical development plans. Typically, expectations for the number of participants and duration of study would be discussed with the Agency during product development, so these factors may not be the | "The finding of substantial evidence of effectiveness is necessary but not sufficient for FDA approval. An approval decision, among other factors ~~things~~, also requires a determination that a drug is safe for its intended use.[7] As all drugs can have adverse effects, evaluating whether a drug is "safe" involves weighing whether the benefits of the drug outweigh its risks. In some cases, ~~one adequate and well-controlled clinical investigation and confirmatory evidence may demonstrate effectiveness,~~ |

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| | cases, one adequate and well-controlled clinical investigation and confirmatory evidence may demonstrate effectiveness, but the clinical trial may not have enrolled a sufficient number of participants or have treated them for a sufficient duration to conclude that the drug is safe. A second trial may be needed to ensure a safety database of adequate size and duration to support an appropriate benefit-risk assessment. Considerations for a safety evaluation, a benefit-risk analysis, and their impact on the acceptability of one trial with confirmatory evidence to support approval are beyond the scope of this guidance." | most relevant examples of instances in which a trial may yield insufficient safety data. We suggest striking this portion for clarity.<br><br>ARM also suggests stating that obtaining sufficient safety data for a benefit-risk assessment to support approval may require either obtaining more data from another clinical trial, as stated, or using a robust pharmacovigilance plan, as is required for gene therapies. The latter approach may be especially appropriate for rare, serious diseases, which may have too small of populations to do a second trial and/or may have high unmet need that frequently makes the benefits sufficiently outweigh the risks with data from one trial, while continuing to monitor safety over a longer term. | ~~but the clinical trial may not have enrolled a sufficient number of participants or have treated them for a sufficient duration to conclude that the drug is safe. A second trial may be needed to ensure a safety database of adequate size and duration to support of~~ an appropriate benefit-risk assessment~~.~~ may need to include either a second clinical trial or a robust pharmacovigilance plan (PVP) to address knowledge gaps and assess longer-term safety. For example, the PVP for gene therapies may include the required long-term follow-up study (reference *Guidance for Industry: Long-Term Follow-Up After Administration of human Gene therapy Products*), which may be sufficient to support safety data from one investigation. Further c~~C~~onsiderations for a safety evaluation, a benefit-risk analysis, and their impact on the acceptability of one trial with confirmatory evidence to support approval are beyond the scope of this guidance." |
| III. Types of Confirmatory Evidence | | | |
| A. Clinical Evidence from a Related Indication | | | |
| Lines 185 -187 | "Under certain circumstances, evidence of effectiveness of a drug from a clinical investigation for a particular indication can provide confirmatory evidence of effectiveness to | ARM Comment: While the guidance provides some factors that affect the determination of what a related indication is, further definition would be helpful of what a related indication is and what kind of data, evidence or rationale | "Under certain circumstances, evidence of effectiveness of a drug from a clinical investigation for a particular indication can provide confirmatory evidence of effectiveness to support approval of the drug in a different but closely related indication. For example, |

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| | support approval of the drug in a different but closely related indication." | FDA would expect for a sponsor to sufficiently demonstrate that a given indication is related to another for the purpose of using one trial as confirmatory evidence for another.<br><br>We also would support the provision of an example, as indicated to the right. | demonstration of clinical efficacy for a therapeutic addressing a common genetic variant of a rare disease could provide confirmatory evidence for a therapeutic targeted toward a much rarer genetic variant of that same disease." |
| B. Mechanistic or Pharmacodynamic Evidence | | | |
| Lines 250 - 259 | "Examples of when mechanistic data may be appropriate for use as confirmatory evidence include the following:<br>• When the disease is caused by a single gene and/or enzyme defect and the drug's mechanism of action corrects the enzymatic or genetic defect or its sequelae. For example:<br>– An enzyme replacement therapy that corrects the underlying enzymatic deficiency in a lysosomal storage disease at the affected target tissues or organs (e.g., laronidase in mucopolysacchari-dosis type I)" | ARM comment: ARM supports FDA acceptance of mechanistic data as confirmatory evidence. A common mechanism of action of gene therapies is to correct a genetic defect/mutation and its sequelae. We therefore recommend that gene therapy be listed as an example of when mechanistic data may be appropriate for use as confirmatory evidence. | "Examples of when mechanistic data may be appropriate for use as confirmatory evidence include the following:<br>• When the disease is caused by a single gene and/or enzyme defect and the drug's mechanism of action corrects the enzymatic or genetic defect or its sequelae. For example:<br>– An enzyme replacement therapy that corrects the underlying enzymatic deficiency in a lysosomal storage disease at the affected target tissues or organs (e.g., laronidase in mucopolysaccharidosis type I)"<br>– A gene therapy that corrects the underlying gene mutation in the disease-relevant tissue. |
| C. Evidence from a Relevant Animal Model | | | |
| Lines 296 - 299 | "Infrequently, however, sponsors can use data from an established animal model of disease as confirmatory | ARM Comment: ARM welcomes Agency flexibility in allowing use of animal data as confirmatory evidence of effectiveness in | "~~Infrequently~~ In some instances, however, sponsors can use data from an established animal model of disease as confirmatory evidence of |

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| | evidence of effectiveness; in such cases, sponsors should discuss in advance these planned nonclinical studies with the appropriate FDA review division." | certain circumstances. We recommend extending the consideration of animal data as confirmatory evidence in circumstances that challenge the ability to gather additional human data, such as for products for rare diseases. | effectiveness, such as in circumstances that challenge the ability to gather additional human data, such as for products for rare diseases; in such cases, sponsors should discuss in advance these planned nonclinical studies with the appropriate FDA review division." |
| E. Natural History Evidence | | | |
| Lines 363 - 368 | "In certain circumstances, natural history data can provide confirmatory evidence to substantiate the results of a single adequate and well-controlled investigation. Such an approach can be useful when there is uncertainty about whether the outcomes observed in the control group accurately reflect those that would have been expected in the absence of the intervention. Natural history data being used as confirmatory evidence should be distinct from any data used as a control for the single adequate and well-controlled clinical investigation." | ARM Comment: ARM supports the Agency position that natural history data can provide confirmatory evidence for a single adequate and well-controlled trial. We appreciate the provision of examples in this section, as well. A footnote may be helpful that refers readers to the 2019 Effectiveness draft guidance for additional information about the use of natural history as a control group. | |
| F. Real-World Data/Evidence | | | |
| Lines 408-413 | "Whether an RWD source may be appropriate to develop RWE that serves as confirmatory evidence | ARM Comment: Examples would be helpful to illustrate situations in which confirmatory evidence developed from an | |

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| | depends on several factors, including but not limited to the reliability and relevance of the RWD source and, when relevant, the quality of the study design and the use of appropriate prespecified statistical methods and analyses. FDA recommends that sponsors discuss with the relevant review divisions any plans to use RWE as confirmatory evidence in a drug development program." | RWD source, such as a post-market registry, combined with one adequate and well-controlled clinical investigation, could be considered sufficient to meet expectations for substantial evidence of effectiveness. | |
| G. Evidence from Expanded Access Use of an Investigational Drug | | | |
| Lines 432 – 439 | "… if the patient outcome information collected under expanded access use of the drug is of sufficient quantity and quality to be highly persuasive, the information may be considered for use as confirmatory evidence. Typically, however, only limited and inconsistent information is available from expanded access … and such information provides an incomplete picture of the course of events, which may make the information unfit for use as confirmatory evidence." | ARM Comment: ARM welcomes Agency acceptance of information collected under expanded access as confirmatory evidence in some instances and appreciates the provision of an example. It would be helpful to provide additional hypothetical or de-identified examples of instances in which expanded access data would be fit for use. | |