Alliance for Regenerative Medicine

March 19, 2020

Dockets Management (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Comments for FDA Docket Number: FDA-2019-D-4964; Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; Draft Guidance for Industry; Availability

The Alliance for Regenerative Medicine (ARM) is an international multi-stakeholder advocacy organization that promotes legislative, regulatory and reimbursement initiatives necessary to facilitate access to life-giving advances in regenerative medicine worldwide. ARM is comprised of more than 350 leading life sciences companies, research institutions, investors, and patient groups that represent the regenerative medicine and advanced therapies community. Our life science company members are directly involved in the research, development, and clinical investigation of cell and gene therapy products, as well as the submission of Investigational New Drug (IND) applications, and Biologics License Applications (BLA) for such products to the Food and Drug Administration (FDA). Many of our member companies have products under development covering a broad range of conditions. ARM takes the lead on the sector's most pressing and significant issues, fostering research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

ARM commends the FDA for the issuance of the draft guidance on demonstrating substantial evidence of effectiveness for human drug and biological products, which is a very important topic to support drug development. We recognize that the draft guidance applies to both small molecule drug and biological products, including cell and gene therapy products. ARM appreciates the recommendations provided in the guidance for demonstrating substantial evidence of effectiveness for human drug and biological products that reflect the evolution of science and use of innovative approaches to demonstrate substantial evidence of effectiveness. As the Agency notes in the draft guidance document, the recommendations reflect the Agency's longstanding flexibility when considering the types of data and evidence that can meet the substantial evidence requirement. We especially appreciate the discussion of examples of clinical circumstances where additional flexibility may be warranted including in rare diseases. This is especially important for the field of cell and gene therapy, where the majority of the development programs are targeting rare diseases. In this letter, ARM shares our thoughts on the draft guidance recommendations, and provides comments and suggestions for the Agency's consideration as they finalize the draft guidance.

General Comments

ARM understands that this draft guidance document is intended to complement and expand on the 1998 guidance entitled, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." However, currently, both the 1998 final guidance and the 2019 draft guidance are available. ARM suggests

that the Agency clarify that the 2019 draft guidance supersedes the 1998 guidance, as the 2019 draft guidance reflects the FDA's current thinking on this topic. Also, ARM suggests that the FDA consider issuance of a separate new guidance specific for demonstrating substantial evidence of effectiveness for rare and serious diseases with unmet medical need. Further, ARM commends the FDA for convening the public workshop on March 3, 2020 on individualized therapeutics (also called Bespoke therapeutics). Bespoke therapeutics have become increasingly feasible because of enhanced understanding of individual patient variations and because of the implications of these variations for treatment and dose selection. ARM understands that this guidance does not provide recommendations directly applicable to such products with n of 1 patient, although there may be some learnings. As such, ARM recommends that the Agency develop a separate guidance on demonstrating substantial evidence of effectiveness for such Bespoke therapies with n of 1 patient.

ARM appreciates the Agency's efforts in being consistent with the January 2020 final guidance for industry (and July 2018 draft guidance for industry) titled "Human Gene Therapy for Rare Diseases." The guidance recommends that sponsors of drugs intended for rare diseases should consider designing their first-in-human trial to be an adequate and well-controlled clinical investigation that has the potential, depending on the trial results, to provide part of the substantial evidence of effectiveness to support a marketing application. However, we note that qualifier "part of" was added to the same language in this new draft guidance. We believe that the addition of "part of" limits the recommendation in the draft (July 2018) and final (January 2020) guidance for industry "Human Gene Therapy for Rare Diseases." Further, it may cause inconsistency and confusion in interpretation of the recommendation. We request that FDA remove "part of" from the final guidance and fully align with the final (January 2020) guidance for industry Human Gene Therapy for Rare Diseases, which states: "Sponsors should consider designing their first-in-human study to be an adequate and well-controlled investigation that has the potential, depending on the study results, to provide evidence of effectiveness to support a marketing application." If the Agency decides to retain the qualifier "part of," then ARM requests that the Agency clarifies that the recommendation does not apply as is to gene therapy products for rare diseases, for which different considerations apply. Also, it would be helpful for the Agency to explain what the addition of "part of" means for other types of drugs and biological products. For example, the Agency may expect additional or confirmatory evidence in some circumstances, but may not have such expectation in other circumstances, depending on the unmet medical need and regulatory flexibility warranted.

ARM appreciates the consideration of and recommendations in the draft guidance for regulatory flexibility when the disease is life-threatening or severely debilitating with an unmet medical need. However, ARM is concerned that the draft guidance does not acknowledge the regulatory flexibility for serious conditions. Based on past precedent, serious conditions in general warrant additional flexibility. There may be serious conditions that are not life-threatening but are associated with high unmet medical need. We encourage FDA to include serious conditions among the conditions for which regulatory flexibility is available and exercised. This would also be in line with the FDA guidance for industry on Expedited Programs for Serious Conditions – Drugs and Biologics. Serious conditions are a qualifying criterion for expedited programs and should be discussed in consideration for conditions where additional flexibility may be warranted. Inclusion of serious conditions in the final guidance will promote consistency with the criterion for expedited programs, which facilitate drug development for serious conditions with unmet medical need in the same spirit as exercise of appropriate regulatory flexibility is intended to. Also, it would be helpful to include a section in the guidance on how the sponsors can effectively leverage expedited programs. For example, how sponsors can use the Regenerative Medicine Advanced Therapy (RMAT) designation and the accelerated approval program in cell and gene therapy programs to facilitate development and demonstration of substantial evidence of effectiveness.

FDA's exercise of appropriate regulatory flexibility when warranted helps promote drug development to address unmet medical needs of patients. However, we note that the guidance does not recognize or discuss the value of patient voice to inform the sponsor's approach to demonstrating substantial evidence of effectiveness. In FDA's final guidance documents on human gene therapy for hemophilia and rare diseases, the Agency notes that patient experience data may provide important additional information about the clinical benefit of a gene therapy (GT) product and states: "Patient experience data[8] may provide important additional information about the clinical benefit of a GT product. FDA encourages sponsors to collect patient experience data during product development, and to submit such data in the marketing application." We recommend FDA to add a section in the guidance on importance of and approaches to consideration of patient perspective. Alternatively, the Agency may recognize the value of patient voice in various aspects discussed in the guidance. For example, the value of patient perspective on trial design and endpoints for rare diseases should be discussed together with the discussion of additional flexibility when the disease is rare. In that respect, benefits related to quality of life and indirect benefits to family and society in the short and long-term could be of value. In addition, or as an alternative, FDA's guidances on patient focused drug development should be referenced in the guidance.

We appreciate the discussion related to use of real-world data (RWD) and real-world evidence (RWE) as well as the discussion of trial design, trial endpoints, number of trials, and statistical considerations in the draft guidance; and we find helpful the examples of clinical circumstances where additional flexibility may be warranted. The use of RWD/RWE makes it possible to understand the patient experience in the real world and product use settings. We commend the FDA's flexibility in acceptance of novel endpoints and multiple sources for cell and gene therapy products development programs, including RWD/RWE, which can help bring down the time and cost of drug development. Further, traditional endpoints sometimes are not directly applicable for cell and GT product development, which necessitates the use of novel approaches and RWD/RWE to facilitate product development. The flexibility in, and acceptance of, multiple sources of clinical data and external data sources that may not be part of the IND is also important to continue to support these efforts. We request that regulatory flexibility in the type of external controls and size of trials or clinical database also be discussed as a separate feature in this section, or within the section on trial design. Also, we request that the guidance acknowledge the use and acceptance of ex-US data for the demonstration of substantial evidence of effectiveness.

In line with the 1998 guidance, the draft guidance discusses that one adequate and well-controlled large multicenter trial can provide substantial evidence of effectiveness. The small patient populations for the rare diseases that cell and gene therapy products are being developed for may not make possible a 'large' trial, however trials can be multi-center. ARM suggests that FDA consider whether one adequate and well-controlled multicenter trial that is not large can also provide substantial evidence of effectiveness. Such trial would retain the benefits of multicenter trials discussed in the draft guidance, such as to include a fairly broad range of subjects and investigation sites and have procedures in place to ensure trial quality (e.g., investigation site selection, monitoring, and auditing). As the guidance notes, a multicenter trial would be generally less vulnerable to certain biases such as selection or measurement bias, are often more generalizable to the intended population, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints. However, with the advances in science and enhanced mechanistic information on disease pathogenesis, the trial may not need to be large to provide the substantial evidence of effectiveness while retaining features of multicenter trials.

We appreciate the discussion of flexibility in trial endpoints for rare diseases. The section notes that for many rare diseases, well-characterized clinical efficacy endpoints appropriate for the disease may need

to be developed. However, developing new endpoints can be resource intensive, and may not be feasible, ethical, or practical in all rare diseases. We suggest FDA to recommend an approach where sponsors should first consider other approaches and use existing endpoints when available, (e.g. in related conditions). Then, if the existing endpoints are not readily applicable in the rare disease, sponsors should explore whether it can be modified for use in the rare disease. Lastly, if an existing endpoint cannot be used as is or as modified, then sponsors should consider developing new endpoints. Also, we request FDA to discuss use of clinical outcome assessments (COAs) as endpoints that would inform regulatory decision making in sections on trial endpoints in the guidance. Also, it would be helpful to reference FDA's anticipated PFDD guidance #4 on this topic. Lastly, ARM suggests that FDA appropriately reference the July 2018 draft guidance on slowly progressive rare diseases with substrate deposition that result from single enzyme defects and approaches recommended in that draft guidance. ARM notes that we do not recommend FDA define "low prevalence" rare disease or attribute a certain population size or number in that or any guidance considering that there is no such legislative or regulatory definition. However, we suggest that the principles recommended in that draft guidance for providing evidence of effectiveness for replacement or corrective therapies for slowly progressive rare diseases with substrate deposition that result from single enzyme defects should be discussed and referenced in this draft guidance on demonstrating substantial evidence of effectiveness.

ARM appreciates the Agency's view that the degree of certainty supporting a conclusion of demonstration of substantial evidence of effectiveness may differ, depending on clinical circumstances (lines 527-530). ARM notes however that patient access considerations are not discussed in the draft guidance. ARM requests that the FDA exercise caution when reaching and communicating in labeling their conclusion of substantial evidence of effectiveness to avoid creating potential issues from a payor and patient access perspective. It would be in the best interest of patients and facilitating access to avoid overly restrictive communication. For example, if FDA determines that there is substantial evidence of effectiveness to approve a new drug for a rare genetic disease that is severely debilitating and often fatal without treatment before age 12 based on studies in children age 6 and older, it would be very confusing for patients and potentially create issues with payors to include extensive Pediatric Use Statements that the safety and efficacy had not been established in patients younger than 6. The March 2019 guidance for industry "Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling" advises that specific statements should be included in the Pediatric Use Section of labeling when there is no evidence to support the safety and effectiveness of a drug for an indication in pediatric patients (either all pediatric patients or in a specific pediatric age group(s)) because studies have not been conducted or are ongoing. The guidance discusses four different scenarios. "Scenario 3" discussed in the guidance for when there is no evidence to support safety and effectiveness of a drug for an indication in pediatric patients is likely to occur for rare diseases which may have an Orphan Drug Designation and studies waived under the Pediatric Research Equity Act (PREA). The referenced regulations in the guidance (21 CFR 201.57(c)(9)(iv)(E) or (F)) require statements that could be misapplied or interpreted as meaning the product is not indicated or should not be used. For rare and serious conditions with high unmet medical need, ARM requests the Agency to create a pragmatic way to allow and direct Label Review and Policy Team members to exercise discretion in applying the Pediatric information in Labeling and Indication and Usage Guidance to reflect the ability to apply expert judgement in consideration of facilitating patient access. The Agency may wish to consider making reference to 21 CFR 201.57(c)(9)(iv)(G) which states: If the sponsor believes that none of the statements described in paragraphs (c)(9)(iv)(B) through (c)(9)(iv)(F) of this section are appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate

and appropriate. ARM appreciates the Agency's efforts to achieve consistency in labeling so that information on the use of prescription drugs in pediatric populations (whether positive, negative, or inconclusive) is consistently placed in the proper sections and subsections within labeling so that the information is clear and accessible to health care providers. However, making reference to existing regulations which indicate when alternate statements may be used is important for rare and serious conditions with high unmet medical need.

In conclusion, ARM appreciates the opportunity to provide comments on this draft guidance to the Agency. Responding to draft guidances provide a significant opportunity to foster development of advanced therapies for diseases with significant unmet medical need. Please reach out to us if you have any questions about our comments or if we can assist the Agency in any way as they finalize this important guidance.

Sincerely,

Robert J. Falb
Director, U.S. Policy and Advocacy

Alliance for Regenerative Medicine

Re: Specific Comments for FDA-2019-D-4964; Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; Draft Guidance for Industry; Availability

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
I. INTRODUCTION		
Lines		
II. STANDARD OF EFFECTIVNESS FOR DRUGS AND BIOLOGICS		
Lines		
A. Statutory standard		
Lines		
B. Scientific basis for the statutory standard		
Lines		
III. THE QUALITY OF CLINICAL EVIDENCE TO ESTABLISH EFFECTIENESS		
Lines		
A. Trial designs		
Lines 179-184	**Guidance text:** "Although randomized double-blinded, concurrently controlled superiority trials are usually regarded as the most rigorous design, as discussed further below, five types of controls are described in section 314.126: placebo concurrent control, dose-comparison concurrent control, no treatment concurrent control, active treatment concurrent control, and historical control (a type of external control)." **Comment:** In addition to the five types of controls, there may be trial designs using more than one type of control in the analysis of a study, or there may be hybrid designs, e.g. designs using a placebo control in addition to an external control to augment the data.	We suggest that FDA add language in final guidance after this text that more than one type of control may be used by sponsors for a product development program or in a study.

1900 L Street NW, Suite 735
Washington, DC 20036

info@alliancerm.org
@alliancerm

www.alliancerm.org

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
Lines 193-197	**Guidance text:** "However, each of the trial designs has distinct considerations; for example, the lack of blinding when using a no treatment control could introduce bias, which may attenuate confidence in the trial's results. The dose-comparison design may support the effectiveness of the highest dose when a positive dose response is seen, but it could leave uncertainty about whether lower tested doses were effective." **Comment:** The guidance notes that each of the trial designs has distinct considerations but lays out limitations for and discusses only two as an example. While FDA have highlighted two possible limitations/biases here, it would be useful to understand FDA's thinking around strengths AND weakness of all 5 types of controls.	We request that FDA expand the discussion to strengths AND weakness of all 5 types of controls mentioned in this section so that sponsors can weigh those pros and cons of study design against their specific products and disease areas.
Lines 226-229	**Guidance text:** "For these reasons, external control designs are usually reserved for specific circumstances, such as trials of diseases with high and predictable mortality or progressive morbidity (e.g., certain malignancies or certain rare diseases) and trials in which the effect of the drug is self-evident (e.g., general anesthetics)." **Comment:** We argue that external control designs may be well-suited for certain serious or life-threatening diseases. Serious or life-threatening diseases have well-understood regulatory definitions. Limiting the use to diseases associated with "high and predictable mortality or progressive morbidity" may be interpreted differently and can be limiting. Further, consider if the discussion should also include trials with large or clear treatment effect, or clarify if that concept	**Proposed change:** "For these reasons, external control designs are usually reserved for specific circumstances, such as trials of **serious or life-threatening** diseases ~~with high and predictable mortality or progressive morbidity~~ (e.g., certain malignancies or certain rare diseases) **where a treatment effect clearly improves outcomes** and trials in which the effect of the drug is self-evident (e.g., general anesthetics)."

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	is included in "self-evident." It appears that the current wording would not capture the concept of large or clear treatment affect, such as where the treatment effect is so large that it would overwhelm potential biases.	
Lines 230-237	**Guidance text:** "Despite the limitations of externally controlled trials compared with concurrently controlled trials, strong support for effectiveness can emerge from externally controlled trials, especially when (1) the natural history of a disease is well defined, (2) the external control population is very similar to that of the treatment group, (3) concomitant treatments that affect the primary endpoint are not substantially different between the external control population and the trial population, and (4) the results provide compelling evidence of a change in the established progression of disease." **Comment:** We appreciate this discussion of situations when strong support for effectiveness can emerge from externally controlled trials. There are additional ways in which sponsors can design their externally controlled trials to overcome the challenges. The language in this section appears more stringent than what FDA applies in oncology: If tumor response is shown in a single arm trial, FDA considers this as substantial evidence in many cancers, even without an external control group. Further, Item #2 "the external control population is very similar to that of the treatment group" should be supplemented or replaced with something to the effect that statistical methods are applied that account for differences	We request that FDA expand the discussion to discuss other examples and acknowledge that these are examples but there are additional ways in which sponsors can address the challenges of externally controlled trials. Also, we propose following changes: **Proposed changes:** "Despite the limitations of externally controlled trials compared with concurrently controlled trials, strong support for effectiveness can emerge from externally controlled trials, especially when (1) the natural history of a disease is well defined, (2) the external control population is very similar to that of the treatment group **or statistical methods are applied that account for differences in subject characteristics between external controls and the treatment group**, (3) concomitant treatments that affect the primary endpoint are not substantially different between the external control population and the trial population, and (4) the results provide compelling evidence of a change in the established progression of disease." The guidance should note that in diseases where spontaneous recovery is known to be extremely unlikely or diseases progression is known to occur (e.g. tumors do not shrink spontaneously), a control group, randomized or external, is usually not required. It is important for FDA to discuss and provide clear recommendations for diseases where such approach is or should be accepted, e.g. because spontaneous tumor regressions do not occur, controls may not be required whether randomized or external.

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	in subject characteristics between external controls and the treatment group. Further, currently, for "disease where spontaneous regression is not observed," FDA has not required an "external control". However, starting with language on Line 231, it appears that the Agency is now requiring external controls. This would be stricter than what is current practice in oncology for diseases where tumors do not shrink spontaneously. In diseases where tumors do not shrink (or spontaneous recovery is known to be extremely unlikely), a control group, randomized or external, to demonstrate this is usually not required. The guidance should clarify their expectations in such cases.	
Lines 240-242	**Guidance text:** "Another example of where there is strong evidence of drug effectiveness is reversal of clinical signs and symptoms following a toxic exposure or overdose after administration of a drug antidote." **Comment:** A design that demonstrates a reversal of signs of toxic exposure by an antidote is actually not an externally controlled trial.	Recommendation that this text be included in a separate paragraph devoted to within subject designs other than cross over. Such a design is much needed, as there are FDA approved drugs based on such designs.
Line 243	**Comment:** We recommend adding reference to FDA guidance for industry on "Rare Diseases: Natural History Studies for Drug Development." Although this guidance refers to rare diseases, the background section states that the principles could also apply to non-rare diseases. Understanding the natural history of a disease is an important component of the "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" guidance and the natural history draft guidance should therefore be cross-referred.	Add reference to guidance for industry on "Rare Diseases: Natural History Studies for Drug Development."

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
Lines 257-264	**Guidance Text:** "Poor execution can render a trial of any design to be not adequate or not well-controlled and, therefore, unable to provide substantial evidence of effectiveness. Examples of this include (1) a randomized, double-blind, placebo-controlled trial where there is extensive drop-out of trial patients (with the potential for informative censoring), and (2) a randomized, double-blind, placebo-controlled trial in which unblinding is common due to an effect of the test drug, and where a modest treatment effect is found on a primary endpoint that is subject to bias when drug assignment is known (e.g., a physician global impression). In these cases, the trials might not be considered adequate and well-controlled." **Comment:** It would be helpful if the Agency could provide more specificity on what equates to "poor" execution. An option would be to articulate that if the unblinding occurs due to obvious effectiveness, then it's *not* poor execution.	
B. Trial endpoints		
Lines 268-280	**Comment:** We recommend FDA to note that the extent of data required to show substantial evidence, especially one versus two studies, may be dependent on the primary endpoint chosen. Two endpoints may be accepted as clinically significant, but one may be considered more clinically meaningful than the other and the choice could influence the extent of data required to show substantial evidence of effectiveness. The draft guidance language does not clarify this point.	
Lines 272-275	**Guidance text:** "Although the statutory standard for effectiveness does not refer to particular endpoints or state a preference for clinical endpoints over surrogate endpoints,	Suggest deleting "in FDA's judgment" and replacing with "based on the totality of the evidence" to read as follows:

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	it is well established that the effect shown in the adequate and well-controlled clinical investigations, must be, in FDA's judgment, clinically meaningful." **Comment:** It is not clear what FDA's judgement of clinically meaningful is, which may vary from review division to review division, and in some cases, may vary based on the condition and the patient population. This creates ambiguity that could adversely impact development programs.	**Proposed change:** "Although the statutory standard for effectiveness does not refer to particular endpoints or state a preference for clinical endpoints over surrogate endpoints, it is well established that the effect shown in the adequate and well-controlled clinical investigations, must be, ~~in FDA's judgment~~ **based on the totality of the evidence**, clinically meaningful."
C. Statistical considerations		
Lines 285-288	**Guidance text:** "The uncertainty about the findings from each trial should be sufficiently small and the findings should be unlikely to result from chance alone, as demonstrated by a statistically significant result or a high posterior probability of effectiveness." **Comment:** We suggest that this section reference section V.A.4 regarding the definition and intended meaning of "statistically significant."	Add reference to section V.A.4. **Proposed change:** "The uncertainty about the findings from each trial should be sufficiently small and the findings should be unlikely to result from chance alone, as demonstrated by a statistically significant result or a high posterior probability of effectiveness. **Also see section V.A.4.**"
IV. THE QUANTITY OF CLINICAL EVIDENCE TO ESTABLISH EFFECTIVENESS		
Lines		
A. Meeting the substantial evidence standard based upon two adequate and well-controlled clinical investigations		
Lines 304-309	**Guidance text:** "Although two positive identically designed and conducted trials can provide substantial evidence of effectiveness, precise replication of a trial is only one of a number of possible means of obtaining substantiation of a clinical finding and, at times, can provide less persuasive evidence of benefit, as it could leave the conclusions of both trials vulnerable to any systematic biases inherent to the particular study design."	Add reference to section V.A.4. **Proposed change:** "Although two positive identically designed and conducted trials can provide substantial evidence of effectiveness, precise replication of a trial is only one of a number of possible means of obtaining substantiation of a clinical finding and, at times, can provide less persuasive evidence of benefit, as it could leave the

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	Comment: We suggest that this section reference section V.A.4 regarding the definition and intended meaning of "positive."	conclusions of both trials vulnerable to any systematic biases inherent to the particular study design. **Also see section V.A.4.**"
1. Two adequate and well-controlled clinical investigations		
Lines		
2. One adequate and well-controlled large multicenter trial that can provide substantial evidence of effectiveness		
Lines 342-350	**Guidance text:** "Reliance on a single large multicenter trial to establish effectiveness should generally be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, severe or irreversible morbidity, or prevention of a disease with potentially serious outcome, and with other characteristics described below, and confirmation of the result in a second trial would be impracticable or unethical. For example, conducting a second trial after a strongly positive trial had demonstrated a decrease in post-infarction mortality, or prevention of pertussis would generally present significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns." **Comment:** This guidance discussion is not consistent with the text in lines 331-340, nor the rest of this section, which state that a large single trial with many sites, broad inclusion criteria etc. may be equivalent to two studies. If lines 331-340 are correct, it is unclear why use of one, large trial, adequately justified and of very high quality with compelling results, could not also be used to support approval in non-high mortality or high-morbidity indications.	

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
B. Meeting the substantial evidence standard based on one adequate and well-controlled clinical investigation plus confirmatory evidence		
Lines 406-407	**Guidance text:** "Confirmatory evidence could include, for example, adequate and well-controlled clinical investigations in a related disease area,…." **Comment:** Suggest FDA add in text to clarify that a right of reference will be necessary.	Suggest addition to clarify. **Proposed change:** "Confirmatory evidence could include, for example, adequate and well-controlled clinical investigations in a related disease area **for products with a legal right of reference**,…."
1. One adequate and well-controlled clinical investigation on a new indication for an approved drug, supported by existing adequate and well-controlled clinical investigations(s) that demonstrated the effectiveness of the drug for its other, closely related approved indication(s)		
Lines		
2. One adequate and well-controlled clinical investigation supported by data that provide strong mechanistic support		
Lines		
3. One adequate and well-controlled clinical investigation with compelling results, supported by additional data from the natural history of the disease		
Lines 453-463	**Comment:** We appreciate the FDA discussion and recommendations in this section when single trial is supported by additional data from the NH of the disease. We suggest FDA to add additional considerations for providing additional evidence to support effectiveness. These may include very consistent results among all subgroups (pre-specified) within the placebo-controlled phase 3 trial; and very consistent results among various "subsets" of subjects from a large NH register database as well as among different NH databases, as compared to the treated subjects. These subsets of NH subjects can be identified based on pre-specified and/or post-hoc statistical methods.	
Line 463	**Comment:** We recommend adding reference to FDA guidance for industry on "Rare Diseases: Natural History Studies for Drug Development." Although this guidance	Add reference to guidance for industry on "Rare Diseases: Natural History Studies for Drug Development."

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	refers to rare diseases, the background section states that the principles could also apply to non-rare diseases. Understanding the natural history of a disease is an important component of the "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" guidance and the natural history draft guidance should therefore be cross-referred.	
Lines 459-463	**Guidance text:** "For example, a single trial showing marked improvement in survival compared to a control group, either external to the trial or concurrent, could be supported by data from separate sources (e.g., a natural history study, case report forms, or registries) that demonstrate a very limited median survival time or other clinically highly important outcome without treatment. In this case, the natural history data would represent confirmatory evidence." **Comment:** While an improvement in survival is important, we suggest also incorporating another example to avoid suggesting that the bar for leveraging NH as confirmatory evidence is limited to improved survival. It is not clear what "clinically highly important" means.	Another example should be added to avoid suggesting that the bar for leveraging NH as confirmatory evidence is limited to improved survival. Also, suggest FDA change to "… or other clinically meaningful outcome without treatment" in this example to read as follows: **Proposed change:** "For example, a single trial showing marked improvement in survival compared to a control group, either external to the trial or concurrent, could be supported by data from separate sources (e.g., a natural history study, case report forms, or registries) that demonstrate a very limited median survival time or other clinically ~~highly important~~ **meaningful** outcome without treatment."
4. One adequate and well-controlled clinical investigation of the new drug, supported by scientific knowledge about the effectiveness of other drugs in the same pharmacological class		
Lines 479-483	**Guidance text:** "Whether this scenario applies to a particular development program depends on a number of factors, including but not limited to: (1) the strength of the evidence for effectiveness from the single trial; and (2) the relevance of the additional data derived from other drugs in the same class, including the similarity between the new drug and	**Proposed change:** "Whether this scenario applies to a particular development program depends on a number of factors, including but not limited to: (1) the strength of the evidence for effectiveness from the single trial; ~~and~~ (2) the relevance of the additional data derived from other drugs in the same class, including the similarity between the new drug and other drugs in the same class, particularly the

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	other drugs in the same class, particularly the pharmacologic activity or specificity of mechanism of action." **Comment:** With regards to relying on data from drugs from the same pharmacological class, we suggest that FDA flag the need for a right of reference, especially in this particular paragraph for sponsors to leverage this pathway.	pharmacologic activity or specificity of mechanism of action**, and (3) whether the sponsor has a legal right of reference to the confirmatory evidence of effectiveness from adequate and well-controlled trials of the other drug(s) in the same pharmacological class.**"
C. Meeting the substantial evidence standard for a new population or a different dose, regimen, or dosage form, based on reliance of FDA's previous findings of effectiveness of an approved drug when scientifically justified and legally permissible		
Lines		
V. EXAMPLES OF CLNICAL CIRCUMSTANCES WHERE ADDITIONAL FLEXIBILITY MAY BE WARRANTED		
Lines 520-524	**Guidance text:** "This may be the case for life-threatening and severely debilitating diseases with an unmet medical need, for certain rare diseases, or potentially even for a more common disease where the availability of existing treatments makes certain design choices infeasible or unethical." **Comment:** We suggest that FDA to add "Serious" diseases to this discussion because disease that meet the definition of serious conditions, as defined in the FDA guidance on Expedited programs for serious conditions and associated with unmet medical need would also benefit from additional flexibility to meet the unmet medical need. Also, we recommend deleting the word "certain" before rare diseases or explain what the intent is with the qualifier. For example, the intent may be that additional flexibility is warranted for rare diseases that are also serious conditions and are associated with unmet need, as the terms "serious condition" and "unmet medical need" are defined and	**Proposed change:** "This may be the case for **serious or** life-threatening **or** ~~and~~ severely debilitating diseases with an unmet medical need, for ~~certain~~ rare diseases, or potentially even for a more common disease where the availability of existing treatments makes certain design choices infeasible or unethical."

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	discussed in FDA guidance on Expedited programs for serious conditions.	
527-530	**Guidance text:** "FDA would not, however, find it responsible to rely on such design choices in other situations in which, for example, the drug will be used for a less serious disease and greater certainty about benefits and risks is needed, or in cases where designs providing more certainty are possible. In all cases, FDA must reach the conclusion that there is substantial evidence of effectiveness to approve a drug; however, the degree of certainty supporting such a conclusion may differ, depending on clinical circumstances (e.g., severity and rarity of the disease and unmet medical need)." **Comment:** We appreciate the Agency's view that the degree of certainty supporting such a conclusion may differ, depending on clinical circumstances. We suggest that FDA also note that the patient input and perspective is also considered, e.g. patient concerns with placebo burden, or in their willingness to accept uncertainty associated with higher potential benefit to meet high unmet medical need.	
A. When the disease is life-threatening or severely debilitating with an unmet medical need		
Lines 543-544	**Guidance text:** "When the disease is life-threatening or severely debilitating with an unmet medical need" **Comment:** Suggest adding "serious" to the section title and discussion.	**Proposed change:** "When the disease is **serious or** life-threatening or severely debilitating with an unmet medical need"
Line 550	**Guidance text:** "As defined in 21 CFR 312, subpart E (21 CFR 312.81), the term "life-threatening" means diseases or	**Proposed change:** Line 550: "….that causes major irreversible morbidity **or disability**."

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	conditions where the likelihood of death is high unless the course of the disease is interrupted, and diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival; the term "severely debilitating" means diseases or conditions that cause major irreversible morbidity." **Comment:** We request FDA to add the consideration for diseases with irreversible disability because 'morbidity' may exclude certain indications that should be considered in this context.	
1. Trial design		
Lines 571-572	**Guidance text:** "While a randomized placebo-controlled trial can provide more definitive evidence of a small treatment effect than any other kind of trial of the same size, there are instances when this design and other concurrently controlled superiority designs may not be feasible or ethical." **Comment:** A better example for when a randomized placebo-controlled trial may not be feasible or ethical would be a serious disease where treatment is available, but could be improved upon.	
2. Trial endpoints		
Lines 584 and footnote 4	**Guidance text:** "Surrogate endpoints that are reasonably likely to predict clinical benefit can be relied on to establish effectiveness under the accelerated approval pathway. Effects on intermediate clinical endpoints can also be a basis for accelerated approval."	FDA should clarify in the guidance how the evidentiary standards and regulatory expectations are different for "intermediate clinical endpoints", as compared to validated surrogate endpoints, or endpoints likely to predict clinical benefit.

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	Comment: Guidance mentioned "intermediate clinical endpoints" and seems to draw a distinction between surrogate endpoints.	
3. Number of trials		
Lines 592-594	**Guidance text:** "Although two adequate and well-controlled clinical investigations remain the standard approach to generating substantial evidence of effectiveness in many disease settings, there are scenarios where the conduct of a second trial is not ethical or feasible." **Comment:** There is some ambiguity around what is deemed ethical or feasible. Suggest FDA provide examples, such as when disease progression is irreversible or when there is a finite period in the disease course where treatment may be impactful.	Suggest FDA provide examples. **Proposed change:** "Although two adequate and well-controlled clinical investigations remain the standard approach to generating substantial evidence of effectiveness in many disease settings, there are scenarios where the conduct of a second trial is not ethical or feasible**, such as when disease progression is irreversible or when there is a finite period in the disease course where treatment may be impactful**."
4. Statistical considerations		
Lines 604-608	**Guidance text:** "A typical criterion for concluding that a trial is positive (showed an effect) is a p value of < 0.05 (two sided). A lower p value, for example, would often be expected for reliance on a single trial. For a serious disease with no available therapy or a rare disease where sample size might be limited, as discussed further below, a somewhat higher p value – if prespecified and appropriately justified – might be acceptable." **Comment:** We commend FDA for articulating their thinking here. We note that this recommendation is applicable to rare diseases but placed in section on life-threatening or severely debilitating diseases with an unmet medical need. Also, it would be helpful if the agency expanded on this section. We understand that prescriptive recommendations	The recommendation should be moved to or also placed or referenced in section V.B.4 on statistical considerations when the disease is rare. Consider noting that totality of the evidence approach would be taken into consideration instead of a specific p-value for a single specific endpoint.

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	may limit flexibility in applying the principles, however, some examples would be helpful around the key message that there is flexibility in the definition of "statistically significant" (and "positive trial"). Classically, it means an alpha of 0.05. But in a rare disease setting, there may be too few patients available for study to conduct a trial large enough to achieve p<=0.05 with adequate statistical power. One alternative would be if the agency would consider totality of the evidence over a specific p-value for a single specific endpoint.	
B. When the disease is rare		
Lines 610	**Comment:** Suggest adding a subsection on NH and highlight specifically that historical controls (e.g. retrospective NH data) may be appropriately used in rare disease.	
1. Trial design		
Lines 643-646	**Guidance text:** "Sponsors of drugs intended for rare diseases should consider designing their first-in-human trial to be an adequate and well-controlled clinical investigation that has the potential, depending on the trial results, to provide part of the substantial evidence of effectiveness to support a marketing application.[33]" **Comment:** As discussed in general comments, addition of "part of" undermines the intent of this recommendation, as included in the Jan 2020 final guidance and July 2018 draft guidance on human gene therapy for rare diseases, cited in footnote #33 of this draft guidance.	**Proposed change:** "Sponsors of drugs intended for rare diseases should consider designing their first-in-human trial to be an adequate and well-controlled clinical investigation that has the potential, depending on the trial results, to provide ~~part of~~ the substantial evidence of effectiveness to support a marketing application.[33]"
2. Trial endpoints		

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
Lines 647-656	**Comment:** COA's are not mentioned as a potential type of clinical endpoint.	Recommend FDA to add a discussion on COAs in line with FDA's recommendations for the anticipated PFDD guidance #4 on developing COAs as endpoints for clinical trials.
Lines 651-652	**Guidance text:** "For many rare diseases, well-characterized clinical efficacy endpoints appropriate for the disease may need to be developed." **Comment:** We agree that in some cases, endpoints and COAs may need to be developed. However, developing new endpoints is resource intensive and may stifle drug development, and should be considered only if it is not possible to re-use or modify to use existing endpoints and COAs, which may have been established in other conditions but have relevance and applicability in the rare disease under investigation. We request FDA to encourage sponsors to use available, as appropriate to inform the choice of endpoints and COAs. Also, when possible, sponsors should use or repurpose after modification existing endpoints and COAs if they are fit for the context of use.	
Lines 652-656	**Guidance text:** "In cases where utilizing clinical endpoints is not feasible because changes in symptoms and disease status occur too slowly to be measured in a clinical trial of reasonable duration, surrogate endpoints may be considered." **Comment:** We appreciate FDA's consideration for use of surrogate endpoints when the change in clinical endpoints, symptoms and disease status is slow. However, we encourage the Agency to exercise flexibility relative to the ideal endpoint's time point, i.e. flexibility in the length of the	

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	measurement or clinical trial when otherwise the clinical endpoint is the most appropriate endpoint for use in a condition. Also, we request the Agency to consider the possibility of multiple primary endpoints where scientifically and clinically meaningful and not necessarily only 'single primary endpoints' where it is so appropriate even if the statistical analysis is complex. Further, we suggest that FDA evaluate the inclusion of patient experience suffering from rare disease to assess effectiveness in rare diseases. Considering the patient perspective on surrogate endpoints can be very valuable to inform drug development and regulatory decision making.	
Line 656	**Comment:** We recommend adding reference to FDA guidance for industry on "Rare Diseases: Natural History Studies for Drug Development." Although this guidance refers to rare diseases, the background section states that the principles could also apply to non-rare diseases. Understanding the natural history of a disease is an important component of the "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" guidance and the natural history draft guidance should therefore be cross-referred.	Add reference to guidance for industry on "Rare Diseases: Natural History Studies for Drug Development."
3. Number of trials		
Lines		
4. Statistical considerations		
Lines 674-677	**Guidance text:** "Statistical approaches to evaluating treatments for rare diseases should consider the feasibility of trial design, sample size, and endpoints, using methods	

Section/Line #	Guidance Text and Comment	Proposed Change (proposed additions in green and deletions struck-out in red font)
	and thresholds for demonstrating substantial evidence that are appropriate to these settings." **Comment:** We appreciate FDA's indication of flexibility and role that statistics can play to demonstrate substantial evidence in consideration of feasibility of trial design, sample size, and endpoints for evaluating treatments for rare diseases. However, it not clear what such approaches may entail. It would be helpful to provide examples.	
C. When conducting a human efficacy trial is not ethical or feasible		
Lines		