



March 19, 2020

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

Re: Comments for Docket No. FDA-2019-D-4964: FDA Draft Guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on this guidance document. ASGCT is a professional membership organization for gene and cell therapy with over 3,500 members. Membership consists primarily of scientific researchers, physicians, other professionals, and students in training. Members work in a wide range of settings including universities, hospitals, biotechnology and pharmaceutical companies, and government agencies. The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease.

The Food and Drug Administration (FDA) recommendations in this draft guidance are welcomed. ASGCT commends FDA attention within the guidance to evidence relating to the following aspects of clinical trials—trial designs, trial endpoints, and statistical methodology—that were not addressed in the 1998 guidance titled *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. The Society agrees in particular with the statement of the need for clarification since 1998 due to the current rapidly evolving landscape of drug development. As stated in the guidance document (lines 44 – 48):

Specifically, there are more programs studying serious diseases lacking effective treatment, more programs in rare diseases, and more programs for therapies targeted at disease subsets. There is a need for more Agency guidance on the flexibility in the amount and type of evidence needed to meet the substantial evidence standard in these circumstances.

Many gene therapies under development address such diseases and disease subsets. We strongly agree that expedient delivery of safe and efficacious gene therapies to patients with no other options is of utmost importance, and we appreciate FDA efforts toward this end through clarification on the evidence required for these therapies. We especially welcome the provision

of the following specific information in the guidance, since these points may be relevant and useful to sponsors of gene therapy trials:

- Reference to “certain malignancies or certain rare diseases” as examples of diseases with high and predictable mortality that may warrant use of external control designs (lines 226 – 228).
- Indication of examples of the circumstances in which strong support for effectiveness can emerge from externally controlled trials—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 (lines 231 – 237).
- Clarification that 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 (lines 305 – 309).
- Regarding reliance on a single large multicenter trial to establish effectiveness, the inclusion of 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 (lines 342 – 346). The Society agrees that the delay in progressing such treatments by requiring confirmation of the results in a second trial would be unethical in these circumstances.
- Identification of the factors that may allow reliance on a single adequate and well-controlled clinical trial plus confirmatory evidence—the persuasiveness of the single trial; the robustness of the confirmatory evidence; the seriousness of the disease, particularly where there is an unmet medical need; the size of the patient population; and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation (lines 396 – 401).
- Identification of examples of confirmatory evidence, especially inclusion of compelling mechanistic evidence in the setting of well-understood disease pathophysiology (e.g., pharmacodynamic data or compelling data from nonclinical testing), or well-documented natural history of the disease (lines 406 – 411).
- Identification of examples of situations in which a single adequate and well-controlled trial, together with confirmatory evidence, can establish effectiveness—for an approved product for a new indication; for a product that has strong mechanistic confirmatory support; for a product with support from data from the natural history of the disease; and for a product that has support from scientific knowledge about the effectiveness of other drugs in the same pharmacological class (lines 413 – 483).
- Indication that mechanistic evidence may generally be obtained from clinical testing using a relevant and well understood pharmacodynamic endpoint not accepted by itself as an endpoint to establish evidence of effectiveness, and from other sources such as animal studies (e.g., those using an established, relevant animal model to study the effect of the drug on a pharmacodynamic marker of known relevance to humans), or a combination of the two (lines 439 – 444).
- Indication that meeting the substantial evidence standard for a new population or a different dose, regimen, or dosage form, may be based on reliance of FDA’s previous

finding of effectiveness of an approved drug when scientifically justified and legally permissible, without new effectiveness or pharmacodynamic data (lines 485 – 505), for example for pediatric use based on effectiveness of the drug in adults, together with scientific evidence that justifies such reliance.

- Identification of examples of clinical circumstances where additional flexibility may be warranted, especially the highlighting of instances in which the disease is life-threatening or severely debilitating with an unmet medical need and when the disease is rare (lines 508 – 677).
- Indication that sponsors may, and should, consider alternative trial designs for rare diseases such as unequal allocation in a randomized controlled trial, or a dose-comparison design, and that if the effect of the drug can be discerned relatively quickly, designs such as cross-over trials should be considered (lines 633 – 638).

General Comments

We offer the following general comments for the Agency’s consideration as they finalize the guidance.

- We find very helpful the sections discussing aspects of clinical trials including trial designs, trial endpoints, and statistical methodology. We request that regulatory flexibility in the type of external controls and the size of trials or clinical database be also discussed as a separate section in the same regard, or within the section on trial design.
- We appreciate the discussion and clarification in the guidance on FDA’s interpretation of the statutory intent for “substantial evidence” of clinical effectiveness related to the number of clinical trials, i.e., two adequate and well-controlled trials versus a single adequate and well-controlled trial supported by additional confirmatory evidence. However, we encourage the FDA to adopt and exercise a totality of the evidence approach in demonstrating and evaluating the substantial evidence of effectiveness. Further, as a feature of this approach, the patient perspective should be considered as well. We note that the guidance does not recognize or discuss the value of the patient voice in informing clinical trial design. We recommend that FDA add a section in the guidance on the importance of the patient perspective and its role in supporting selected endpoints and clinical trial design.
- We find helpful the discussion and recommendations in the guidance regarding reliance on a single large multicenter trial to establish effectiveness. As noted previously, the Society agrees that the delay in progressing such treatments by requiring confirmation of the results in a second trial would be unethical in these circumstances. However, we encourage FDA to consider scenarios where a large multicenter trial may not be feasible, such as in rare diseases and/or trials designed to evaluate safety and efficacy of a gene therapy. Specifically, with the advances in science and increased understanding of disease pathogenesis, trials for products with clear understanding of the mechanism of action, such as gene therapy products targeting the underlying genetic defect or pathophysiology of the disease, may not need to be “large” to provide the substantial evidence of effectiveness.
- ASGCT appreciates the inclusion of life-threatening or severely debilitating diseases with an unmet medical need and rare diseases among examples of clinical circumstances

where additional flexibility may be warranted. However, we are concerned that the section does not include serious conditions as a type of condition for which additional flexibility is warranted. There are serious conditions that are not life-threatening but are associated with significant impact on quality of life and a high unmet medical need. We encourage FDA to include serious conditions in section V, as defined in the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (September 2017). A serious condition is a qualifying criterion for expedited programs and should be discussed in consideration for conditions for which additional flexibility may be warranted. Also, FDA has in the past exercised appropriate flexibility for serious conditions. Inclusion of serious conditions in section V will promote consistency with FDA’s practice and criterion for expedited programs, which facilitate drug development for serious conditions with unmet medical need.

- We appreciate 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). We encourage the agency to ensure potential labeling is not overly restrictive (e.g., pediatric use statements with arbitrary age limitations), which would ultimately prevent access to potentially transformative treatments. We request the Agency create a pragmatic way to allow and direct label reviewers and policy team members to exercise discretion in applying the guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice* (March 2019), to reflect the review team's ability to apply expert judgement.

Specific Comments

The following specific recommended changes are provided for FDA consideration:

Section/ Lines	Comment/Issue	Proposed Change
I. INTRODUCTION		
61 – 63	<p>“The Agency accepts clinical endpoints that reflect patient benefits (i.e., how patients feel, function, or survive) or validated surrogate endpoints³ (i.e., those that have been shown to predict a specific clinical benefit) as the basis for traditional approval.”</p> <p>Comment: As ASGCT recommended at its liaison meeting with FDA on November 18, 2019, validated biomarkers should be applicable to gene therapy clinical trials to support traditional approval. Reference to the Table of Surrogate Endpoints (https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure) may assist</p>	<p>“The Agency accepts clinical endpoints that reflect patient benefits (i.e., how patients feel, function, or survive) or validated surrogate endpoints (i.e., those that have been shown to predict a specific clinical benefit or are listed on the Table of Surrogate Endpoints) as the basis for traditional approval for drugs and biological products, including gene therapies.”</p>

	sponsors in determining surrogate endpoints that are allowed to be used for traditional approval.	
63 – 67	<p>“In contrast to traditional approval, accelerated approval can be based on a demonstrated effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit but where there are not sufficient data to show that it is a validated surrogate endpoint. Effects on intermediate clinical endpoints⁴ can also be a basis for accelerated approval.”</p> <p>Comment: ASGCT appreciates that subsequently in the guidance document, FDA notes that one adequate and well-controlled clinical investigation may be considered with support by data that provides strong mechanistic support. We recommend referring sponsors to this section of the guidance whenever it is relevant to highlight this important information.</p>	<p>“In contrast to traditional approval, accelerated approval can be based on a demonstrated effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit but where there are not sufficient data to show that it is a validated surrogate endpoint. Effects on intermediate clinical endpoints⁴ can also be a basis for accelerated approval (discussed in Section IV.B).”</p>
II. STANDARD OF EFFECTIVENESS FOR DRUGS AND BIOLOGICS		
A. Statutory Standard		
123-124	<p>“FDA has interpreted the law as generally requiring at least two adequate and well-controlled clinical investigations, each convincing on its own, to establish effectiveness (discussed in Section IV.A.1).”</p> <p>Comment: We appreciate FDA’s discussion on interpretation of the statutory standard. However, the draft guidance overall discusses alternative means for establishing effectiveness that can be, and have been, used. Additionally, FDA has “interpreted” the referenced regulation, which does not require as such. Consider moving the footnote #7 to where the characteristics of adequate and well controlled trials are described so it is less about the number of trials, and more about the totality of evidence that provides substantial evidence of effectiveness. Also, we suggest rephrasing the sentence as proposed.</p>	<p>Suggested changes: “Traditionally, FDA has interpreted the law as generally requiring at least two adequate and well-controlled clinical investigations, each convincing on its own, to establish effectiveness (discussed in Section IV.A.1).”</p>

III. THE QUALITY OF CLINICAL EVIDENCE TO ESTABLISH EFFECTIVENESS

A. Trial Designs

179-184	<p>“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).”</p> <p>Comment: ASGCT appreciates the listing of five types of control. There may be trial designs using more than one type of control in the same trial, such as trials using multiple types of external controls to augment a smaller placebo arm.</p>	ASGCT requests FDA to acknowledge that more than one type of control may be used in a product development program or in a study.
193-197	<p>“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.”</p> <p>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 has highlighted two possible limitations/biases here, it would be useful to understand FDA’s thinking around strengths AND weakness of all five types of controls.</p>	We request that FDA expand the discussion to strengths AND weakness of all five 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.
226-229	“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	“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

	<p>effect of the drug is self-evident (e.g., general anesthetics).”</p> <p>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.</p> <p>Further, ASGCT requests consideration of whether the discussion should also include trials with large or clear treatment effect, or clarification if that concept is included in “self-evident.” It appears that the current wording would not capture the concept of large or clear treatment effect, such as when the treatment effect is so large that it would overwhelm potential biases.</p>	<p>certain rare diseases) for which a treatment effect clearly improves outcomes and trials in which the effect of the drug is self-evident (e.g., general anesthetics).”</p>
230-237	<p>“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.”</p> <p>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.</p> <p>Further, Item #2, “the external control population is very similar to that of the treatment group,” should be supplemented or</p>	<p>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.</p> <p>Also, we propose the following 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</p>

	replaced with something to the effect that statistical methods are applied that account for differences in subject characteristics between external controls and the treatment group.	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.”
B. Trial endpoints		
268 – 270	<p>“One of the characteristics of an adequate and well-controlled clinical investigation is that “the methods of assessment of subjects’ response are well-defined and reliable.¹⁴ Such a method of assessment can be a clinical endpoint¹⁵ or, where appropriate, a surrogate endpoint.¹⁶”</p> <p>Comment: ASGCT appreciates that subsequently in the guidance document, FDA notes that one adequate and well-controlled clinical investigation may be considered with support by data that provides strong mechanistic support. We recommend referring sponsors to this section of the guidance whenever it is relevant to highlight this important information.</p>	<p>“One of the characteristics of an adequate and well-controlled clinical investigation is that “the methods of assessment of subjects’ response are well-defined and reliable. Such a method of assessment can be a clinical endpoint or, where appropriate, a surrogate endpoint (discussed in Section IV. B).”</p>
272-275	<p>“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, clinically meaningful.”</p> <p>Comment: It is not clear what <i>FDA’s judgement</i> 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.</p>	<p>Suggest deleting “in FDA’s judgment” and replacing with “based on the totality of the evidence” to read as follows: “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 preponderance of the evidence, clinically meaningful.”</p>
C. Statistical Considerations		
285-288	<p>“The uncertainty about the findings from each trial should be sufficiently small and the findings should be unlikely to result from</p>	<p>Add reference to section V.A.4: “The uncertainty about the findings from each trial should be</p>

	<p>chance alone, as demonstrated by a statistically significant result or a high posterior probability of effectiveness.”</p> <p>Comment: We suggest that this section reference section V.A.4 regarding the definition and intended meaning of “statistically significant.”</p>	<p>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.”</p>
IV. THE QUANTITY OF CLINICAL EVIDENCE TO ESTABLISH EFFECTIVENESS		
A. Meeting the substantial evidence standard based upon two adequate and well-controlled clinical investigations		
304-309	<p>“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.”</p> <p>Comment: We suggest that this section reference section V.A.4 regarding the definition and intended meaning of “positive.”</p>	<p>Add reference to section V.A.4: “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. Also see section V.A.4.”</p>
<i>2. One adequate and well-controlled large multicenter trial that can provide substantial evidence of effectiveness</i>		
363-365	<p>“Moreover, an effect on a meaningful, objective endpoint, such as certain imaging endpoints, may complement a more subjective endpoint, such as a clinician- or patient-reported outcome.”</p> <p>It would be helpful to cite the Patient-Focused Drug Development (PFDD) discussion documents on clinical outcomes assessment (CRO) and patient-reported outcomes (PROs) here.</p>	<p>ASGCT suggests adding reference to FDA’s PFDD discussion documents on COA (https://www.fda.gov/media/132505/download) and PROs (https://www.fda.gov/media/116277/download).</p>
B. Meeting the substantial evidence standard based on one adequate and well-controlled clinical investigation plus confirmatory evidence		
406-407	<p>“Confirmatory evidence could include, for example, adequate and well-controlled</p>	<p>Suggest addition to clarify: “Confirmatory evidence could include, for example, adequate and</p>

	<p>clinical investigations in a related disease area...”</p> <p>Comment: Suggest FDA add in text to clarify that a right of reference will be necessary.</p>	<p>well-controlled clinical investigations in a related disease area for products with a legal right of reference, ...”</p>
<p><i>2. One adequate and well-controlled clinical investigation supported by data that provide strong mechanistic support</i></p>		
444 - 448	<p>“An example is enzyme replacement therapy, where a single adequate and well-controlled clinical investigation that demonstrates the therapy’s efficacy is supported by evidence that the condition is caused by the enzyme deficiency and by earlier results that show the therapy increases enzyme activity to biologically active levels at the appropriate site and/or reduces disease-specific substrates.”</p> <p>Comment: ASGCT commends the use of the example of enzyme replacement therapy as an instance of strong mechanistic support. Increased enzyme production for a genetic disease in which an enzyme is absent or diminished provides strong mechanistic support for gene therapy as well and should be considered both as a surrogate endpoint and as a substitute for a second controlled trial, especially for small trial populations for serious conditions with unmet needs.</p>	<p>“Examples are enzyme replacement therapy and gene therapy for enzyme deficiencies, where a single adequate and well-controlled clinical investigation that demonstrates the therapy’s efficacy is supported by evidence that the condition is caused by the enzyme deficiency and by earlier results that show the therapy increases enzyme activity to biologically active levels at the appropriate site and/or reduces disease-specific substrates.”</p>
<p><i>3. One adequate and well-controlled clinical investigation with compelling results, supported by additional data from the natural history of the disease</i></p>		
453-463	<p>Comment on sub-section: We appreciate the FDA discussion and recommendations in this section regarding when a single trial is supported by additional data from the NH of the disease. We recommend including additional considerations to support the use of this approach, including an observation of consistent results among all subgroups (pre-specified) within the placebo-controlled phase 3 trial; and 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</p>	<p>ASGCT requests including recommendations in this section based on the comment on this section.</p>

	identified based on pre-specified and/or post-hoc statistical methods.	
459-463	<p>“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.”</p> <p>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.</p> <p>It is not clear what “clinically highly important” means.</p>	<p>ASGCT requests FDA to add another example to avoid interpretation that the bar for leveraging NH as confirmatory evidence is limited to improved survival.</p> <p>Also, we suggest FDA change to: “... or other clinically meaningful outcome without treatment” in this example to read as follows: “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.”</p>
<p><i>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</i></p>		
479-483	<p>“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 pharmacologic activity or specificity of mechanism of action.”</p> <p>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</p>	<p>ASGCT proposed addition: “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 pharmacologic activity or specificity of mechanism of action, and (3) whether the sponsor has a legal authority for right of reference to the</p>

	paragraph for sponsors to leverage this pathway.	confirmatory evidence of effectiveness from adequate and well-controlled trials of the other drug(s) in the same pharmacological class.”
V. EXAMPLES OF CLINICAL CIRCUMSTANCES WHERE ADDITIONAL FLEXIBILITY MAY BE WARRANTED		
520-524	<p>“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.”</p> <p>Comment: We suggest that FDA add “serious” diseases to this discussion because diseases that meet the definition of serious conditions, as defined in the FDA guidance for industry <i>Expedited Programs for Serious Conditions – Drugs and Biologics</i> (September 2017), and associated with unmet medical need would also benefit from additional flexibility to meet the unmet medical need.</p> <p>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 discussed in the FDA guidance for industry <i>Expedited Programs for Serious Conditions – Drugs and Biologics</i> (September 2017).</p>	Proposed changes: “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.”
527-530	“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	

	<p>such a conclusion may differ, depending on clinical circumstances (e.g., severity and rarity of the disease and unmet medical need).”</p> <p>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 note that the patient input and perspective is also considered.</p>	
A. When the disease is life-threatening or severely debilitating with an unmet medical need		
543-544	<p>“When the disease is life-threatening or severely debilitating with an unmet medical need”</p> <p>Comment: Suggest adding “serious” to the section title and discussion</p>	<p>Proposed change: “When the disease is serious or life-threatening or severely debilitating with an unmet medical need”</p>
<i>3. Number of Trials</i>		
592-594	<p>“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.”</p> <p>Comment: There is some ambiguity around FDA’s determination of what would be deemed as <i>not ethical or feasible</i>. We 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.</p>	<p>ASGCT suggests that FDA provide examples. Proposed addition: “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.”</p>
<i>4. Statistical considerations</i>		
606 – 608	<p>“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.”</p>	<p>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 a totality of the evidence approach would be taken into consideration instead of a specific p-value for a single specific endpoint.</p>

	<p>Comment: We appreciate this indication of greater flexibility in p value level for serious diseases with unmet need and for cases in which the available sample size may be limited. While ASGCT supports rigorous research, the Society is also concerned with providing potential treatments for diseases with great unmet need in an expeditious manner. We would encourage broader discussion and further policy around appropriate p values.</p> <p>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.</p> <p>Also, it would be helpful if the Agency expanded on this section. We understand that prescriptive recommendations 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 a study to conduct a trial large enough to achieve $p \leq 0.05$ with adequate statistical power. One simple alternative criterion would be if the Agency permitted, for example, $\alpha=0.1$. Another alternative would be if the Agency would consider totality of the evidence over a specific p value for a single specific endpoint.</p>	<p>Also, ASGCT suggests following changes: “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.”</p>
B. When the disease is rare		
610	<p>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.</p>	<p>ASGCT requests adding a subsection on NH in line with comment.</p>
<i>2. Trial endpoints</i>		
652 – 655	<p>“In cases where utilizing clinical endpoints is not feasible because changes in symptoms</p>	<p>“In cases where utilizing clinical endpoints is not feasible because</p>

	<p>and disease status occur too slowly to be measured in a clinical trial of reasonable duration, surrogate endpoints may be considered.”</p> <p>Comments: ASGCT appreciates this indication of greater flexibility in the timing of attainment of clinical endpoints. Also, 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 measurement or clinical trial when otherwise the clinical endpoint is the most appropriate endpoint for use in a condition. Further, we recommend additional language that reflects that for some gene therapies, such as is the case for Luxturna for an inherited retinal disease, the conventional measure (e.g., of improved visual acuity) may not ever be attained by some patients, although the functional gains may be dramatic. As stated above, the Society encourages consideration of use of mechanistic evidence in support of use of surrogate endpoints.</p>	<p>changes in symptoms and disease status occur too slowly to be measured in a clinical trial of reasonable duration, or because the response to treatment is functionally significant but not measurable by conventional clinical endpoints, surrogate endpoints may be considered. As stated previously, compelling mechanistic evidence in the setting of well understood disease pathophysiology may be considered for use as a surrogate endpoint.”</p>
<i>4. Statistical Considerations</i>		
674-677	<p>“Statistical approaches to evaluating treatments for rare diseases should consider the feasibility of trial design, sample size, and endpoints, using methods and thresholds for demonstrating substantial evidence that are appropriate to these settings.”</p> <p>Comment: We appreciate FDA’s indication of flexibility and the 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 is not clear what such approaches may entail. It would be helpful to provide examples.</p>	

Thank you for consideration of these comments. Please do not hesitate to let ASGCT know if you have questions.

Sincerely,

Adora Ndu

Adora Ndu, PharmD, JD
Chair, ASGCT Regulatory Affairs Committee