

November 21, 2005



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

Re: [Docket No. 2005D-0310] – Draft Guidance for Industry on Gene Therapy Clinical Trials—Observing Participants for Delayed Adverse Events; Availability

Merck & Co., Inc. is a leading worldwide human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations. MRL tests many compounds as potential drug and biologic candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing Merck product candidates through developmental testing and clinical trials, Merck scientists address issues affected by this proposed Guidance. We have extensive experience in the non-clinical, clinical, process and analytical development of product candidates and have utilized that experience to author the comments below.

Merck commends the Food and Drug Administration (FDA or the Agency) for issuing draft guidance on observing participants in gene therapy clinical trials for delayed adverse events. The FDA has provided formal guidance on gene therapy since 2000, including convening meetings of the Biological Response Modifiers Advisory Committee in order to solicit advice. In addition, the June 2004 public workshop co-sponsored by FDA with various other groups provided important perspectives on the topic of long-term follow-up. We appreciate the time and effort of the FDA in developing, gathering and disseminating information on this important topic. We support the risk-based approach described in the draft guidance which describes the assessment of risk as being a continuous process based on the characteristics of the vector, a case-by-case approach. We envision that increased experience with the "new" technology of gene therapy will provide additional information that will be taken into account when decisions are made

about reducing, eliminating or increasing the frequency of long-term follow-up observations.

Clinical trials for gene therapy products may be conducted worldwide. As such, the strategy for long term follow-up has global impact. We recommend that the FDA seek opportunities to harmonize the risk-based approach proposed in the draft guidance with the approaches promoted by international regulatory agencies, possibly through the International Conference on Harmonization. In addition, analysis of applicable deidentified data contained in clinical trial data registries, health management organization databases or other valid databases of information may drive important considerations for post-approval monitoring of gene therapy products. Development of infrastructure to facilitate long-term monitoring of both those enrolled in clinical trials and those administered the approved product will be essential in order to capture useable information from patients over a long time period.

Our specific comments on the draft guidance follow below. We present the location description and current text from the draft guidance document followed by our recommendation.

Location of Text	Current Text	Suggested Edit	Comment
Page 1, footnote 1, second bullet	The guidance does not cover...Vaccines used to prevent infectious diseases even if they use products analogous to those used for gene therapy (consult OVR, CBER)	The guidance does not cover...Traditional vaccines used to prevent infectious diseases (consult OVR, CBER for guidance on the extent of clinical follow-up). <u>If the vaccine contains human DNA sequences, these products are considered gene therapy and should be assessed as described herein.</u>	We are aware of examples of vaccines carrying human DNA sequences that are considered by CBER as gene therapy products. It is important for sponsors to know if they should be following guidance for gene therapy products when developing this type of vaccine. Please provide clarification in the footnote and in the definition of a Gene Therapy Product provided on page 5 (see next line).
Page 4, Gene Therapy Products (definition)	All products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells <i>in vivo</i> or transferred to cells <i>ex vivo</i> prior to administration to the recipient.	<u>Vaccines that carry human DNA sequences for the purpose of eliciting an immune response to the translated DNA sequence are also considered gene therapy products.</u>	We suggest that this sentence be added to the definition of Gene Therapy Products in order to clarify that these vaccines indeed are considered in this category of products.
Page 5, Transgene (definition)	An exogenous gene that is introduced into a host <u>genome</u> .	An exogenous gene that is introduced into a host <u>cell</u> .	Recommend the Agency consider using the word cell instead of genome. The use of the word “genome” in the context of this sentence suggests integration. The latter is not true for all the vectors that are covered by this guidance.

Location of Text	Current Text	Suggested Edit	Comment
Page 6, Section IV A. Criteria to assess potential delayed risks of gene therapy	Throughout: integration and persistence		As these terms are integral to the framework assessing the risk of gene therapy products, we request that CBER provide definitions of integration and persistence.
Page 8, 2 nd bullet point at the end of the page	The transgene provides functional replacement of a host gene; the transgene product is potentially immunogenic.	The transgene provides functional replacement of a host gene; the transgene product and is potentially immunogenic.	For clarity, we recommend editing the sentence as indicated. For example, some vaccines that are considered Gene Therapy products are immunogenic, but this bullet point would apply only when their transgene provides functional replacement of a host gene as well.

Location of Text	Current Text	Suggested Edit	Comment
Page 10, 3 rd bullet point	Use at least 5 animals per gender per group per sacrifice time point for rodents	Use at least 5 animals per gender per group per sacrifice time point for rodents, <u>if the DNA for these animals is to be pooled. If the DNA from these animals will be analyzed separately, then the number can be reduced to 3 animals per gender per group.</u>	We would like the Agency to consider the use of 3 rodents per gender per group per sacrifice time point. In the past we used 5 animals/group/time point, but the DNA was pooled. However, more recently we have been analyzing individual tissues samples instead of pooling the tissues from the individual animals prior to processing, and are now considering using 3 animals/group/time point instead. Thus, 6 data points will be available per group per time point. For nonrodents, 3-5 animals is still applicable regardless of whether the samples are pooled or not.
Page 10, 7 th bullet point, 3 rd and 4 th lines.	Include appropriate safety endpoints in your biodistribution study in order to assess any potential correlation between vector presence/persistence and adverse findings. These safety endpoints should include clinical observations, body weights, clinical pathology, gross organ pathology, and histopathology.	<u>If safety endpoints have not been evaluated already in a separate toxicity study using the same animal model,</u> include appropriate safety endpoints in your biodistribution study in order to assess any potential correlation between vector presence/persistence and adverse findings. These safety endpoints should include clinical observations, body weights, clinical pathology, gross organ pathology, and histopathology.	We propose the Agency considers editing the language as suggested.

Location of Text	Current Text	Suggested Edit	Comment
Page 11, Point 2, 3 rd bullet, 1 st sub-bullet	Use three samples per tissue.	Use three <u>replicate DNA</u> samples per tissue <u>sample</u> .	We propose the Agency considers editing the language as suggested. Please also refer to the comment made below concerning “Page 11, Point 2, 3 rd bullet, 3 rd sub-bullet.”
Page 11, Point 2, 3 rd bullet, 2 nd sub-bullet	Each sample should contain at least 1 µg genomic DNA, or test sufficient replicates to equal a total of 3 µg if the assay capacity is less than 1 µg DNA per sample.		We propose the Agency considers removing this recommendation. This is no longer scientifically justified since state-of-the-art PCR does not require 1 µg per reaction, but rather can use much smaller amounts of DNA while still providing the required sensitivity (as per the draft guidance) of ≤100 copies per µg of DNA. Similarly the recommendation on the testing of a total of 3 µg if the assay capacity is less than 1 µg DNA per sample is not scientifically justified given the advances in technology and will be burdensome.

Location of Text	Current Text	Suggested Edit	Comment
Page 11, Point 2, 3 rd bullet, 3 rd sub-bullet	Analysis of one sample should include introduction of vector DNA control while two of the three samples collected should be tested in the absence of any introduced vector DNA.	The presence of inhibitors of the PCR reaction should be assessed by spiking representative DNA samples from each tissue type with positive control vector DNA and performing the quantitative PCR assay, and/or by dilution experiments using sample DNA that would reveal whether a potential inhibitor effect had been relieved.	We recommend using less prescriptive language since there are several ways to assess PCR inhibition. For example, we normally assess inhibitors by spiking the DNA samples from the control rats in the study, not the samples from the vector-treated animals. If the latter are used, the inhibitor analysis is complicated by the presence of vector DNA. Alternatively, another assessment that can be used in conjunction with the spiking of control samples is to dilute the samples to determine whether a potential inhibitory effect has been relieved. A suggested text is presented for the Agency's consideration.
Page 12, 4 th paragraph, line 5			Reference 9 should have been reference 10 (Wang <i>et al.</i>) instead.

Location of Text	Current Text	Suggested Edit	Comment
Page 12, last bullet point in the page.	Sentence starting... “If the vector is persistent, we recommend...”		As per our comment concerning page 6 above, it would be helpful if the Agency could provide definition as to what persistence means. For example, if the level of vector is low at the last time point, but is not significantly difference than the previous time point, would that be considered a persistent vector? Perhaps a cut-off value after a certain period of time, similar to that presented on the draft DNA Vaccine Guidance distributed earlier this year (2005), might be useful.
Page 12, last bullet point in the page.	Sentence starting... “If the vector is persistent, we recommend...”	For example, integration of the vector into the host genomic DNA can be assessed in the preclinical biodistribution study samples that are positive at the later time points. A sensitive and reliable method is based on gel purification of the high molecular weight genomic DNA, followed by re-analysis of the sample by PCR, to determine the level of vector remaining associated with the genomic DNA (Ledwith BJ <i>et al.</i> Plasmid DNA vaccines: investigation of integration into host cellular DNA following intramuscular injection in mice. <i>Intervirology</i> , 2000, 43:258-72.)	We recommend adding the additional suggested text regarding potential integration assessments at the end of the indicated bullet point.

Location of Text	Current Text	Suggested Edit	Comment
Page 13, paragraph labeled “1.”	If the studies show no evidence for persistence due to integration of the genetic material or development of latency...	If the studies show no evidence of <u>integration</u> for persistence due to integration of the genetic material or development of latency...	Suggest simplifying this sentence for clarity as indicated.
Page 13, paragraph labeled “2.”	If the studies show no evidence for integration of the genetic material but studies for latency and reactivation...	If the studies show no evidence <u>of</u> for integration of the genetic material , but studies <u>of</u> for latency and reactivation...	Suggest simplifying this sentence for clarity as indicated.
Page 14, Table 1, footnote #1			Footnote reference #1 should be put after the first “No” in the table (i.e., “No ¹ ”). That footnote applies only when the vector doesn’t integrate.
Page 19, F section paragraph, lines 2-5.	In at least two preclinical studies performed in mice, integration of genetic material from a retroviral vector into mouse cell DNA was reported to cause malignant transformation (Refs. 10 and 11).		Please verify the accuracy of the references. Reference 10 (Wang Z <i>et al.</i> Detection of integration of plasmid DNA into host genomic DNA following intramuscular injection and electroporation. <i>Gene Ther</i> , 2004, 11:711-21) is not applicable to this text. Since reference 9 was inaccurate (see comment above “Page 12, 4 th paragraph, line 5”) it may be possible that references 9 and 10 have been switched.

Location of Text	Current Text	Suggested Edit	Comment
VI. References			Recommend adding Ledwith BJ <i>et al.</i> Plasmid DNA vaccines: investigation of integration into host cellular DNA following intramuscular injection in mice. <i>Intervirology</i> , 2000, 43:258-72 as a reference (see one of the comments on Page 12 above)
VI. References	11. Modlich... mutagenesis. Blood 2005; 1-38.	11. Modlich... mutagenesis. Blood 2005; 1-38. <u>105 (11) 4235-46.</u>	Please verify page reference, as the current numbers may be inaccurate.

Conclusion

In summary, we support the development and finalization of this guidance document. We have identified areas for further clarification and have commented on specific potential issues. To address the need for further clarification of these points, we recommend the guidance be revised as noted herein.

We appreciate the opportunity to share our comments with respect to the Draft Guidance for Industry on Gene Therapy Clinical Trials—Observing Participants for Delayed Adverse Events. Please do not hesitate to contact me, should you have any questions.

Sincerely,



Taryn Rogalski-Salter, PhD
 Director
 Regulatory Policy