



May 19, 2005

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

Re: [Docket No. 2005D-0047] – Draft Guidance for Industry: Considerations for Plasmid Deoxyribonucleic Acid Vaccines for Infectious Disease Indications; Availability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 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 vaccine 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 vaccine candidates and have utilized that experience to author the comments below.

Merck commends the Food and Drug Administration (FDA) for updating the 1996 guidance document "Points to Consider on Plasmid DNA Vaccines for Preventive Indications" based on increased experience with the type of vaccine covered in the guidance. We support the continued development of this guidance document but have a general comment on the scope of the guidance. The guidance is intended to assist in the development of DNA vaccines to prevent infectious diseases. The guidance is not necessarily applicable to DNA vaccines for the treatment of established diseases as there may be a different benefit risk determination for products used to treat established diseases. We can envision a vaccine candidate with indications for both prevention and for therapeutic use. In this case, we challenge this differentiation as it would be unreasonable to ask manufacturers to produce the same type of molecule to different

standards for different indications. For consistency, we suggest that the scope of the guidance be modified to include those DNA vaccine products having both a preventive and a therapeutic indication.

Our specific comments on the draft guidance follow below. We present the section description and subject line from the guidance document followed by our recommendation.

Section I Introduction

“For the purposes of this document, DNA vaccines are defined as purified preparations of plasmid DNA designed to contain one or more genes from a pathogen as well as regulatory genetic elements to enable production in a bacterial host system”. We believe this definition is too restrictive as experimental vaccines may be derived from the DNA of an attenuated virus which is no longer a pathogen. We suggest that the text be changed as follows *“...to contain one or more genes from ~~a pathogen~~ an organism as well as...”*

Section II B Manufacturing Issues, Bulk plasmid product release testing

“When a single manufacturing facility is used to manufacture more than one DNA vaccine product, we recommend that you perform identity tests capable of distinguishing individual plasmids”. This statement may be misconstrued. We agree with the need to perform identity tests capable of distinguishing the different plasmids manufactured in one facility but these assays should not necessarily be expanded to encompass purity testing without a clear understanding of their sensitivity. As technology continues to advance, we envision that ultra sensitive assays may be developed making it possible to detect previously undetectable levels of contaminants (in the order of parts per million). Although such contamination levels should be considered negligible, we would appreciate guidance in terms of the threshold level of detection. Our recommendation is to reword the sentence to clearly state that the tests are used to confirm identity: *“When a single manufacturing facility is used to manufacture more than one DNA vaccine product, we recommend that you perform a test capable of confirming identity of the various plasmids produced in the facility”.*

“Assays that monitor in vivo immunogenicity of the DNA vaccine are preferred”. We challenge the need for an *in vivo* animal potency assay as these assays have historically been variable and somewhat insensitive to detecting changes in the tested molecule. Additionally, a line previous states *“we will allow sponsors considerable flexibility in the selection of potency assays”.* We recommend that this sentence be deleted *“~~Assays that monitor in vivo immunogenicity of the DNA vaccine are preferred~~”.*

Section III A DNA Vaccine Modifications, Changes to the Insert or Vector

“Changes to the DNA sequence of the insert gene or vector sequences of a DNA vaccine would require the submission of a new IND (See section 351 of the PHS Act and 21CFR Part 312).” For clarity, we are requesting more information be added to this sentence. As written, the wording may generate confusion among sponsors who may struggle with

how literally to interpret the sentence; such as including point mutations or single codon deletions.

Section IV D Preclinical Immunogenicity and Safety, Tolerance

“Based on these findings and other considerations, we recommend that prior to the use of a DNA vaccine in children or newborns that: i) you first test the vaccine for safety and immunogenicity in adults, and ii) you utilize appropriate preclinical models to evaluate the potential of such vaccines to induce neonatal tolerance”. In this sentence, we suggest changing the word “utilize” to “consider whether there are” given that there are usually no good preclinical models to evaluate tolerance. Additionally, we suggest changing the words “such vaccines” to “the vaccine” as the discussion has been referring to the vaccine in the singular.

Section IV E Preclinical Immunogenicity and Safety, Challenge/Protection, Cytokines, Prime/Boost

“When plasmid DNA vaccines are used in vaccination strategies employing a corresponding subunit vaccine, such as in prime and boost study designs, we recommend that you submit specific preclinical information to support the safety and tolerability of the proposed dose, schedule, and route of administration of each vaccine combination”. We suggest that the following clarification be added to this discussion: “Preclinical toxicity studies may not be necessary for each regimen if there is adequate safety data on the individual treatment arms”. Additionally, since “combination” is often associated with vaccines that contain multiple individual vaccines, we suggest that the word *combination* be changed to regimen.

Section IV F Preclinical Immunogenicity and Safety, Local Reactogenicity and Systemic Toxicity Studies

“We recommend that you conduct these studies using the highest dose of vaccine planned for clinical use”. We recommend that you add the phrase “when possible” to the sentence. *“We recommend that, when possible, you conduct these studies using the highest dose of vaccine planned for clinical use”*. In some exceptional cases the clinical dose might be higher than the dose that can be evaluated in animal studies. For example, the clinical dose volume may exceed the volume that could be administered to the animal models. In those cases, use of the N+1 rule (administration of one additional dose to the animals than the number of doses planned to be administered in the clinic) in addition to the body weight safety margins should offer sufficient reassurance that not attaining the maximum human dose by a few fold (usually 2-4 fold) will not compromise the safety evaluation. Conversely, newer technologies such as gene guns or electroporation may in fact support the delivery of very low doses of DNA vaccine (microgram quantities). Preclinical testing using intramuscular injection of much higher doses may not easily correlate to the human system. In Section IV. A. (Preclinical Immunogenicity and Safety, General Considerations) we suggest the Agency reiterate that the route of administration and the device used in preclinical studies should be representative of the clinical situation.

Section IV G Preclinical Immunogenicity and Safety, Biodistribution and Integration Analysis

“Publications resulting from the use of DNA vaccines in clinical studies under IND indicate that intramuscular, subcutaneous, intradermal, or particle-mediated delivery does not result in long-term persistence of plasmid at ectopic sites, and that ≤ 30 copies of plasmid per 10^5 host cells persist at the site of injection after 60 days (see Section VI, References).” We agree that plasmid DNA delivered by intramuscular injection generally does not result in long-term persistence of plasmid DNA at ectopic sites. However, our experience with biodistribution studies diverges from that mentioned in the agency’s statement regarding the amount of DNA remaining at the injection site after 60 days. To date, all of Merck’s published biodistribution studies have demonstrated that after 60 days the plasmid DNA levels are > 30 copies of plasmid per 10^5 cells. For example, in one of Merck’s publications listed in the guidance references (Ledwith et al., Intervirology, 2000), the plasmid DNA levels detected in the quadriceps were approximately 1,000 to 4,000 copies per 1.5×10^5 cells at the 6-week time point, and approximately 200 to 800 copies at the 6-month time point. In a more recent unpublished study, the plasmid DNA levels in the quadriceps were approximately 30,000 to 50,000 copies at the 6-week time point, and approximately 10,000 to 20,000 copies at the 6-month time point.

“This would include assessing any adjuvant or active excipient or active excipient in the vaccine, and/or the use of a device to deliver the vaccine.” For clarity, we suggest moving the discussion on adjuvants and delivery to Section IV. A. General Considerations. The discussion of adjuvants and devices and any effects on toxicity is a general consideration for plasmid DNA vaccines and is therefore more relevant in Section A. Novel adjuvants and devices may raise safety issues that might require special evaluations and this point is lost as it is currently presented in a section on Biodistribution and Integration Analysis.

“The panel of tissues typically includes the blood, heart, brain, liver, kidney, bone marrow, ovaries/testes, lung, mesenteric lymph nodes, spleen, adrenal gland, muscle at the site of administration and subcutis at the injection site.” Our typical panel of tissues collected for intramuscular administration of a DNA plasmid vaccine does not include the bone marrow or the adrenal gland, but does include all the other tissues listed as well as the inguinal and iliac lymph nodes, although more recently the mesenteric lymph node has not been included. We suggest the Agency provide the rationale for each of the tissues selected for the panel; such as bone marrow and adrenal gland. Based on our experience, we would like the agency to consider stipulating in the guidance that the “draining” lymph nodes (i.e., relevant to the injection site) should be collected instead of the mesenteric lymph nodes.

“The presence of the DNA vaccine is typically evaluated using a semi-quantitative real time polymerase chain reaction (Q-PCR) study validated for sensitivity and specificity.” For clarity, we suggest changing the word “study” to “assay”.

“We have determined that integration studies are not necessary when biodistribution/persistence studies demonstrate that plasmid DNA does not persist in any tissue of any animal at levels exceeding 30 copies per 10⁵ cellular genomes at 60 days post vaccination.” We agree that if the level of plasmid DNA is < 30 copies per 10⁵ cellular genomes at 60 days post vaccination that no integration studies are required. We suggest the Agency provide a rational or reference regarding the potential risk of insertional mutagenesis and carcinogenicity associated with integration.

“Typically, Q-PCR is used to detect plasmid DNA in genomic DNA preparations. Specifically designed PCR primers may be used to distinguish between integrated and non-integrated plasmids.” We suggest that these sentences in the guidance be replaced by the following sentences: “Total plasmid DNA levels in tissues are generally measured using a Q-PCR assay of total DNA. For tissues with plasmid levels >30 copies per 10⁵ cells at 60 days post vaccination, integration of the plasmid DNA should be assessed. Typically, a gel purification method designed to separate extrachromosomal plasmid DNA from high molecular weight genomic DNA is used, in combination with a Q-PCR assay to assess integration. In this method, Q-PCR is used to quantitate the amount of plasmid DNA remaining associated with the genomic DNA after gel-purification of the genomic DNA. Additionally, specifically designed PCR primers may be used to confirm integration and identify genomic integration sites.”

Conclusion

In summary, we support the continued development 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 FDA Draft Guidance for Industry; Considerations for Plasmid Deoxyribonucleic Acid Vaccines for Infectious Disease Indications. Please do not hesitate to contact me, should you have any questions.

Sincerely,



Taryn Rogalski-Salter, PhD
Director
Regulatory Policy