NIH Comments on FDA's Draft Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications

Docket # 2005D-0047

May 18, 2005

The National Institutes of Health (NIH) has the following comments on the *Draft Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications*. NIH appreciates FDA's interest in gathering input on the draft document. These comments reflect perspectives, in particular, of the National Institute of Allergy and Infectious Diseases (Division of AIDS and the Vaccine Research Center) and the National Cancer Institute (Division of Cancer Biology/Cancer Etiology Branch), that are based on a broad experience in the development of DNA vaccines, including nearly two dozen DNA vaccine candidates for prophylactic indications (e.g., for HIV/AIDS, Ebola, SARS, and WNV), 13 of which have reached the clinic.

First, the guidance seems primarily directed to products going into Phase 1 clinical development as would be appropriate given that most DNA plasmid vaccines are in that phase of development currently. However, with the exception of the discussion on potency, it is not clear whether the guidance would apply to all phases of clinical development. It would be helpful to clarify whether later phase clinical development studies should be taking different approaches and whether there are plans to develop specific guidance for later phase studies.

Second, the guidance does not address some of the key issues that investigators, industry and funding agencies are currently considering and on which guidance would be helpful. These include:

- Are measurements of residual antibiotic in the product needed? There are difficulties in measuring residual antibiotic in the presence of high concentrations of plasmid DNA, and, although FDA has asked sponsors about this issue, it is not clear whether FDA expects such measurements to be taken for plasmid DNA vaccines. It would be helpful if the guidance indicated in Section II whether or not an effort should be made to measure the presence of residual antibiotic and, if so, how such measurements can be accomplished.

- Modifications to the method and route of administration of the plasmid vaccine. In addition to guidance on modifications to the sequence of the DNA plasmid vaccine, it would be helpful to have guidance on modifying the method and route of administration of the vaccine. Specifically, what would be the preclinical biodistribution and toxicology requirements to proceed to phase I testing where there may be previous human experience or extensive preclinical safety experience using the same method or route to deliver different, but similar, plasmids.

- Testing prime-boost regimens. It would be helpful to know whether it is necessary to test prime-boost regimens in repeated-dose toxicology studies (as opposed to testing the individual components in separate studies). We have not found pre-clinical toxicity of prime-boost regimens to be synergistic and toxicities identified for the individual components were the same as those seen in prime-boost toxicology studies. As such, we would suggest that the Guidance should not require prime-boost repeated-dose toxicology studies in most cases.

- A section on clinical issues would be beneficial. Guidance on the following specific clinical issues, for example, would be helpful:
    - How long after last vaccination must contraceptive use/safe sex practices be maintained to ensure safety? In addressing this issue, please consider the following:
        - Reproductive toxicology has not been performed on most products in early clinical development.
        - Clinical trials can last for a year or more, even Phase 1 studies, and pregnant/lactating women are generally excluded. Maintaining contraceptive use would require most prospective female subjects to forgo having a child for at least two years (i.e., more than 9 months for pregnancy prior to the trial + however many months of lactation prior to the trial + the time on trial during which pregnancy must be avoided). For healthy young women, this is a long time and their decisions about family planning may change over time.
        - From a safety standpoint, biodistribution of the DNA plasmid vaccine to the gonads is not actually seen for most vaccines delivered intramuscularly.
    - Should subjects with allergies to antibiotics that may be present in trace residual amounts in the final product be excluded from the study? In addressing this issue, please consider the following:
        - Since many of the plasmid vaccines contain the kanamycin resistance gene, kanamycin is used during fermentation. Although the purification methods are expected to remove residues, an assay for residual levels is technically infeasible because of interference (as noted above).
        - Kanamycin is not generally used clinically, and our clinicians report that allergies to aminoglycosides are quite rare.
        - Information about allergies to aminoglycosides cannot be reliably determined by patient history.
        - Since clinical trial procedures generally require subjects to remain in the clinic for 15-30 minutes after vaccination in the rare event of anaphylaxis, it is not clear that screening subjects for allergies to residual antibiotics enhances subject safety.
    - Is monitoring for auto-antibody production in the clinical phase still necessary? Guidance in Section IV (C) on autoimmunity suggests that FDA may no longer expect such monitoring during clinical studies. Please clarify whether this is in fact the case.

Third, flexibility would be helpful regarding Section II (B) on bulk plasmid release testing (i.e., not the final formulated bulk immediately prior to filling, which is generally considered as part of the final product release).

- Tests formerly recommended for final containers (i.e., in the 1996 guidance) have now been moved to the bulk. The Guidance should allow flexibility about whether tests should be of the bulk or whether they should remain as tests of the final containers or final formulated bulks.

Specifically, the tests for endotoxins or pyrogenic substances are generally expected to be performed on the final containers [21 CFR 610.13(b)].

- The Guidance should be flexible about whether tests of potency are required on the bulk or the final formulated bulk/containers. Some tests of potency, such as expression, may be appropriate at the unformulated bulk stage, but if bioassays (i.e., *in vivo* immunogenicity) are expected as product development advances, testing potency on the unformulated (and possibly monovalent) bulk might not be appropriate.

Fourth, in the final sentence of the first paragraph of Section IV (C), the Guidance does not distinguish between autoimmunity associated with anti-dsDNA antibodies and other forms of autoimmunity. Although it states that pre-clinical studies to assess "whether vaccination causes autoimmune disease" are no longer expected, a paragraph later it refers to concerns about autoimmunity in some cases (e.g., plasmids encoding self-antigens). If there are lingering concerns about autoimmunity in specific cases, it may make more sense to end the sentence with "whether vaccination induces anti-dsDNA antibodies" rather than "autoimmunity."

Fifth, regarding Section IV (E), it would be clearer in the first sentence to delete the phrase "When appropriate and where possible" and begin the text with "We encourage animal challenge. . . ." Since this testing is encouraged and not mandated, the inclusion of the initial phrase unduly weakens the safety aspects without providing examples or criteria of what is "appropriate and possible."

Sixth, regarding Section IV (G) regarding the level of residual biodistribution at "the site of injection,"

- Guidance on residual biodistribution levels in terms of copies of plasmid/microgram of DNA extracted from the tissue rather than in copies of plasmid/number of cells. While extraction of DNA from tissue culture cells or blood cells may be determined based on number of cells, these biodistribution studies are being performed on tissue for which weight (grams) rather than cell numbers is measured. Generally, a certain amount (weight) of DNA is used per PCR reaction and, thus, reporting copies number per weight of extracted DNA is more logical and direct than relating the copy numbers to numbers of cells. While there is a direct relationship between weight of DNA extracted and number of cells, the number of cells is generally not measured from a tissue specimen, whereas weight of DNA extracted is, making it the logical unit for reporting the denominator in biodistribution studies.

- For intramuscular injection, please clarify whether you are referring to the muscle or including the overlying subcutis and skin as part of the "site of injection."

- The value indicated as persisting at 60 days in the site of injection (based on published literature) may be the experience when DNA plasmid vaccines were given at doses such as 100 micrograms in mice. However, when multiple milligrams of DNA are given (as they currently are), residual levels at the muscle are often present at the level of 100's or even 1000's of copies/microgram of DNA at day 60 in a minority of animals. Moreover, if the subcutis/skin is considered, sometimes a majority of animals still have PCR signals at day 60, and these are generally on the order of 100's or 1000's of copies/mcg of DNA but can be up to 10^5 or 10^6 in a rare animal. A manuscript of some of these data (from the VRC vaccine candidates) is currently being prepared for submission for publication. However, the experience described herein also includes what has been seen for DAIDS-sponsored DNA plasmid vaccines as well, many of which have already been permitted by FDA/OVRR to proceed into clinical studies on the basis of such data. As such,

- Please reconsider the dataset and determine how applicable it is to the current clinical situation when multiple milligrams of DNA are being delivered rather than micrograms of DNA.

- Please clarify whether the value cited in the Guidance specifically refers, for intramuscular injection, to levels in the muscle, which are lower and present in a minority of animals at day 60, or including the subcutis/skin, which are higher and more consistent (i.e., sometimes present in a majority of animals).

- Please cite the published studies referenced in the Guidance.

We would like to thank the FDA for providing updated guidance on this platform technology and seeking input on it. We appreciate the opportunity to share our perspectives.