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Points to Consider on Plasmid DNA Vaccines for Preventive Infectious Disease Indications

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POINTS TO CONSIDER ON PLASMID DNA VACCINES FOR PREVENTIVE INFECTIOUS DISEASE INDICATIONS

FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Vaccine Research and Review

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POINTS TO CONSIDER ON PLASMID DNA VACCINES FOR PREVENTIVE INFECTIOUS DISEASE INDICATIONS[1]

I. INTRODUCTION

The use of purified preparations of plasmid DNA (deoxyribonucleic acid) constitutes a new approach to vaccine development. Plasmid DNA vaccines may find application as: preventive vaccines for viral, bacterial, or parasitic diseases; immunizing agents for the preparation of hyperimmune globulin products; therapeutic vaccines for infectious diseases; or for other indications such as cancer. This document is intended to provide manufacturers with preliminary guidance regarding the manufacture and preclinical evaluation of plasmid DNA vaccines intended for clinical studies in preventive infectious disease indications and to assist manufacturers in the preparation of Investigational New Drug Applications (INDs) for use of these vaccines. To facilitate interactions between the Center for Biologics Evaluation and Research (CBER) and manufacturers, a common understanding

[1]This Points to Consider document is an informal communication under 21 CFR 10.90(b)(9) that reflects the best judgement of FDA employees at this time. It does not create or confer any rights, privileges or benefits for or on any person, nor does it operate to bind or obligate FDA in any way.

should exist regarding the biological and physical properties of plasmid DNA vaccines.

For the purposes of this document, plasmid DNA vaccines are defined as purified preparations of plasmid DNA designed to contain a gene or genes for the intended vaccine antigen as well as genes incorporated into the construct to allow for production in a suitable host system. Plasmid DNA vaccines currently under development are constructs derived from bacterial plasmids that contain one or more genes from an infectious agent. These plasmids possess DNA sequences necessary for selection and replication in bacteria; eukaryotic promoters and enhancers; and transcription termination/polyadenylation addition sequences for gene expression. This document presumes that bacteria are to be used to produce the plasmid DNA preparations.

Plasmid DNA vaccines are biological products within the meaning of the Public Health Service Act and are regulated by CBER (42 U.S.C. 262). The regulations that govern the use of biological products apply to plasmid DNA vaccines (See e.g., 21 CFR Parts 600, 601, and 610). Other guidance documents that are available from CBER may contain information that is

relevant to plasmid DNA vaccines (Attachment). Concerns associated with the manufacture, preclinical evaluation, and clinical studies for these vaccines are similar to those for other biological products. However, because the current state of scientific knowledge with respect to the use of plasmid DNAs as preventive vaccines is limited, manufacturers/sponsors should give particular emphasis to the preclinical safety evaluation.

This document is intended to assist manufacturers with their product development plans as they are applied to the development of preventive vaccines for infectious diseases. Plasmid DNA vaccines which are intended for use as preventive vaccines and therapeutic vaccines for infectious diseases should be submitted to the Office of Vaccines Research and Review (OVRR) where primary review responsibility is assigned. Concerns related to plasmid DNA products intended for therapeutic indications other than infectious diseases should be directed to the Division of Applications Review and Policy (DARP), Office of Therapeutics Research and Review (OTRR) which will have primary review responsibility for those products. The ?Points to Consider in Human Somatic Cell and Gene Therapy” addresses products in this category. FDA

published a notice of availability for this document in the **FEDERAL REGISTER** on November 29, 1991 (56 FR 61022). Please note that the preclinical recommendations discussed later is this document may not always apply in the case of therapeutic products.

As with other guidance and PTC documents FDA does not intend this document to be all inclusive. It is intended to provide information and does not set forth requirements. Manufacturers may follow the procedures outlined in this document or may choose to use alternative procedures that are not provided in this document. Prior to using alternative procedures a manufacturer may wish to discuss the matter with FDA to prevent expenditure of resources generating data that FDA may later determine to be unacceptable. Although this points to consider document does not create or confer any rights for or on any person and does not operate to bind FDA or the public, it does represent the agency's current thinking on issues related to plasmid DNA vacines.

II. CBER APPROACH TO REGULATION OF PLASMID DNA PREVENTIVE VACCINES

Manufacturing and preclinical development concerns associated with the use of plasmid DNA vaccines are similar to those for other biological products. CBER will evaluate each new vaccine on a case-by-case basis with particular emphasis on each component of the vaccine as it may relate to the safety and potential efficacy of the product. Of concern is the source of the DNA incorporated into the vector, including eukaryotic promoters and enhancers; termination/polyadenylation addition sites; antibiotic resistance markers; and other selection markers. In order to limit the possibility for chromosomal integration, homology of plasmid DNA sequences to known sequences in the human genome should be examined and described, and strong homology avoided if possible. Viral promoters and mammalian and viral termination and polyadenylation signals are frequently used, however, the results of expression and safety studies should dictate the choice of regulatory control sequences used in plasmid DNA constructs. Antibiotic resistance is commonly employed as a selection marker. In considering the use of an antibiotic resistance marker, CBER is advising manufacturers against the use of penicillin or other ß-lactam antibiotics as these antibiotics can, in certain individuals, result in allergic reactions ranging in severity from skin rashes to

immediate anaphylaxis. When an antibiotic resistance marker is required in a plasmid DNA vaccine construct, CBER advises the use of an antibiotic such as kanamycin or neomycin. These aminoglycoside antibiotics are not extensively used in the treatment of clinical infections due to their low activity spectrum, prevalence of kanamycin-resistant bacteria, and their problematic therapeutic index with toxicities including irreversible ototoxicity and nephrotoxicity. Specifications for the level of antibiotic present in the final container should be established and should consider the minimum level of antibiotic that will give an unintentional clinical effect. The use of alternative antibiotic resistance markers or the use of suppressor tRNA genes in a plasmid construct intended as plasmid DNA vaccine should be discussed with CBER prior to full scale development of a new vaccine product.

Until such time that CBER has accrued sufficient information regarding the safety of plasmid DNA preventive vaccines, a new plasmid construct using a common vector and differing only in the antigen to be expressed may be considered a new product and subject to preclinical safety evaluation as delineated in later sections. Once CBER has more experience in the review of plasmid DNA vaccine products, abbreviated preclinical

development programs may be proposed for common plasmid vectors. Full product characterization and development may not be necessary prior to the initiation of a phase 1 clinical study and this may be discussed with CBER prior to submission of an IND application.

III. PRODUCT CONSIDERATIONS FOR AN IND SUBMISSION

The following considerations are intended to clarify the type and extent of information that should be included in an IND application for a new plasmid DNA preventive vaccine. It may also be useful to refer to the ?FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products". The notice of availability for this document published in the **FEDERAL REGISTER** on April 26, 1996 (61 FR 18612). This document discusses changes manufacturers may apply to product manufacturing processes without performing additional clinical studies to demonstrate safety and efficacy.

A. Product Manufacture and Characterization

When preparing an IND application for a new plasmid DNA

vaccine, the following specific product information should be submitted. The application should describe all components that were used during manufacture as well as those present in the final product. The application should describe in detail the plasmid DNA vaccine vector construction, including the source and diagrams of all plasmids used, and all intermediate recombinant DNA cloning procedures. Prior to licensure, the DNA sequence of the plasmid DNA should be provided for each vaccine construct by direct sequencing of the plasmid present in the Master Cell Bank. Preliminary clinical investigations may proceed with plasmid DNA products characterized using a combination of direct sequence and restriction enzyme analysis. In the case where the same plasmid vector is used to express a different inserted gene, manufacturers should discuss with CBER whether abbreviated sequence information including the inserted gene or genes and flanking regions will be adequate. During production, other methods of sequence verification, such as restriction enzyme mapping and polymerase chain reaction (PCR) may be employed at intermediate steps.

For the purposes of this document and consistent with products currently under development, plasmid DNA vaccines are

envisioned as being produced primarily in bacterial host systems. With this consideration in mind, developers of these vaccines should provide the genotype, phenotype, and source of the bacterial cells, as well as the procedures used to generate a clonal population. Specific guidance for the establishment of Master Cell Banks (MCB) and Working Cell Banks (WCB) is described in the ?Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (1993)". Both the MCB and WCB should be tested to ensure that they are free from bacteriophage and other adventitious agent contamination and for the maintenance of specific relevant characteristics, (e.g., RecA, Kan^r, etc). The manufacturing process should be described in sufficient detail so as to enable an assessment of the safety of the product. If changes in product manufacture occur during the development and preclinical safety evaluation, a clear summary should be provided illustrating all differences between lots of vaccine used in preclinical studies and those intended for use in clinical studies.

B. Specifications for the Bulk Plasmid Product

If bulk and final product are the same (i.e., if production

runs yield one lot and no further steps in formulation are performed), then testing as described below may be redundant and unnecessary. Bulk plasmid products should be tested for the properties described below. Standard assay(s) of adequate specificity and sensitivity can be used. Assay methods should be evaluated by testing known amounts of reference materials, spiked samples, or other appropriate measures, and data documenting assay performance should be submitted to the IND.

The DNA content in the bulk plasmid DNA vaccine and the presence of other cell-derived contaminants such as RNA (ribonucleic acid) and proteins should be evaluated. The A_{260}/A_{280} ratio of absorbance may be useful in this regard. A test for homogeneity of size and determination of plasmid structure (i.e., supercoiled vs. linear and relaxed circular DNA or concatamers should be performed). Agarose gel electrophoresis may be a useful technique to collect this information. A test for contaminating RNA or host DNA should also be included in the analysis. Blot hybridization techniques (Southern and Northern) in combination with gel electrophoresis will add to the sensitivity of the procedures. Appropriate tests to detect contaminating proteins also should be performed. The use of silver stained gels will provide a

high degree of sensitivity to detect contaminating proteins and would be preferred over Coomassie Blue stained gels. In addition, immunologic techniques, such as enzyme-linked immunosorbent assay (ELISA) or Western blot, may be useful to detect contaminating host proteins.

The identity of the DNA plasmid vaccine may be determined by restriction enzyme digestion with multiple enzymes. In cases of production of similar constructs in the same manufacturing facility, it is recommended that tests capable of distinguishing individual plasmids be performed. A test for sterility to detect aerobic and anaerobic bacteria should be performed. Specific preclinical tests may be appropriate for products having specific safety concerns such as those DNA plasmid vaccines incorporating co-stimulatory cytokine genes or formulated with novel lipid or adjuvant components.

Whenever possible, a potency assay should measure the level of production and immunogenicity of the gene product expressed by the plasmid vaccine. Expression of the gene inserted into the plasmid vaccine can be determined by transfection of appropriate cells and demonstration of antigen expression by an appropriate assay, wherein sensitivity and specificity have

been determined. The selection and implementation of a potency assay may be discussed with CBER to ensure acceptability of the design.

C. Final Product Lot Release Testing

During early product development and clinical investigation, specifications and criteria for lot release should be defined. Plasmid DNA vaccine products intended for phase 1 clinical studies should be tested for potency, general safety, sterility, purity, quantity, and identity. A test for potency may be an in vitro or in vivo test to evaluate the specific ability of the vaccine to effect a given response, such as an immune response in mice or the production of the pertinent antigen in a transfected cell line. The general safety test should be performed in mice and guinea pigs on each lot of plasmid DNA vaccine to detect extraneous toxic contaminants potentially introduced during manufacture. [FDA promulgated a final rule on May 14, 1996 (61 FR 24227) entitled "Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products" that exempts therapeutic DNA plasmid products.] A test for sterility should be performed. A test for purity should be

performed on each lot to ensure that the product is free of extraneous material except for that which is unavoidable due to the manufacturing process. Other tests for quality of the final product should include an evaluation for residual moisture (required for licensed products) if the product is lyophilized, and a test for the presence of pyrogenic substances. Each lot of vaccine should be tested to establish the identity of the material in the final container. In addition to final product lot release, in-process testing should also be performed to ensure manufacturing consistency and product safety. Acceptance criteria and acceptable limits should be established and the results reported for each lot of vaccine to be used for clinical studies. For plasmid DNA vaccine products in their final container form, adventitious agent testing may be limited to sterility tests.

RNA, protein, and bacterial genomic DNA are possible contaminants that may be introduced during product manufacture, and the presence of these possible contaminants should be monitored in the product. Plasmid-derived DNA species such as linear and relaxed circular DNA may be less effective in expressing the inserted antigen gene. There should be a specification for the minimum amount of

supercoiled DNA present. This parameter should be a major criterion measured during stability studies.

IV. CONSIDERATIONS FOR PLASMID DNA VACCINE MODIFICATIONS

CBER generally considers significant changes in the antigen or plasmid regulatory genes in a plasmid DNA preventive vaccine vector to constitute a new product, that should be the subject of a new IND application. This policy will be evaluated on a periodic basis as plasmid DNA vaccines enter clinical study and CBER gains experience in the review of these products. However, related plasmid DNA vaccines that contain similar antigen genes intended for expression (e.g., influenza HA genes) may in some cases be considered members of a panel, analogous to panels of monoclonal antibodies and described in informational amendments to a single IND. Each member of a panel should meet all specifications included in release testing and should receive appropriate preclinical testing. Please refer to the "Draft Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1994)" for further information. FDA published a notice of availability for this document in the **FEDERAL REGISTER** on August 3, 1994 (59 FR 39571). If the plasmid DNAs

are similar in nucleotide sequence, are used for the same indication, and have similar predicted biological effects, the preclinical testing needed may be abbreviated after consultation with CBER. Data that are needed for full product characterization and development may not be required prior to beginning phase 1 trials.

Changes in manufacture implemented prior to product approval should be fully described in the IND application. If a sponsor can demonstrate comparability, additional clinical safety and/or efficacy trials with the new product will generally not be needed. FDA may determine that two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency. Please refer to the ?FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products" for further information.

A. Plasmid DNA Preventive Vaccine Vector Structure

Changes in a plasmid DNA vector, exclusive of the antigen gene intended for expression, may generally result in the plasmid

vaccine being considered a new product. Alteration of a single base-pair in a control region of the DNA plasmid may alter its safety properties, in which case a full evaluation of safety in preclinical studies may be needed. Other alterations may not affect the safety profile of the plasmid DNA vaccine vector and may be considered for abbreviated safety testing.

A change in the inserted gene with no change in the plasmid DNA vaccine vector may in some cases be considered as a modification requiring only abbreviated testing. For example, if the same plasmid vector is used to express a series of related proteins, then the safety issues for each DNA plasmid vaccine are only those presented by the insert and its expressed product. As the immune response to the inserted antigen gene may vary and since the gene products expressed by the plasmid DNA vaccine might raise specific safety concerns, FDA will determine the degree of required testing on a case-by-case basis. Sponsors should consult with CBER early in development to discuss these issues for individual products.

In some cases, preclinical testing such as tissue localization, assessment of germ line alteration, and animal

pharmacology/toxicology studies may not need to be repeated. Instead, the relevant safety studies could focus on safety related to expression of the inserted gene or genes. Possible adverse effects might include expression of the antigen gene in inappropriate tissue sites, overexpression, or unexpected immune responses, such as inappropriate modulation of the immune response resulting in immunopathology.

B. DNA Sequence Information

The complete DNA sequence of each plasmid construct intended for licensure should be determined. Initial phase 1 clinical investigations may be initiated with a complete restriction enzyme analysis of the plasmid vector and the DNA sequence of the inserted gene. In the case of multiple related plasmids, adequate characterization may include sequencing of the inserted gene and enough sequence of flanking regions and control regions to characterize the insertion and verify integrity of flanking regions.

C. Lipids, Microsphere Encapsulation, Cytokines

The use of novel components and delivery systems, such as the

use of novel cationic lipid preparations to enhance uptake and expression of a plasmid DNA vaccine administered by intranasal immunization, may necessitate specific preclinical evaluation to ensure safety. The use of specialized delivery systems such as the encapsulation of the plasmid DNA vaccine in poly (DL-lactide-coglycolide) (PLG) microspheres may also necessitate preclinical evaluation. Similar considerations apply if other components, such as cytokine genes, are added to plasmid DNA vaccine vectors.

CBER intends to consider and evaluate alternative methods for plasmid DNA vaccine manufacture and preclinical safety evaluation. We encourage DNA plasmid vaccine developers to initiate an early dialogue with CBER prior to finalizing the design of plasmid constructs, manufacturing processes, or development of the pivotal preclinical Good Laboratory Practice (GLP) studies to support safety evaluation of the vaccine.

V. PRECLINICAL IMMUNOGENICITY AND SAFETY EVALUATION

A. General Considerations

The preclinical evaluation of plasmid DNA vaccines is an

important aspect of their development as candidate vaccine products. In designing preclinical studies, the primary consideration should be the intended clinical use, since the primary goal of preclinical studies is to obtain enough relevant data to allow initiation of a phase 1 clinical study. Both in vivo and in vitro studies may be employed to assess whether the product may be used safely in clinical studies. The type, duration, and scope of animal studies and other tests will vary with the duration and nature of the proposed clinical investigations. For example, a preventive vaccine intended for one-time administration will have supporting data different from a therapeutic vaccine that may be administered repeatedly. The pivotal animal safety study(ies) should be performed in accordance with GLP regulations (21 CFR 58). The use of non-traditional animal models of disease or challenge studies may also be useful for certain indications. Relevant animal models may also include the use of aged animals for the evaluation of vaccines proposed for use in elderly populations.

B. Immunogenicity Evaluation

During the preclinical development of these new vaccines,

sponsors should develop adequate assays for the assessment of the immunological potency of the vaccine. These results will be useful in choosing a proposed dose for clinical studies. The preclinical studies should be designed to assess the immune response, including seroconversion rates, geometric mean antibody titers and, if possible, cell-mediated immune responses in vaccinated animals. These studies should also be designed to collect information regarding the duration of antigen expression and whether long-term expression will result in tolerance or autoimmunity. Where appropriate and when possible, animal challenge/protection studies with the corresponding infectious agent are encouraged early in development to demonstrate the rationale for the use of the investigational vaccine. For those DNA plasmid vaccine constructs that co-express cytokine genes, specific preclinical studies should be considered to assess whether modulation of the cellular or humoral components of the immune system might result in unintended adverse consequences, such as generalized immunosuppression, chronic inflammation, autoimmunity or other immunopathology. When plasmid DNA vaccines are used in vaccination strategies employing a corresponding subunit vaccine, such as in prime and boost study designs, specific preclinical information should be

submitted to support the schedule and route of administration with each vaccine combination.

C. Local Reactogenicity and Systemic Toxicity Studies

Studies designed to assess systemic toxicity may be combined with the assessment of local site reactogenicity. The design of these studies should include dose-ranging and dose-escalation, considering the anticipated dose and schedule of administration in clinical studies. The assessments written into the preclinical study protocols should include toxicity to potential target organs, including the hematopoietic and immune systems. Preclinical studies should also include clinical pathology, gross evaluations, and histopathology of tissues.

Local site reactogenicity studies should include detailed clinical and histological evaluations of injection-site tissue obtained from biopsies or term necropsy samples. Studies should be designed to assess the distribution or tropism of the vaccine for specific tissues. These studies should define the duration of vaccine immunogen expression and persistence of the vector in somatic cells containing the plasmid DNA

vaccine. The preclinical studies should be designed to determine whether the plasmid DNA vaccine has an immunotoxic effect, either by inducing tolerance to the antigen encoded by the vaccine or by inducing autoimmunity. These studies should also be designed to assess whether antibody responses are elicited to contaminating bacterial proteins in the vaccine.

D. Genetic Toxicity

Integration of the plasmid DNA vaccine into the genome of the vaccinated subjects is an important theoretical risk to consider in preclinical studies. The concern is that an integrated vaccine may result in insertional mutagenesis through the activation of oncogenes or inactivation of tumor suppressor genes. In addition, an integrated plasmid DNA vaccine may result in chromosomal instability through the induction of chromosomal breaks or rearrangements. The performance of a preclinical study to assess integration should focus on the potential of the plasmid DNA vaccine to recombine with endogenous host DNA sequences. Studies designed to address the potential for integration should use the most sensitive methods available. For example, PCR studies using primers derived from the vaccine can be used to

examine tissue distribution and to distinguish between integrated versus non-integrated plasmids in genomic DNA preparations. Use of separative electrophoretic methods can assist in the preparation of genomic DNA samples free of contaminating plasmids for use in such a study as can the use of rare restriction sites engineered into the plasmid construct.

Localization studies designed to determine the distribution of the DNA plasmid vaccine after administration should be performed. Whenever feasible, testing should include both the intended route of administration (e.g. subcutaneous, intramuscular, intradermal, intranasal), as well as a group of animals treated intravenously, as a "worst-case" scenario. The presence of the DNA plasmid vaccine in surrounding and distal tissues as well as the vaccination site should be evaluated using the most sensitive detection methods available. If aberrant or unexpected localization occurs, studies should be conducted to determine whether the presence of the DNA plasmid vaccine is associated with a pathologic response. The studies should also include evaluation of the persistence of both the gene and its product in the target and non-target organs.

The effects of overexpression of antigen from the DNA plasmid vaccine should also be considered. Aberrant expression of some proteins may lead to an inappropriate activation of the immune system, resulting in the generation of acute or chronic inflammatory responses, autoimmune sequelae, and destruction of normal tissues. Where generation of an autoimmune response is potentially a risk in either the clinical trial or the preclinical testing, preclinical studies should be conducted over a long enough period to allow development of these disorders to appear.

E. Reproductive Toxicity Studies

Plasmid DNA preventive vaccines should be evaluated for migration to gonadal tissue and possible germline alterations in both male and female animals. This may be assessed through the performance of PCR on gonad-derived DNA preparations from male and female animals vaccinated with a plasmid DNA vaccine. Additional studies may be needed if the product is expected to affect normal physiological processes related to fertility, maintenance of pregnancy, or fetal development and will depend on factors such as the age and health status of the proposed subject population and the intended use. The FDA guidelines

entitled ?Detection of Toxicity to Reproduction for Medicinal Products" and the ?Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility" may be useful for assessing the effect of vaccination on reproductive function and male fertility. The manufacturer should have early discussions with CBER on these issues prior to the submission of an IND application.

F. Tumorigenicity Studies

Tumorigenicity studies may be appropriate under certain conditions. A tumorigenicity study should be considered if the results of the preclinical studies to assess integration of the plasmid DNA vaccine provide clear evidence of integration activity or broad tissue distribution, or if the vaccine is intended for chronic use in non-life threatening clinical situations. This type of study may also be relevant if the plasmid DNA vaccine construct has extensive DNA sequence homology to the human genome or if the vector contains sequences of known oncogenic potential. Manufacturers should carefully evaluate whether to proceed with product development should their particular construct exhibit integration activity.

CBER will evaluate each proposal for a clinical study of a vaccine candidate on a case-by-case basis. Preventive vaccines intended for normal healthy volunteers should have little to no risk associated with their use, thus having a potential high benefit to risk ratio. The study of therapeutic vaccines intended to treat severe or life threatening chronic infections or cancer may be acceptable in the presence of a higher level of risk or uncertainty. As noted previously, specific guidance regarding the use of plasmid DNA products for indications other than infectious diseases may be obtained from OTRR. CBER intends to use sound scientific principles in the consideration and evaluation of new methods or alternative procedures for the evaluation of safety. For further information please refer to the ?Points to Consider in Human Somatic Cell Therapy and Gene Therapy”.

VI. USE OF ADJUVANTS AND DEVICES TO DELIVER THE VACCINE

The use of adjuvants and/or facilitators for the plasmid DNA vaccine should be supported by specific preclinical evaluation to ensure the safety of the combination. It is important to note for licensure purposes that the adjuvant or facilitator alone would not be licensed. Rather, it is the specific

combination of vaccine and adjuvant or facilitator that would be licensed. If a device, yet to be approved, is used to deliver the vaccine, the device application will be reviewed by the Center for Devices and Radiological Health (CDRH). An IND submitted for a clinical study of the vaccine should cross-reference the Investigational Device Exemption (IDE) application for the device submitted to CDRH. A custom device used only for vaccine delivery may not require a separate device approval but may be considered a combination product and reviewed as part of a Product License Application (PLA).

VII. PRE-IND MEETINGS

During product development, sponsors are encouraged to schedule a pre-IND meeting with CBER to discuss specific concerns related to manufacture, preclinical development, and clinical studies. In OVRR such a meeting may be scheduled one month in advance through submission of an ?Executive Summary" for the presentations at the meeting. Such a summary should include a product outline with a proposal or the actual specifications for the product, the manufacturing process, the preclinical development plan and the design of the proposed phase 1 clinical study. A meeting may be made more productive

by submitting a list of questions to be addressed during the meeting in addition to the materials enclosed in the ?Executive Summary.”

VIII. IND SUBMISSIONS

A. General Considerations

The following will assist FDA in the review of IND applications. An IND or a Master File (MF) should be submitted in triplicate. All the pages of the submission should be numbered. It is important to provide photographs, not photocopies, of all data that do not reproduce well, such as gels and chromatography data. The IND application should have a signed and completed Form 1571. In addition, any cross-reference to other IND or MF applications should be as specific as possible, including submission dates and page numbers where the cross-referenced information can be found.

B. Clinical Investigations

The data needed to support phase 1 trials should focus on safety, though some demonstration of immunogenicity is expected. Additional data from more detailed testing and results of process validation will be needed at later stages in product development as well as additional evidence of potency and efficacy. Sometimes product formulation is changed as product development progresses and manufacturers want to use data from one formulation to support trials with different formulations. In this case, comparability of the different formulations should be demonstrated by quantitative assays including biological potency testing. Conducting later phase trials with a product differing greatly from an earlier formulation might require repeating all or part of earlier clinical phase testing. Please refer to the ?FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products" for further information.

IX. CONCLUSION

This document is intended to provide manufacturers with information on concerns that are associated with the new technology of plasmid DNA preventive vaccines and to provide

early guidance to the regulated industry. The goal is to create a regulatory environment that will encourage innovation and at the same time ensure that products are both safe and effective. Manufacturers of plasmid DNA vaccines can assist in achieving this goal by pursuing innovative strategies for preclinical evaluation through the design of studies that will identify problems early in product development. The interactions with the FDA may also improve through an understanding of the regulatory review process and preparation of a well-managed product development plan.

The issues presented in this document were chosen to assist manufacturers developing plasmid DNA vaccines. Manufacturers of these products should concentrate their efforts on the pivotal preclinical safety issues. Finally, the ideas presented here are generally advisory. This topic will be revisited periodically as CBER gains more experience in the regulatory review of submissions for plasmid DNA vaccines.

Approved by Director, Center for Biologics Evaluation and Research:

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Kathryn C. Zoon, Ph.D.

Director

Center for Biologics Evaluation and Research

ATTACHMENT

REGULATIONS AND APPLICABLE GUIDANCE DOCUMENTS

U.S. CODE OF FEDERAL REGULATIONS

* 21 CFR PART 50 - Protection of Human Subjects
* 21 CFR PART 56 - Institutional Review Boards
* 21 CFR PART 58 - Good Laboratory Practices for Nonclinical Laboratory Studies
* 21 CFR PART 210 - Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General
* 21 CFR PART 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals
* 21 CFR PART 312 - Investigational New Drug Application
* 21 CFR PART 600 - Biological Products: General
* 21 CFR PART 601 - Licensing
* 21 CFR PART 610 - General Biological Products Standards

POINTS TO CONSIDER DOCUMENTS

* Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA

Technology (4/85)

* Points to Consider in Human Somatic Cell Therapy and Gene Therapy (8/91)
* Supplement to the Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology: Nucleic Acid Characterization and Genetic Stability (4/92)
* Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (7/93)
* Draft Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1994)

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH) DOCUMENTS

* ICH; Guideline on Detection of Toxicity to Reproduction for Medicinal Products (9/94)
* ICH; Guideline on Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility (4/96)
* ICH; Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (7/96)

FDA GUIDELINES

* Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics (2/87)
* Guideline on General Principles of Process Validation (5/87)
* Guideline on Sterile Drug Products Produced by Aseptic Processing (6/87)
* Guideline on Validation of the Limulus Amebocyte Lysate Test As An End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices (12/87)
* Guideline for the Determination of Test Residual Moisture in Dried Biological Products (1/90)
* Guideline on the Preparation of Investigational New Drug Products (3/91)
* FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products (4/96)