Guidance for Industry

Clinical Considerations for Therapeutic Cancer Vaccines

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
October 2011

Contains Nonbinding Recommendations

Table of Contents

I. INTRODUCTION 1

II. BACKGROUND 2

III. CLINICAL TRIAL DESIGN CONSIDERATIONS 2

A. Considerations for Both Early and Late Phase Clinical Trials 3

1. Patient population 3
2. Monitoring the immune response 5
3. Biomarkers as evidence of efficacy 6
4. Adjuvants used to stimulate immune response 6
5. Multi-antigen vaccines 7
6. Disease progression/recurrence immediately or shortly after the initial administration of cancer vaccines 7
7. Concomitant and subsequent therapies 8

B. Considerations for Early Phase Clinical Trials 8

1. Starting dose and dosing schedule 9
2. Booster and maintenance therapy 10
3. Dose escalation 10
4. Single-arm versus randomized phase 2 trials in early development 11

C. Considerations for Late Phase Clinical Trials 11

1. Safety profile from early phase clinical trials 12
2. Endpoints 12
3. Statistical issues 12
4. Control issues 13
5. Delayed vaccine effect 13
6. Autologous vaccine trials 14
7. Accelerated approval regulations 14

IV. REFERENCES 16

Contains Nonbinding Recommendations

Guidance for Industry[1]

Clinical Considerations for Therapeutic Cancer Vaccines

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides sponsors who wish to submit an Investigational New Drug application (IND) for a therapeutic cancer vaccine with recommendations on critical clinical considerations for investigational studies of these products. This guidance will discuss considerations common to phase 1 and phase 2 clinical trials (collectively referred to as "early phase clinical trials") and phase 3 clinical trials (referred to as "late phase clinical trials"), as well as considerations that are unique to specific stages of clinical development of therapeutic cancer vaccines. This guidance provides recommendations for the design of clinical trials for cancer vaccines conducted under an IND (Title 21 Code of Federal Regulations (21 CFR) Part 312) to support a subsequent biologics license application (BLA) for marketing approval. This guidance finalizes the draft guidance of the same title dated September 2009.

The products discussed in this guidance are therapeutic cancer vaccines intended to result in specific responses to a tumor antigen, and are intended for the treatment of patients with an existing diagnosis of cancer. These products are regulated by the Center for Biologics Evaluation and Research (CBER) and are referred to as "cancer vaccines" throughout this document. These cancer vaccines mediate their therapeutic effect through in vivo induction or amplification of the antigen-specific host immune response. This guidance does not apply to vaccines for preventative and therapeutic infectious disease indications, to products intended to induce or augment a non-specific immune response, or to products intended to prevent, or decrease the incidence of cancer in individuals without a prior history of that cancer. Furthermore, this guidance does not apply to adoptive immunotherapeutic products which may mediate their therapeutic effect by targeting the tumor directly, such as T cell or NK cell products. Adoptive immunotherapeutic products and cancer vaccines have different mechanisms of action and therefore this guidance is not applicable to development of those products.

[1] This guidance has been prepared by the Office of Cellular, Tissue and Gene Therapies in FDA's Center for Biologics Evaluation and Research.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The mechanism of action for most cancer vaccines is thought to be mediated through induction of an antigen-specific T cell response or amplifying a pre-existing antigen-specific T cell response, especially cytotoxic T cell responses. Cancer vaccines induce responses to tumor-specific antigens that are processed by the immune system through antigen-presenting cells (APCs). These APCs then present antigenic determinants in a Human Leukocyte Antigen (HLA)-restricted fashion to T cells which in turn can attack tumor cells that express cognate antigenic determinants. T cells can also provide help for B cell responses that produce antibodies, which in some cases could lead to tumor cell death. The course of antigen presentation and processing, activation of lymphocytes, and tumor cell killing, is expected to require a substantial time in vivo. Thus, development of a cancer vaccine can present different considerations for clinical trial design than development of a more traditional biological product or cytotoxic drug for the treatment of cancer.

FDA has held or participated in several meetings to discuss development of cancer vaccine products. For example, on February 8-9, 2007, CBER co-sponsored a workshop with the National Cancer Institute entitled, "Bringing Therapeutic Cancer Vaccines and Immunotherapies through Development to Licensure." In consideration of the input FDA received from stakeholders, this guidance provides recommendations for the design of clinical trials for cancer vaccines conducted under an IND to support a subsequent BLA for marketing approval.

III. CLINICAL TRIAL DESIGN CONSIDERATIONS

During the early phase clinical trials, studies for a new cancer vaccine are normally conducted to determine optimal dose and dosing schedule, potential biological and clinical activity, and safety profile. In contrast, during late phase clinical trials, studies are conducted to demonstrate efficacy and safety in a defined population. The results from late phase trials may potentially support a BLA submission.

A. Considerations for Both Early and Late Phase Clinical Trials

Clinical considerations that are relevant to both early and late phase clinical trials include the following:

1. Patient population

    a. Disease setting

    The conventional model for clinical development of a chemotherapeutic agent involves initial testing in patients with advanced metastatic diseases and different tumor types to determine the maximum tolerated dose (MTD) and optimal schedule as well as assessment of clinical activity through tumor shrinkage (objective tumor responses). Therefore, assessment of the MTD and clinical activity, through tumor shrinkage that is apparent within the first 8 weeks on investigational therapy, can be assessed with short observation periods in clinical trials of traditional cytotoxic therapy. Subsequent development then examines the agent in a metastatic setting of a single tumor type for efficacy and safety generally in a large, usually randomized and controlled setting. Once its efficacy and safety are demonstrated in the setting of metastatic disease, the same agent may then be developed and tested in subjects who have minimal burden of disease or no evidence of residual disease (Refs. 1 and 2).

    In contrast, the time to development of an anti-tumor immune response needed for activity/effectiveness of a cancer vaccine generally requires 2-3 months.

    In addition, patients with relapsed or recurrent metastatic disease usually have received multiple treatments (e.g., cytotoxic and/or immunosuppressive chemo- and radio-therapies) for their cancer. These therapies may be detrimental to the immune system, minimizing the potential responsiveness to the cancer vaccine being tested. In contrast, testing cancer vaccines in patients with no evidence of residual disease or minimal burden of disease, as discussed in this guidance, may provide adequate time for the cancer vaccine to elicit a detectable immune response. However, demonstration of efficacy would require following the subjects for evidence of disease recurrence. Therefore, the disadvantage of this approach is that clinical development may require more patients and time. Consequently, developers of cancer vaccines need to weigh the advantages and disadvantages of testing these agents in patients with metastatic diseases versus patients with no evidence of residual disease or minimal burden of disease.

b. Patient population tumor heterogeneity

Cytotoxic agents are usually tested in phase 1 clinical trials in a population that includes a heterogeneous mix of tumor types at various clinical stages. The primary goal of these phase 1 studies is often to determine the MTD and the safety profile of the tested agents; therefore, the possibility that any given agent may have a different effect on different tumor types is accepted in these trials. Agents that are found to have an acceptable toxicity are then tested in phase 2 clinical trials with a relatively homogenous patient population and a defined tumor type.

Although it may be acceptable to test heterogeneous patient populations with a common antigen in early phase trials, this approach is unlikely to provide interpretable evidence of efficacy for the purposes of licensure. In addition, there are particular challenges with the approach of enrolling patients with heterogeneous tumor types and stages into early phase trials of cancer vaccines. Differences in the clinical stage of the disease and prior treatments can affect the potential response to the cancer vaccine. This is especially problematic with vaccines that are made from autologous patient materials, as each patient and tumor histology is different, resulting in different vaccine preparations. As a result, interpretation of trial results from a heterogeneous patient population can be especially challenging, and the objectives of the trials may not be achieved. Thus, in selecting the patient population for cancer vaccine testing in early phase trials, careful consideration should be given to the heterogeneity of the patient population.

c. Co-development of cancer vaccines and tests for targeted antigen

When the proposed mechanism of action involves a specific antigen or other therapeutic target, consideration also should be given to developing an assay or mechanism to measure the target antigen expression in tumor tissues of individual patients and using that information in subject selection or response monitoring. These assays are generally regulated by the Center for Devices and Radiological Health (CDRH). Therefore, sponsors developing cancer vaccines who are considering including the use of an assay in the labeling of the cancer vaccine, or sponsors of such assays who are planning to develop the assay for use with a specific cancer vaccine should request a meeting with both the relevant product review office (CBER) and the relevant device review division (CDRH). Discussions begun early in the development process, ideally before submission of an IND and/or Investigational Device Exemption (IDE), may help ensure that product development provides data that establish the safety and effectiveness of the therapeutic product and assay pair. This is

particularly important where use of the assay turns out to be necessary to the safe and effective use of the therapeutic product (referred to as companion diagnostics) (Refs. 3-5).

2. Monitoring the immune response

The proposed mechanism of action of cancer vaccines is that they mediate their anti-tumor activities by eliciting or amplifying an immune response. We consider immune monitoring as mainly exploratory, especially in early phase clinical trials, with the major goals of establishing proof-of-principle for the proposed pharmacological effect and showing immunogenicity of the administered antigens. To this end, monitoring of the immune response can be useful as follows:

- To assess variations in immunocompetency that may affect the study results. Responses against known immunogens (e.g., keyhole limpet hemocyanin or tetanus for humoral immunity; phytohemagglutinin for cellular responses) and HLA typing could assess patient population heterogeneity and assess any HLA link/bias to product activity.

- In early phase clinical trials, to optimize the dose and schedule, determine whether the vaccine induces the intended immune responses, assess immune tolerance, provide proof-of-concept, and aid the decision-making process concerning further product development and later clinical trial design.

- In later phase clinical trials, to provide data regarding the types, magnitudes and duration of response and the possible correlation with clinical efficacy parameters.

A clinically effective anti-tumor response involves a multi-component process; therefore, multiple monitoring assays may be needed to identify and measure the components of the immune responses. Assays that measure the immune response(s) thought to be the most important and relevant components of the anti-tumor response should be developed. If possible, at least two immunological assays should be used in an attempt to monitor the proposed immunologically-mediated anti-tumor response. Assay standardization should include specific parameters to control for general variability in an immune response across study sites. The assay parameters, such as assay conditions, sensitivity and specificity of the assay, any in vitro amplification step involved, positive and negative controls, cutoff values for determining the positive and negative test results from patients' specimens, and the statistical analytical methods to be used for the test results, should be clearly described in the clinical protocol prior to the initiation of the clinical trials.

If the specific antigen has not been identified or appropriate reagents specific for target antigens are not available, then developing a specific immune response assay can be challenging. In situations where antigen-specific immune monitoring assays cannot be established, it may be possible to assay T cell or antibody responses to whole tumor cells or tumor cell lysates in vitro or in vivo by delayed type hypersensitivity (DTH) testing to standard antigens. To determine the specificity of host immune response, appropriate controls (including common antigens (e.g., influenza, Candida, tetanus toxoid)) should be included in the DTH assay. Even when common antigens are not available, the possible value of global measures of T cell or antibody levels and activity can be discussed with CBER. We encourage sponsors to have these discussions with CBER as early as possible (Ref. 3).

Exploratory studies that evaluate the elimination of antigens on tumors may be helpful in monitoring immune response or evaluating mechanisms of resistance to immunotherapies. However, elimination of antigens may not be indicative of efficacy and therefore cannot be the primary evidence of efficacy in a BLA.

3. Biomarkers as evidence of efficacy

FDA supports development of exploratory biomarkers for proof-of-concept and scientific understanding of mechanism of action. However, the development of biomarkers as surrogates for efficacy is beyond the scope of this guidance.

4. Adjuvants used to stimulate immune response

Cancer vaccine formulations may contain adjuvants used in conjunction with vaccine antigens to augment or direct the specific immune response to an antigen. Prior to clinical administration of the vaccine-adjuvant combination, the potential toxicity of the adjuvant alone, and of the investigational clinical vaccine-adjuvant combination, should be assessed in preclinical studies as appropriate. The design of these preclinical studies should mimic the planned clinical immunization regimen and route of administration. General requirements for inclusion of such adjuvants in licensed biological products are described in 21 CFR 610.15. These requirements include submission of evidence that adding the proposed adjuvant to a product does not adversely affect the safety or potency of the product (21 CFR 610.15(a)). Information supporting the value of adding the adjuvant should be provided, preferably at an early stage of vaccine development, and may include evidence of enhanced immune response or antigen-sparing effects, and data supporting selection of the dose of the adjuvant.

When products which may have independent clinical activity (e.g., cytokines) are used as adjuvants to enhance the effects of vaccine antigens, the study design and control group(s) should be discussed with FDA. Study design requirements will be considered on a case-by-case basis.

5. Multi-antigen vaccines

Cancer vaccine formulations may contain multiple tumor-associated antigens in order to generate multiple tumor-specific immunologic responses and potentially hinder potential tumor escape mechanisms. In general, each component of a multi-antigen vaccine may not need to be individually evaluated for safety and activity, this will be considered on a case-by-case basis.

6. Disease progression/recurrence immediately or shortly after the initial administration of cancer vaccines

In oncologic practice, investigational and approved treatments are generally discontinued when patients experience disease progression. Because of the time required for the host (patient) to elicit or amplify an immune response to a cancer vaccine (i.e., tumor-specific immune response), the vaccine may have a delayed effect in the study subjects. In this situation, clinical progression may occur before the vaccine has had sufficient time to be effective. Therefore, clinical progression that is asymptomatic and/or is not likely to result in life-threatening complications with further progression (e.g., Central Nervous System (CNS) metastases or impending fractures from bony metastases) may not be sufficient reason for discontinuation of administration of a cancer vaccine.

One potential approach to this situation would be for the study protocol to clearly define the extent and location of clinical disease progression for which continued vaccination will be continued. The following are potential clinical situations in which sponsors may wish to consider providing provisions in the protocol for continued vaccination despite evidence of disease progression:

- Subjects continue to meet all other study protocol eligibility criteria.
- No dose limiting toxicity (DLT) has been observed, and all toxicities resolved to the baseline level, consistent with the study eligibility criteria.
- No deterioration of subject performance status.
- No curative salvage therapy exists for the indication (e.g. resection of pulmonary metastases in osteosarcoma patients).
- Does not delay imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases).
- Clinical evidence from early phase clinical trials suggests delayed effects.

The informed consent document provided to subjects must describe any reasonably foreseeable risks or discomforts to the subject (21 CFR 50.25(a)(2)) (e.g., the possibility of disease progression or recurrence) and other alternative treatment options.

7. Concomitant and subsequent therapies

One of the recent advances in the immunotherapy field is the realization that effective destruction of a tumor involves multiple coordinated immune mechanisms. These mechanisms include, but are not limited to, enhancement of the activities of antigen presenting cells, activation of effector T cells, and removal of suppressor T cells. The ultimate therapeutic effect of cancer vaccines may be diminished or enhanced by other cytotoxic or immunomodulatory treatments. Therefore, such cytotoxic or immunomodulatory effects of other treatments should be considered in the overall product development plan and specifically in the clinical trial design. Justification should be provided for the use of concomitant therapy (e.g., chemotherapy, biotherapy, radiotherapy, laser therapy), including the mode of action, dose and schedule of the concomitant therapy, and potential for negative or positive interactions of the concomitant therapy with the vaccine.

When standard therapies are available, consideration should be given to the timing and sequencing of these therapies, relative to the schedule of cancer vaccine administration, to optimize the evaluation of the safety and potential biological activities of the cancer vaccine. Preclinical exploration of the different options of timing and sequencing of cancer vaccine and standard therapy (such as cytotoxic chemotherapy) can help guide clinical development. Trial design details, including eligibility criteria and stratification factors, should be carefully considered in order to minimize the impact of standard therapies on the study's ability to detect the cancer vaccine's biological activity.

In certain instances, the use of other therapies may constitute a combination product (21 CFR 3.2(e)). The implications of development of a potential combination product should be discussed with FDA during the early stages of product development to obtain recommendations that are tailored to a specific product/combination product.

Induction of an effective response to a cancer vaccine may affect the efficacy of subsequent cytotoxic, targeted or other cancer therapy. Therefore, the nature and duration of subsequent therapies should be documented.

B. Considerations for Early Phase Clinical Trials

The primary goals of the early phase clinical trials of a cancer vaccine are to: assess the safety of the product; determine the optimal dose and dosing schedule for the product; and identify and study the potential biological activities to provide scientific data to guide further product development.

1. Starting dose and dosing schedule

The selection of the starting dose and the subsequent dose escalation scheme, as well as the dosing schedule, for initial clinical trials of a cancer vaccine should be supported by data generated from the preclinical studies and/or prior human experience.

When feasible, preclinical in vitro and in vivo proof-of-concept (POC) studies are recommended to provide the rationale for the proposed clinical trial. These studies, in conjunction with appropriately designed preclinical studies characterizing the toxicology of the cancer vaccine, should guide the clinical doses and initial clinical dosing schedule. The dose levels used in the preclinical toxicology studies should be based on dose levels that showed biological activity in preclinical POC studies. The objective of these preclinical studies is to identify a dose level, such as a no-observed-adverse-effect-level, if applicable, that can guide initiation of clinical dosing, after consideration of relevant biological or physiological parameters (e.g., body weights, antigen expression, clinical pathology, pathology).

Since potential vaccine-related toxicities may be related to the presence of the target antigen in normal tissues, or to the presence of an unrelated protein in normal tissues that may contain a peptide sequence similar to a peptide in the vaccine, the presence of target antigen in normal human tissues should be determined. For peptide vaccines, sequence homology searches should be conducted to assist in prediction of potential vaccine-related toxicities.

Assessment of the kinetics of the immune response of the cancer vaccine product in preclinical studies may also provide insight into the potential in vivo activity and safety profile of the vaccine, and help guide dose selection and the timing of subsequent vaccinations in humans.

In general, due to the predicted mechanism(s) of action of these vaccine products, as well as species-specific variation in immune response activity, there is no predefined conversion factor to enable extrapolation from a safe dose in animals to a potentially safe starting dose in humans. The sponsor should submit justification, with supporting scientific data, for the extrapolation modality used to determine the proposed clinical starting dose, dose escalation scheme, and dosing schedule.

When a particular cancer vaccine belongs to a class of agents that has been previously administered to humans, a body of safety and activity data may already exist. In such situations, depending on the relevance of the available clinical data, additional preclinical studies may not be needed to support the starting dose and

dosing schedule. The sponsor should provide comprehensive information in the IND, including existing clinical data regarding the activity and safety profile, to support the safety of the cancer vaccine in the proposed trial.

2. Booster and maintenance therapy

Sponsors may wish to explore vaccination boosters and maintenance therapy to evaluate long-term immunogenicity and its correlation with clinical outcomes. The conduct of preclinical studies to evaluate such regimens is recommended, and subsequent clinical studies should be designed to support the safety and effectiveness of such regimens.

3. Dose escalation

The traditional standard dose escalation schedule in the development of cancer therapeutics uses the so-called "3 + 3 design" to avoid selection of a phase 2 clinical trial dose that causes a treatment-limiting toxicity in more than 17% of subjects, a standard considered acceptable as an outpatient therapeutic for patients with limited options and life-threatening diseases. In a "3 + 3 design," three patients are initially enrolled into a given dose cohort. If there is no DLT observed in any of these subjects, the trial proceeds to enroll additional subjects into the next higher dose cohort. If one subject develops a DLT at a specific dose, an additional three subjects are enrolled into that same dose cohort. Development of DLTs in more than 1 of 6 subjects in a specific dose cohort suggests that the MTD has been exceeded, and further dose escalation is not pursued.

Many cancer vaccine trials have used the "3 + 3 design," and the results show that, except in very rare situations, an MTD for a cancer vaccine may not be identified. In these trials, the dose-toxicity curve may be so flat that the highest dose that can be administered is limited by manufacturing or anatomic issues rather than toxicity. Therefore, this "3 + 3 design" may not be the most suitable approach to gathering information from early phase trials of cancer vaccines, and alternative trial designs should be considered.

Given the relatively acceptable safety profile of some classes of cancer vaccines, alternative dose-escalation approaches, such as accelerated titration or continuous reassessment, may be considered instead of the standard "3 + 3 design". When using such designs, the protocol should describe acceptable parameters for the dosing endpoint (supported by data). Irrespective of which dose-escalation approach is chosen, the study protocol should clearly define DLTs, the subject "off-treatment" criteria, and the study stopping rules that will ensure subject safety. When no DLT is expected or achieved, optimization of other outcomes, such as the immune response, can be useful to identify doses for subsequent studies.

When cancer vaccines are tested in combination with other therapeutic agents or devices, or administered through invasive procedures, or to anatomic sites that carry a significant safety concern, a standard dose-escalation approach may be indicated to determine the safety profile of the vaccine or combination.

4. Single-arm versus randomized phase 2 trials in early development

FDA recommends that IND sponsors take care to design early phase clinical trials that provide POC data, optimize the dose and dosing schedule, and provide a detailed understanding of the activity of the new agent relative to therapies currently available for the purported indication. This early phase data should be available prior to the transition to randomized late phase clinical trials that are designed to establish efficacy and confirm safety.

When designing a phase 2 clinical trial, the advantages and disadvantages of single-arm versus randomized phase 2 trials should be considered. Results from single-arm studies may overestimate the time-to-event treatment effects of the investigational agent for various reasons. In addition, time-to-event endpoints in the single-arm setting must rely on historical controls and are therefore subject to selection bias in identification of that historical population, and confounding by the change in the standard of care over time.

Single-arm studies can be, and often are, used to demonstrate tumor shrinkage by cytotoxic agents; however, such evidence of therapeutic activity is more difficult to obtain in situations where the product is a cancer vaccine that may not be expected to cause tumor shrinkage. Therefore, due to their mechanism of action, single-arm studies of cancer vaccines may not provide reliable anti-tumor activity data to guide subsequent product development, although such studies may better characterize and estimate immunologic effects.

Randomized phase 2 trials, due to their limited sample sizes, typically lack the statistical power for conclusive demonstration of the treatment effect of the investigational agent and provide a more limited patient experience for generalization of treatment effects to the general patient population. However, such randomized phase 2 trials can provide more reliable data to guide the design of the later phase confirmatory trials (e.g., help to determine the appropriate sample size and estimate treatment effect) and take into account potential negative effects, including tolerance induction.

C. Considerations for Late Phase Clinical Trials

Early phase clinical trials evaluate safety, optimize the dose and dosing schedule, and provide evidence of biological drug activity. Later phase studies are intended to gather additional information about effectiveness and safety. FDA encourages sponsors to initiate late phase trials using the most biologically effective dose and schedule based on

early phase clinical studies. The following sections discuss endpoint selection for clinical trials to evaluate cancer vaccines. Sponsors are encouraged to meet with FDA to discuss a late phase clinical trial design, including endpoint selection (Ref. 6).

1. Safety profile from early phase clinical trials

Late phase clinical trial design should consider the safety data from early phase clinical trials. It is important that a product have an adequate safety profile before moving forward to phase 3 clinical trials. Sponsors are encouraged to discuss safety issues with CBER at meetings such as end-of-phase 2 meetings (Ref. 3). If safety issues are identified in the early phase clinical trials, these issues need to be evaluated carefully during phase 3 clinical trials, including appropriate subject monitoring. For example, for cancer vaccines, autoimmune phenomena may represent a potentially debilitating side effect that will need monitoring during the progress of the trial and in long-term follow-up. The length of follow-up will depend on a number of factors, including natural history of the disease and product characteristics. For gene therapy studies, please see the FDA guidance entitled "Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events," dated November 2006 (Ref. 7).

2. Endpoints

One of the most important aspects of designing a late phase trial is to choose a clinically meaningful endpoint. Demonstrable clinical benefits vary with cancer type and status of disease. Clinical benefits that have supported drug approval have included important clinical outcomes (e.g., increased survival, symptomatic improvement) but also have included effects on established surrogate endpoints. Consideration of the recommendations in the FDA guidances entitled "Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics," dated May 2007 (Ref. 2), "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," dated May 1998 (Ref. 8), and "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," dated December 2009 (Ref. 9), may be particularly useful for both design and endpoint selection. Endpoints based on tumor assessments, as discussed in section III.B of the May 2007 guidance, may not be appropriate endpoints for a late phase clinical trial for a cancer vaccine.

3. Statistical issues

The overall clinical effect of a cancer vaccine should be evaluated in the context of the currently available therapeutic options. FDA recommends use of a superiority trial design to demonstrate a cancer vaccine's treatment effect on a chosen endpoint.

In certain clinical settings, the effect size of the available therapy(ies) may be well established. In these limited situations, a noninferiority (NI) trial design and analysis may be considered. However, the design of a NI trial is complex; therefore, sponsors should include early consultation with the FDA and careful consideration of the recommendations in the FDA draft guidance entitled "Guidance for Industry: Non-Inferiority Clinical Trials,[2]" dated March 2010 (Ref. 10).

Adaptive trial designs will be considered on a case-by-case basis. Sponsors should consider the recommendations in the FDA draft guidance entitled "Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics[3]," dated February 2010 (Ref. 11).

Imbalances in subsequent therapies may confound the interpretation of study results, particularly when the primary endpoint is overall survival. Therefore, the study should document the nature and duration of subsequent therapies, and appropriate sensitivity analyses should be pre-specified.

4. Control issues

To avoid the biases that can be introduced in the conduct of the trial and which confound the analyses of the trial results, cancer vaccine trials should have appropriate controls, either an active comparator or placebo. Studies involving a placebo should be carefully considered and planned. Withholding an available therapy with proven safety and efficacy may be unethical.

Blinding of subjects, investigators, and evaluators may be helpful to decrease the risk of bias in the study results. However, either cancer vaccines or co-administered immune stimulatory agents can cause reactions that make the subjects treated with the vaccine easily identifiable. To maintain blinding of treatment assignment, the study may need to provide separate personnel for each of the following: study agent administration; post-administration subject care; and endpoint assessment.

5. Delayed vaccine effect

As a consequence of their immunological mechanisms of action, cancer vaccines may require considerable time after administration to induce immunity. Therefore, tumors in subjects treated with cancer vaccines may show early progression followed by subsequent response. This potential phenomenon should be considered in the design of later phase clinical trials, particularly if nonclinical data or early phase clinical trials suggest that the phenomenon exists and time-to-event endpoints are used. Due to delayed effect of the vaccine, the endpoint curves may show no effect for the initial portion of the study. If the vaccine is

[2] This draft guidance, when finalized, will represent FDA's current thinking on this topic.
[3] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

effective, evidence of the effect may occur later in the study. This delay in the effect may lead to an average effect that is smaller than expected and thus may require both an increase in sample size to compensate for the delay and a careful assessment of trial maturity for the primary analysis. In addition, possible violation of the proportional hazards assumption should be considered when selecting a statistical method for the primary analysis.

6. Autologous vaccine trials

Design of studies using autologous vaccine products that are derived from the subjects' own tumors poses unique challenges and deserves special consideration. Manufacturing such vaccines may take up to several months. If complete remission or stable disease is an eligibility criterion, the time required for manufacture may mean that some trial subjects may become ineligible for vaccine administration because of disease recurrence or progression.

Additionally, manufacture of autologous vaccine product may not be possible for every subject for a wide variety of source material and/or manufacturing process reasons. Regardless of the cause, a sponsor's inability to treat randomized subjects with the vaccine may adversely affect the statistical power of the clinical study. Therefore, consideration should be given to optimization of the vaccine manufacturing process before the late phase clinical trials are initiated, to increase the proportion of the randomized subjects who receive the vaccine.

7. Accelerated approval regulations

FDA's accelerated approval regulations in 21 CFR Part 314, Subpart H (for drugs) and 21 CFR Part 601, Subpart E (for biologics) apply to new drug and biological products that (1) have been studied for their safety and effectiveness in treating serious or life-threatening illnesses, and (2) provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy) (21 CFR 314.500 and 601.40). In this setting, FDA may grant approval on the basis of adequate and well controlled clinical trials establishing that the drug or biological product has an effect on a surrogate endpoint that *is reasonably likely*, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit (21 CFR 314.510 and 601.41).[4]

[4] These regulations do not explicitly define the term *available therapy*. The Center for Drug Evaluation and Research (CDER) and CBER have determined that in regulations where the terms are not otherwise defined, the terms *available therapy* and *existing treatments* should be interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions. FDA recognizes that there are cases where a safe and effective therapy for a disease or condition exists but is not approved for that particular use by FDA. However, for purposes of the accelerated approval regulations, only in exceptional cases will a treatment that is not FDA-regulated (e.g., surgery) or that is not labeled for use but is supported by compelling literature evidence (e.g., certain established oncologic treatments) be considered *available therapy*. See the FDA guidance entitled "Guidance for

FDA has accepted tumor shrinkage as an appropriate surrogate endpoint in the setting of a population of cancer patients with advanced disease and tumors that are refractory to existing therapies. However, as previously discussed, cancer vaccines may not induce tumor shrinkage; therefore, accelerated approval based on tumor responses may not represent a feasible path to licensure for cancer vaccines.

Approval under the accelerated approval regulations is subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. A single late phase trial may support both accelerated approval, based on an intermediate endpoint, and confirmation of effectiveness, based on further follow-up of survival in the same trial. Thus, confirmatory postmarketing studies could be underway at the time of accelerated approval. If a sponsor is contemplating licensure by the accelerated approval pathway, the sponsor should consider the need to develop a plan to confirm clinical benefit following licensure. If the postmarketing studies fail to demonstrate clinical benefit or the applicant fails to perform the required postmarketing study with due diligence, FDA may withdraw approval, following the withdrawal procedures set forth in the regulations at 21 CFR 601.43.

Industry: Available Therapy," dated July 2004 (Ref. 12). The guidance also discusses the phrase "meaningful therapeutic benefit to patients over existing treatments."

IV. REFERENCES

1. Guidance for Industry: FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products (December 1998) accessible at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071657.pdf.
2. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007) accessible at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf.
3. Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products (February 2000) accessible at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf.
4. Guidance on IDE Policies and Procedures (January 1998) accessible at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm.
5. Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices (July 2011) accessible at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf.
6. Guidance for Industry: Special Protocol Assessment (May 2002) accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf.
7. Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (November 2006) accessible at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078719.pdf.
8. Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998) accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf.
9. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (December 2009) accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.
10. Draft Guidance for Industry: Non-Inferiority Clinical Trials (March 2010) accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf.
11. Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics (February 2010) accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf.
12. Guidance for Industry: Available Therapy (July 2004) accessible at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126637.pdf.