Guidance for Industry

Clinical Considerations for Therapeutic Cancer Vaccines

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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Guidance for Industry[1]

Clinical Considerations for Therapeutic Cancer Vaccines

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I. INTRODUCTION

This guidance provides you, sponsors who wish to submit an Investigational New Drug application (IND) for a therapeutic cancer vaccine, 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 (which collectively may be referred to as "early phase clinical trials") and phase 3 clinical trials (which may be referred to as "late phase clinical trials") and that are unique to specific stages of clinical development of these biological products.

The products discussed in this guidance are for therapeutic cancer vaccines, referred to as "cancer vaccines" throughout this document, intended to be administered to patients with an existing cancer for the purpose of treatment. This guidance does not apply to products intended to be administered to patients to prevent or decrease the incidence of cancer. Furthermore, this guidance does not apply to adoptive immunotherapeutic products such as T cell or NK cell products. Although clinical trials involving these products share certain overlapping features with those involving cancer vaccines, adoptive immunotherapeutic products have different mechanisms of action and unique requirements with respect to product development.

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.

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

II. BACKGROUND

The mechanism of action for most cancer vaccines is thought to be mediated through amplifying a native T-cell response, especially cytotoxic T cells. Cancer vaccines, as antigens, are processed by the adaptive immune system through antigen-presenting cells (APCs). These APCs then present antigenic determinants in a Human Leukocyte Antigen (HLA) - restricted fashion to T cells and/or B cells, which in turn can attack tumor cells that express cognate antigenic determinants or can 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 considerable time in vivo, especially if vaccination requires several doses. Thus, development of a cancer vaccine can present different considerations for clinical trial design than development of a traditional cytotoxic drug or biological product for the treatment of cancer.

FDA has held or participated in several meetings to discuss development of cancer vaccines. 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 we received from stakeholders, this guidance provides recommendations for the design of clinical trials for cancer vaccines conducted under an IND (21 CFR Part 312) to support a subsequent license application for marketing approval, a biologics license application (BLA), submitted to CBER.

III. CLINICAL TRIAL DESIGN CONSIDERATIONS

During the early phase clinical trials, studies for a new cancer vaccine are conducted to determine optimal dose and dosing schedule, potential biological activities, and safety profiles. In contrast, during late phase clinical trials, studies are conducted to demonstrate efficacy and safety in a defined population. The results from such trials may support an application for licensure.

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 optimal dose, schedule, and maximum tolerated dose (MTD). When initial testing is conducted in a patient population with advanced metastatic disease, patients can be

enrolled, dosed, and evaluated in a reasonably short time frame. Since most patients with advanced metastatic disease would have a relatively quick disease progression, any potential activity of the cytotoxic agents on the disease status would be detected during relatively short trials. 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 or no evidence of residual disease.[2]

Testing cancer vaccines using the conventional model may not allow time for development of an anti-tumor immune response needed for activity/effectiveness because of the potentially short time interval from administration of study agent to subsequent disease progression in patients with metastatic cancer. In addition, patients with metastatic diseases usually have received multiple treatments (e.g., cytotoxic and/or immunosuppressive chemo- and radio-therapies) for their cancer, which 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 immune response elicited by the cancer vaccines to develop and manifest. The disadvantage is that clinical development may take longer. 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.

When standard therapies are available, consideration should be given to incorporating the timing and sequencing of these therapies with cancer vaccine administration to optimize the evaluation of the safety and potential biologic activities of such a treatment regimen.

b. Patient population tumor heterogeneity

Cytotoxic agents are usually tested in phase 1 studies in a population that includes a heterogeneous mix of tumor types at various clinical stages. The possibility that any given agent may have a different effect on

[2]See FDA's guidances entitled "Guidance for Industry: FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products" dated December 1998 accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071657.pdf and "Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" dated May 2007 accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf.

different tumor types is accepted in these trials since the primary goal of the phase 1 studies of cytotoxic agents is often to determine the MTD and the safety profile of the tested agents. Agents that are found to have an acceptable toxicity are then tested in phase 2 trials with a relatively homogenous patient population and a defined tumor type.

However, there are particular challenges with the approach of enrolling patients with heterogeneous tumor types and stages in testing cancer vaccines in early trials. Differences in the clinical stage of the disease and prior treatments can affect the potential response to the cancer vaccine. This is particularly 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, careful considerations should be given with regard 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, consideration 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 patient selection as well as response monitoring. If the development of a novel assay is involved, the sponsor should propose a plan for co-development of the assay with the cancer vaccine in early discussions with FDA, before the sponsor submits its IND, so that we, FDA, can provide advice on scientific, clinical, and regulatory issues at an appropriate stage of product development. (Ref. 1)

2. Monitoring the immune response

The proposed mechanism of action of cancer vaccines is that they mediate their anti-tumor activities by eliciting an immune response. Among other factors, monitoring of the immune response can be very important for the following reasons:

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

- In later phase clinical trials to provide data for comparison of the clinical efficacy parameters with the types and magnitudes of immune responses.

Mounting a clinically effective anti-tumor response involves a multi-component process coordinated to mediate the effect. Therefore, multiple monitoring assays may be needed to identify and measure the component 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. We recommend that, if possible, at least two immunological assays should be used in an attempt to monitor the proposed immunologically-mediated anti-tumor response. The assay parameters, such as assay conditions, 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.

Developing a specific immune response assay can be challenging if the specific antigen has not been identified or appropriate reagents specific for target antigens are not available. 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. When even that type of antigenic material is not available, the possible value of global measures of T cell or antibody levels and activity, including DTH testing to standard antigens, can be discussed with CBER. We encourage sponsors to have these discussions with CBER as early as possible (Ref. 1).

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

In oncologic practice, patients are usually taken off current treatment when they have disease progression/recurrence. Because cancer vaccines need time to elicit an immune response that could manifest as biological activity (i.e., a tumor specific immune response), a delayed effect can be expected in the subjects who have received the vaccines. Shortly after the initial cancer vaccine administration, subjects may experience disease progression prior to the onset of biological activities or effects from the vaccine (delayed effects).

One potential approach to this situation would be to clearly define a description of disease status for which continued vaccination is intended in the clinical study protocol. The following are potential clinical situations in which you may wish to consider providing provisions in the protocol for continued vaccination.

- 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 entry eligibility criteria.
- Subjects may only receive the same dose and schedule that was given before disease progression/recurrence occurs/reoccurs.

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). It is also important to explain the protocol's provisions for these situations.

B. Considerations For Early Clinical Trials

The primary goals of the early cancer vaccine clinical trials are to: study the safety profile of the product; study the optimal starting dose and dosing schedule for the product; and identify and study the potential biological activities to provide scientific data on which to base further product development.

1. Starting dose and dosing schedule

It is important that the selection of the starting dose and the subsequent dose escalation schedule, as well as the dosing schedule, for initial clinical trials of a cancer vaccine be supported by data generated from the preclinical in vitro and in vivo studies and/or prior human experience.

Preclinical in vitro and in vivo proof-of-concept studies to establish the rationale for the starting dose and dosing scheme in conjunction with appropriately designed preclinical toxicology studies to assess the safety of the intended clinical product should guide the clinical dose levels and dosing schedule design. The dose levels used in the toxicology studies should be based on dose levels that showed biological activity in proof-of-concept studies and should bracket and exceed the proposed clinical dose levels in an attempt to identify a no-observed-adverse-effect-level (NOAEL). Due to the general mechanisms of action of these vaccine products, there is no predefined conversion factor to enable extrapolation from a safe dose in animals to a human starting dose. It is important that the sponsor provide justification, with supporting scientific data, for the extrapolation modality used to determine the clinical starting dose and dosing scheme in the IND.

The preclinical studies should incorporate a dosing schedule that mimics the intended schedule for the early phase clinical trial as closely as possible. The sponsor should provide justification for conducting a proposed clinical trial if a proposed clinical trial will include a greater number of immunizations with the

cancer vaccine than preclinical studies included. We encourage sponsors to meet with FDA as early as possible in product development to discuss the preclinical data needed to support a proposed clinical trial (Ref. 1).

For cancer vaccines that have been previously administered to humans, it may be possible to derive the starting dose and the dose escalation scheme from this prior human experience. We recommend that the sponsor provide comprehensive information in the IND, including the activity and safety profile, from the existing clinical data to support the safety of the cancer vaccine in the proposed trial.

When a particular cancer vaccine belongs to a class of agents that has been tested extensively in clinical trials, a considerable body of safety and activity data may already be established for this product class. In such situations, depending on the relevance of the existing clinical data that is submitted by the sponsor, the conduct of additional preclinical studies may not be needed to support the starting dose. We recommend that the sponsor contact CBER to discuss this issue prior to conducting the additional preclinical studies.

2. Dose escalation

The traditional standard dose escalation schedule in the development of cancer therapeutics uses the so-called "3 + 3 design" established to avoid doses that invoke a treatment limiting toxicity to <20% of patients, a standard considered acceptable as an outpatient therapeutic for patients with limited options and life-threatening diseases. In this situation, three patients are initially enrolled at a given dose cohort. If there is no dose limiting toxicity (DLT) observed in any of these subjects, the trial proceeds to enroll additional subjects to the next higher dose cohort. If there is one subject who develops a DLT, an additional three subjects are enrolled at that dose. Further development of DLTs in the expanded dose cohort (>1 of 6) 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 is not identified. This may suggest that this design may not be the most suitable approach to gathering information from early phase cancer vaccine trials and that 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, we recommend that you consider alternative clinical trial design approaches to gather data that are informative regarding dose escalation for cancer vaccine trials. Given the relatively tolerable safety profile of some classes of cancer vaccines, alternative dose escalation approaches, such as accelerated titration, may be considered instead of the standard 3 + 3 design. When using such designs, acceptable parameters for the dosing endpoint (supported by data)

should be described in the protocol. Irrespective of which dose escalation approach is chosen, the study protocol should clearly describe the definition(s) of DLTs, the subject "off-treatment" criteria and the study stopping rules that will ensure patient safety.

When cancer vaccines are tested in combination with other components or administered through invasive procedures or to anatomic sites that carry a significant safety concern, a traditional standard dose escalation approach may be indicated in order to determine the safety profile of the treatment without undue risk.

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

We recommend that the sponsor take care to design early phase clinical trials that provide data to support a solid proof-of-concept, optimization of the dose and schedule, and a detailed understanding of the activity of the new agent relative to what is currently available for the purported indication 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, you should consider the advantages and disadvantages of single-arm versus randomized phase 2 trials. Results from single-arm studies usually overestimate the treatment effect of the investigational agent, and when performed in single study centers, the subjects enrolled may not be completely representative of the true patient population. Single-arm studies can be, and often are, used to demonstrate tumor shrinkage by cytotoxic agents; however, 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. Time-to-event endpoints in the single-arm setting must rely on historical controls and are therefore subject to bias and confounding. Randomized phase 2 trials, although typically lacking the statistical power for conclusive demonstration of the treatment effect of the investigational agent, can provide value in the design of the later phase confirmatory trials (e.g., helping to determine the appropriate sample size and estimating treatment effect).

C. Considerations For Late Phase Clinical Trials

Early phase clinical trials evaluate safety, optimize the dose and schedule, and identify evidence of biological drug activity. Later phase efficacy studies evaluate clinical benefit. 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.[3]

[3] See FDA's "Guidance for Industry: Special Protocol Assessment" dated May 2002 (May 17, 2002), accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf.

1. Safety profile from early phase clinical trials

Late phase clinical trial design should be based on the safety data from early phase clinical trials to define eligible patient populations, primary and secondary trial endpoints, assumptions of treatment effect and sample size as well as other trial parameters.

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. 1). If safety issues are identified in the early phase clinical trials, these issues need to be evaluated carefully during phase 3 clinical trials with appropriate patient monitoring. For cancer vaccines, autoimmune phenomena, for example, represent a potentially devastating side effect that will need monitoring during the progress of the trial and in long-term follow-up.

2. Endpoints for licensure

One of the most important aspects in 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. We recommend consideration of the recommendations in FDA's "Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" dated May 2007, accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf, and FDA's "Guidance for Industry: Cancer Drug and Biological Products – Clinical Data in Marketing Applications" dated October 2001, accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM71323.pdf, prior to discussions with us regarding your choice of endpoints for your late phase clinical cancer vaccine trial. While these guidances may be helpful to you, it is important to keep in mind that endpoints based on tumor assessments, which are discussed in the guidances in sections III.B and III.D, respectively, may not necessarily be appropriate endpoints in a late phase clinical trial for a cancer vaccine.

3. Superiority versus noninferiority design

Although cancer vaccines may have mechanisms of actions that differ markedly from those of current, conventional chemotherapeutic agents, their overall clinical effect should be evaluated in the context of the currently available therapeutic options. Because these differences in mechanism of action may contribute to

difficulty in determining a noninferiority margin relative to an established therapeutic agent, we recommend use of a superiority trial design to demonstrate a cancer vaccine's treatment effect on a chosen endpoint over the control. However, in certain clinical settings in which an FDA-approved treatment is available, the effect size of the available therapy may be well established. In these limited cases, a noninferiority (NI) trial design and analysis may be considered. When an equivalence/NI trial is designed, the statistical analysis plan of the clinical protocol should specify *a priori* the NI margin chosen and the justifications for the chosen margin. We recommend early consultation with the FDA if an equivalence/NI trial design is being considered.

4. Control issues

To avoid the biases that can be introduced in the conduct of the trial and in the analyses of the trial results, cancer vaccine trials should have appropriate controls, either using an active comparator or placebo control. If using a placebo, the withholding of treatment should not lead to serious harm, such as death or irreversible morbidity. Studies involving a placebo should be carefully considered and planned. Either cancer vaccines or co-administered immune stimulatory agents can cause reactions that make the patients treated with cancer vaccines easily identifiable in these trials. To maintain this blind, the team administering the product may need to separate from the teams performing post-procedure subject care and endpoint assessment. We recommend consulting with FDA on selection of a control.

5. Delayed vaccine effect

As a consequence of their immunological mechanisms of action, considerable time might be needed for cancer vaccines to induce immunity after administration, and it frequently has been proposed that tumors in some subjects treated with cancer vaccines may show early progression followed by subsequent response.

To take the potential of this phenomenon into consideration in the later phase clinical trials of products for which nonclinical data or early phase clinical trials suggest that it may exist, we recommend that the statistical analysis plan contain specific definitions of outcome events (e.g., protocol specific criteria for responder and non-responder subjects) for the following scenarios:

- Initial tumor progression followed by subsequent regression with continued administration of cancer vaccine.
- Initial tumor progression followed by subsequent regression with continued administration of cancer vaccine and then followed by additional progression.

In general, time-to-event endpoints are measured from the time of randomization. Due to delayed effect of the vaccine, the endpoint curves of the trial results may show no effect for the initial portion of the study. If the treatment is effective, separation of the curves may occur later in the study after the vaccine effect has become established. This may violate the proportional hazard assumptions necessary when applying Cox modeling and may necessitate an increase in sample size to provide sufficient power to test a statistical hypothesis.[4]

6. Autologous vaccine trials

Design of studies using autologous vaccine products that are derived from the patients' own tumors poses unique challenges and deserves some special considerations. Manufacturing such vaccines can take a considerable period of time and in some instances, may take up to several months. If complete remission or stable disease are eligibility criteria, the time required for manufacture may mean that, some trial subjects may not remain eligible 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 enrolled subjects with active product will adversely affect the statistical power of the clinical study. Therefore, consideration should be given to optimization of the vaccine manufacturing process prior to late phase clinical trials in an effort to increase the proportion of the patients who are randomized to the treatment arm and receive the active product.

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

[4] In brief, a Cox model is a statistical technique for exploring the relationship between the survival of a patient and several explanatory variables.

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).[5]

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 be expected to induce tumor shrinkage.

Time-to-event endpoints other than survival have in some situations also been considered to be appropriate surrogate endpoints for clinical benefit in the licensure of cancer therapeutics.

Approval under the accelerated approval regulations will be 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 outcome. Postmarketing studies would usually be studies already underway. 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 post-marketing study with due diligence, FDA may withdraw approval, following a Part 15 hearing.

D. Concomitant 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. Effects of this nature should be considered in the overall product development plan and specifically in the clinical trial design. You should provide justification for any concomitant therapy, including the mode action, dose

[5] These regulations do not explicitly define the term *available therapy*. The Center for Drug Evaluation and Research 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 FDA's "Guidance for Industry: Available Therapy" (July 2004) (July 23, 2004, 69 FR 44039) accessible at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126637.pdf. The guidance also discusses the phrase "meaningful therapeutic benefit to patients over existing treatments".

and schedule of the concomitant therapy (e.g., chemotherapy, biotherapy, radiotherapy), and interactions of the concomitant therapy with the vaccine. In addition, parallel development of diagnostic tests to be used to determine patient eligibility or staging may raise similar considerations.

In certain instances, the use of other therapies may constitute a combination product (21 CFR 3.2(e)). You should discuss these issues with FDA during the early stages of product development so that we can provide you guidance that is tailored to your product.

IV. REFERENCE

1. 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