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30 July 2004

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

Re: Docket No. 2004N-0181: Critical Path Initiative Docket [Federal Register: 22 April 2004 (Volume 69, Number 78)]

Dear Sir or Madam:

This letter is in response to the FDA white paper entitled "Challenge and Opportunity on the Critical Path to New Medical Products," which presents an analysis of the "growing crisis in moving basic discoveries to the market."^[1] The paper provides an excellent overview and discussion of the Critical Path Initiative: it identifies potential problems and outlines proposed solutions that are innovative and thought provoking. In addition, the initiative is a call to action for all stakeholders to initiate efforts to improve the drug development critical path (i.e., safety assessment [nonclinical], demonstration of medical utility [clinical], and industrialization [chemistry, manufacturing, and controls]) by helping the FDA identify key components that require innovation to increase the speed of development of safe and effective products.

This response has been prepared by Cato Research (CATO). As part of this response, CATO would like to bring to your attention and highlight a development problem that warrants review and potential prioritization as part of the Critical Path Initiative: development of cancer immunotherapeutics, particularly, therapeutic cancer vaccines. Many therapeutic cancer vaccines may never become available to patients under the current review requirements. Although, as stated in the white paper, "FDA often approves vaccines based on their meeting validated surrogate markers for achieving protective levels of immunity," this is not the case for therapeutic cancer vaccines. In this response, CATO will (1) outline examples of promising therapeutic cancer vaccines that have been or could be lost from the current pipeline and possible solutions to prevent their loss and (2) bring to your attention and highlight an example you may want to use in the future of an orphan product approved for an important public health need where innovative and strategic effort by the FDA was a critical component to its success. As part of this response, CATO would like to volunteer to assist the FDA in further improving the drug development critical path as part of this important initiative, if the FDA would deem that assistance to be of use. In a similar fashion to the FDA, CATO, as a full-service contract research organization, is well positioned to help identify challenges associated with the drug development critical path, albeit on a much smaller scale.

Highlight: Developing Oncology Immunotherapeutics under the Current Clinical Benefit Paradigm — Therapeutic Cancer Vaccines and the Need for Innovative Approaches

A serious need exists to identify medical paradigms requiring innovative approaches and "modernization" of tools to advance the development of promising medical products. Particularly in the development of products for serious and life-threatening diseases (e.g., cancer), sponsors often find clinical data that suggest marginal benefit in the intention-to-treat (ITT) analysis, while the analysis of a smaller, selected subset of patients appears to show significant clinical benefit. For example, for effective therapeutic cancer vaccines, a clear benefit has been demonstrated for patients who show the desired immune reaction after dosing, such as raising an antibody titer. At the same time, the safety risk of administration of such therapeutics is generally low. Unfortunately, prospective determination of those patients who would

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show the necessary immune reaction is impossible because specific immunogenicity cannot be measured until after administration of the drug. Definitive covariant factors to determine the ability to produce an immune reaction and the extent of an immune reaction have not been identified for many therapeutic cancer vaccines. Strategies that may help address the challenges faced in the development of therapeutic cancer vaccines include the following:

- Additional consideration of positive risk-benefit ratio
- Consideration of appropriate clinical trial design
- Development of alternative methods for evaluating treatment comparisons

A new generation of targeted therapeutics for the treatment of cancer is emerging from the growing knowledge base of biomedical drug discovery. Based on a biological approach, novel cancer therapeutics currently under development include agents in the areas of vascular targeting, antisense, gene transfer, immunotherapy, and apoptotic induction. These innovative treatments hold the promise of improved therapeutic choices for selected cancer patient populations and have the benefit of diminished side effects compared with traditional cytotoxic therapies. This document will review the development status of several examples from the growing class of targeted cancer vaccines, specifically Theratope[®] vaccine (Biomira Inc.), Melacine[®] melanoma vaccine (Corixa Corporation), and Insegia[™] (Aphtron Corporation). A review of these programs indicates there is no optimal solution for determining clinical benefit for therapeutic cancer vaccines under the current drug development paradigms. This document proposes greater consideration of the risk-benefit ratio, consideration of alternative trial designs, and expansion of prospective definitions of subpopulations to facilitate the development of these promising therapies.

Brief Overview of Cancer Vaccines in Development (selected examples)

Therapeutic cancer vaccines specifically targeted to epitopes on tumors are relatively new tools in the fight against cancer. Cancer vaccines are generally composed of tumor cell epitopes, known tumor growth factors, or tumor cell DNA and are designed to stimulate the patient's immune system to produce antibodies against the desired molecule. In effect, the vaccines are designed to use the body's own defenses to attack or starve the tumor, resulting in an anticipated outcome of inhibition of disease progression and increased survival. Several types of therapeutic cancer vaccines^[2, 3] are currently under development, including the following:

- Whole tumor cell
- Gene-modified tumor cells
- Plasmid (naked) DNA
- Peptides
- Viral gene transfer vectors
- Antigen-modified dendritic cells

Although cancer vaccines represent a very active area of development world wide (as of 06 July 2004, www.cancer.gov lists 13 cancer vaccines in clinical development), few cancer vaccines have been approved, and none are currently available in the United States.

Example 1: Theratope Vaccine (Biomira Inc.)

Breast cancer is the most common type of cancer among women in the United States. The number of new cases of breast cancer in women is expected to be 215,990 in 2004, accounting for nearly one in every three cancers diagnosed in women.^[4] Breast cancer is also the second leading cause of death in women in the United States; 40,110 deaths are expected in 2004.^[4]

Theratope vaccine (Biomira Inc.) consists of a synthetic version of the tumor-associated antigen sialyl (STn) linked to a protein carrier that is known to stimulate the immune system. The Theratope complex was designed to selectively stimulate an immune response to STn. In clinical studies, Theratope was well tolerated, the most common side effects being flu-like symptoms and local injection-site reactions.^[5]

In June 2003, Biomira Inc. and its partner, Merck KGaA, announced the completion of a large Phase 3 trial of Theratope for women with metastatic breast cancer that did not meet the predetermined statistical endpoints of time to disease progression and overall survival.^[5] However, an exploratory analysis showed a statistically significant survival advantage for a prestratified subset of women who received hormonal therapy and Theratope vaccine compared with those who received hormonal therapy and the control vaccine. In the exploratory analysis, women in the Theratope vaccine arm (n=180) survived a median of 36.5 months, while those in the control vaccine arm (n=170) survived a median of 30.7 months (Cox p=0.039).^[6] The survival for women not receiving hormonal therapy was not significantly different between the two treatment arms.^[6]

In an analysis of survival based on IgG antibody response to Theratope vaccine, antibody titers were measured against the following three factors: STn, KLH (the carrier molecule), and ovine submaxillary mucin (OSM), a naturally occurring mucin that contains clustered STn side chains. The results showed that only antibody titers against OSM were predictive of improved survival.^[6] Patients with an anti-OSM response at or above the median level survived longer than those patients whose responses were less than the median (p=0.08).^[6] For patients in the hormone subset treated with Theratope vaccine, the survival difference between those with anti-OSM responses at or above median and those with less than the median response was statistically significant (41.1 vs. 25.4 months, log-rank p=0.01).^[6] Survival was not significantly influenced by antimonomeric STn or anti-KLH response.^[6] Because of the complexity of the human immune response, it is unknown why anti-OSM is more predictive than KLH or STn. Moreover, due to the inability to prospectively identify, prior to randomization, those patients likely to respond to OSM, the design of pivotal trials using traditional approaches for cytotoxic agents based on an ITT basis disregards the significant clinical benefit to this subset of patients.

Although the subset analyses of women who produced an antibody titer to OSM after receiving Theratope vaccine in combination with hormonal therapy showed promising benefit to this patient population, Merck KGaA announced in 2004 that it had elected to no longer pursue development of this cancer vaccine, citing the need for additional large-scale trials.^[7] The additional trials would likely have shown similar results, requiring subset analyses that are not accepted under the current review paradigm.

Example 2: Melacine Melanoma Vaccine (Corixa Corporation)

Stage IV malignant melanoma is a lethal form of skin cancer. Median survival for patients with metastatic disease is 6 to 9 months with a 5-year survival rate of only 5%. This year, approximately 55,100 new cases of skin melanoma will be diagnosed in the United States, and 7,910 people will die of this disease.^[4]

Melacine melanoma vaccine (Melacine vaccine; Corixa Corporation) is a targeted oncology therapeutic that consists of lysed (broken) cells from two human melanoma cell lines combined with a proprietary adjuvant (Detox™ adjuvant, also known as Enhanzyn™ adjuvant). The product is administered as a repeated vaccination over a 12-week dosing schedule. Patients who respond may receive less frequent maintenance vaccinations. Melacine vaccine is well tolerated; the most frequently reported adverse events after administration were flu-like symptoms (asthenia, pain, myalgia, and fever) and application-site disorders (injection-site pain and granulomas at the injection site).^[9]

Efficacy analysis of approximately 300 patients with melanoma (primarily Stage IV) treated in uncontrolled Phase 2 and controlled Phase 3 trials of the Melacine vaccine showed that a few patients treated with the vaccine achieved an objective response (complete or partial response) with long-term survival; objective response rates ranged from 6% to 17%.^[9] On the basis of the composite results of these trials, the Melacine vaccine in 2000 was approved for marketing in Canada as an immunotherapy for the treatment of disseminated melanoma.^[8,9] To date, no safety concerns have been identified.

Seeking further support for approval in the United States, under the premise that a vaccine that showed some efficacy in patients with advanced disease would be substantially more effective in patients with minimal residual disease, Corixa Corporation (Corixa) initiated clinical development of the Melacine vaccine in earlier-stage patients (Stage II melanoma).^[9] Based on new biomedical findings, a retrospective analysis of clinical responses of patients receiving the Melacine vaccine for metastatic melanoma was performed, and an association between certain Human Leukocyte Antigen (HLA) genotypes and clinical responses was found. This association was especially strong for patients expressing two or three of the HLA alleles. In the additional Phase 3 clinical trial of the vaccine as adjuvant immunotherapy versus observation after surgical resection, the vaccine was administered over a 2-year period, and a total of 689 patients were enrolled. The protocol was amended to include HLA Class I (HLA-A, HLA-B, and HLA-C) serologic typing. The results showed that expression of two or more of the five HLA antigens originally identified (HLA-A2, -A28, -B44, -B45, and -C3) was associated with superior outcome.^[9-11] Additional analyses indicated that the major component of this effect was contributed by expression of HLA-A2 and HLA-C3.^[10, 11] Of note, expression of either HLA-A2 or HLA-C3 in the absence of the vaccine was of no clinical benefit to patients, indicating that simple expression of these particular HLA genes is not a prognostic factor for positive outcome in this group of patients.^[10, 11]

At FDA's request, poststudy data analyses were performed, which showed that Melacine vaccine continued to provide an improvement in overall disease-free survival, although the statistical significance was lost ($p > 0.05$). However, the analysis of clinical benefit in patients who were positive for expression of either major histocompatibility complex (MHC) Class I HLA-A2 or -C3 genes showed a highly statistically significant clinical benefit of Melacine compared with observation in terms of increased disease-free survival ($p = 0.005$).^[9] Furthermore, the FDA requested data mining analyses that again demonstrated a clearly statistically significant improvement in overall survival in Class I MHC HLA-A2- or HLA-C3-positive patients who received Melacine compared with observation ($p = 0.003$).^[9]

Melacine vaccine is now available to patients in Canada, but its future development in the United States market is far from certain. In October 2001, Corixa announced that, although the results from the first adequate and well-controlled trial of Melacine vaccine for Stage II melanoma showed significantly greater overall disease-free survival for patients treated with the vaccine compared with observation, the results of the trial were robust only for the subpopulation of patients expressing HLA-A2 or HLA-C3.^[10] Accelerated approval of the Melacine vaccine was deemed not an option for regulatory approval by FDA and a second adequate and well-controlled trial in Class I MHC HLA-A2- and HLA-C3-positive patients would be required.^[10, 11] The results of the first adequate and well-controlled trial would be reviewed as supportive data for approval if a second adequate and well-controlled trial confirmed the clinically significant benefit ($p < 0.05$).^[11] Corixa estimates the additional trial as requested by FDA would take another 8 to 10 years to conduct. Consequently, Corixa announced last year that the company has decided to halt further development in the United States of this therapy for melanoma patients.

Example 3: Insegia (Aphton Corporation)

In 2004, more than 160,000 new cases of gastrointestinal adenocarcinomas are expected to be diagnosed in the United States, including adenocarcinomas of the pancreas (31,860), colon (106,370), and stomach (22,710).^[4] Combined, these cancers will kill 99,780 Americans this year alone.^[4] Because of the poor results obtained with standard chemotherapies, research efforts for these three cancer types are focused on new target molecules as well as combination therapies.

Insegia (Aphton Corporation) is a therapeutic cancer vaccine that stimulates the immune system to develop antibodies to the hormone gastrin 17 (G17). Neutralizing gastrin inhibits cancer cell growth, proliferation, and metastasis, leading to cell death (apoptosis). Insegia (also known as G17DT or gastrimmune) is administered as a series of three intramuscular injections over a 4- to 8-week dosing schedule along with booster doses thereafter. Clinical studies of Insegia demonstrate that colorectal, gastric, and pancreatic cancer patients that produce an antibody titer to G17 after administration of Insegia had prolonged survival compared with those who did not. This effect was independent of other covariates analyzed for survival. Moreover, the likelihood of developing an immune response to Insegia was independent of the health status of those patients receiving the vaccine. Relevant to this, even advanced gastrointestinal cancer patients (in some studies during co-administration with chemotherapy or in chemotherapy-refractory patients) showed a 60-80% positive antibody titer. In these studies, treatment with Insegia was safe and well tolerated with the most frequently associated adverse events being injection-site reactions and fever.

Insegia prolonged survival in a Phase 3, placebo-controlled, study testing Insegia as a monotherapy for patients with advanced pancreatic cancer, who were not indicated to receive chemotherapy. Importantly, patients who generated anti-G17 titers showed a highly significant survival benefit compared to those patients who did not generate anti-G17 titers or patients who received placebo.^[12] Analysis of the Kaplan Meier plots showed that antibody responders to Insegia had a median survival of 176 days compared with 63 days for nonresponders and 83 days for the placebo group ($p=0.003$, log rank homogeneity test).^[12]

Extensive clinical experience with Insegia has consistently shown that median survival in the subset of patients who raise an anti-G17 titer is statistically significantly longer than the median survival of patients who do not demonstrate such a response.^[13] A summary of selected results are shown in Table 1.

Table 1. Overview of Insegia Results^[13]

Study	Median Survival (days)		p-value
	Antibody Titer Positive	Antibody Titer Negative	
Pancreatic cancer*	176	63	$p=0.003$
Gastric cancer†	303	149	$p=0.008$
Colorectal cancer†	274	169	$p<0.001$

* Placebo-controlled trial of Insegia monotherapy. Median survival was 83 days for the placebo group.

† Open label trial of Insegia in combination with standard of care.

Unfortunately, as seen with other cancer vaccines (e.g., Theratope vaccine), prospective identification of the patients who will demonstrate an anti-G17 response is currently impossible; none of the other various possible covariates, including health status, were predictive across the various types of cancer tested.^[13] Although the correlation between response to Insegia and survival remained statistically significant even after adjusting for other covariates for survival, the current review paradigms prevent consideration of this positive subset analysis as the basis of approval.

Cancer Vaccine Development Consideration #1: Risk-Benefit Ratio

In clinical drug development, the risk-benefit ratio is a measure of the risk of doing harm or injury compared with the potential therapeutic benefits of administration of the drug. FDA has the stated mission of promoting the protection of the health and safety of the United States public through continual review of the safety, efficacy, and quality of data of premarketed and postmarketed products and weighing of the risk-benefit ratio. The risk-benefit ratio varies depending on the condition being treated. For example, in the case of life-threatening illnesses (e.g., cancer), the acceptable risk for a drug may be higher than those for non-life-threatening illnesses (e.g., conjunctivitis).

Cytostatic agents, such as most immunotherapeutics, generally do not show the same efficacy profile as cytotoxic agents. Although cytotoxic agents are designed to eradicate cancerous cells, cytostatic agents are expected to halt further progression of the disease and cause only limited tumor regression. By their mechanism of action, vaccines are intended to act as cytostatic agents and may show an additive or synergistic effect when treated in combination with chemotherapy. Consequently, significant tumor regression may be difficult to achieve with vaccines or other immunotherapeutics or targeted therapies. The current approach to define a surrogate endpoint of efficacy related to tumor response (by WHO [World Health Organization] or RECIST [Response Evaluation Criteria In Solid Tumors] guidelines) is tailored to tumor reduction or shrinkage by cytotoxic agents, as measured by the proportion of patients showing a complete or partial response. In light of their expected cytostatic activity, the clinical benefit of oncology vaccines should be considered to include stabilization of the disease, as defined by “stable disease” or increased time before disease progression.

In contrast to cytotoxic agents that generally show pronounced risks with respect to their safety profile, cytostatic agents offer significant advantages to patients in terms of improved tolerability and can be used as adjunctive or maintenance therapy in biologically relevant patient populations. As cytostatic agents, cancer vaccines generally show relatively benign safety profiles with the most frequently reported adverse experiences typically including flu-like symptoms, generalized pain, myalgia, fever, and administration-site disorders (injection-site pain and granulomas at the injection site).

The benefits of immunotherapeutics and cancer vaccines should be determined in the context of the clinical condition they are designed to treat. For example, in patients who have the appropriate biological marker, the benefits of Melacine vaccine administration are undeniable, and the safety risks to cancer patients lacking such a marker are minimal. In review of cancer vaccines that, in addition to a positive-trending ITT analysis, hold meaningful benefits for antibody titer-positive patients and minimal risk to antibody titer-negative patients, the positive risk-benefit ratio of these products should be given significant consideration when determining the value of approval.

Cancer Vaccine Development Consideration #2: Clinical Trial Design

The standard ITT analysis requires inclusion of all patients randomized in the study regardless of whether the patient received study drug. The basis of the ITT analysis is to avoid misrepresentation of the clinical data. Specifically, in the case of noncompliance and dropouts, exclusion of patients could lead to biasing of the study findings if the noncompliance or study withdrawal was because of side effects, failure to improve, or any other factor that is related to outcome. The ITT analysis assumes that an appropriate patient population can be prospectively identified via well-defined inclusion and exclusion criteria. In the case of cancer vaccines, this necessitates inclusion of patients who lack the appropriate biological sensitivity and fail to mount a specific immune reaction, such as an antibody titer. Although ITT analyses are undoubtedly useful in determining efficacy for most investigational products, consideration of other types of analyses should also be considered when evaluating the clinical benefit of therapeutics for which

mechanism of action is dependent upon a specific biological response and the risk associated with the administration of such a product is minimal.

Although progress is being made, particularly by applying genomic and proteomic definitions of patient samples, large patient populations are needed to identify those patients that can benefit or who are particularly receptive to an immunotherapeutic compound. In this regard, the approval process for Iressa® (AstraZeneca) is illustrative. Iressa was approved based on a marginal clinical benefit in refractory non-small-cell lung cancer patients. Only after a consistent and remarkable benefit was observed in a small (10% to 15%) subpopulation of patients who received the drug as part of a large compassionate-use protocol conducted during and after the approval process, further research showed the benefit to be confined to a single gene mutation. Such identification of an efficacy population is highly beneficial for selective treatment and further understanding of targeted therapy of this product class; however, this approach is impractical in the current development of most targeted therapies.

The placebo-controlled parallel-group design is one of the most common trial designs employed for the evaluation of a drug's efficacy. Using this traditional design for the evaluation of cancer vaccines has often proven to be a major barrier to the development of these products because clinical benefit is only expected in a selective subpopulation of patients (i.e., benefit is only expected to be apparent in those patients who raise an antibody titer [titer-positive] to the vaccine). The overall clinical benefit in patients treated with the therapeutic cancer vaccine compared with those treated with placebo easily masks a selective efficacy in the immunoreactive subpopulation. The inability to determine prospectively which patients will be titer positive creates a significant, if not insurmountable, hurdle for some cancer vaccines because the detection of efficacy in the subset of patients necessitates the conduct of large clinical trials that are often infeasible because of the sizeable financial investment, extended timelines, limited availability of the patient population, and high risks of failure to which all drugs are subject (e.g., a new drug entering Phase 1 only has a 8% chance of reaching the market^[14]).

Study designs for the development of an immunotherapeutic agent could include initial testing of the patients' immune function. However, such general immunogenicity tests have proven nonpredictive for the specific immunoreaction (i.e., antibody titer) towards a specific antigen or epitope. Alternatively, all patients could first be treated with the immunotherapy, then only those that mounted the specific antibody titer would be randomized for additional treatment (Figure 1). This study design has the attraction that it identifies those patients who produce antibody titers before randomization, and therefore it provides a selective immune reactive subpopulation.

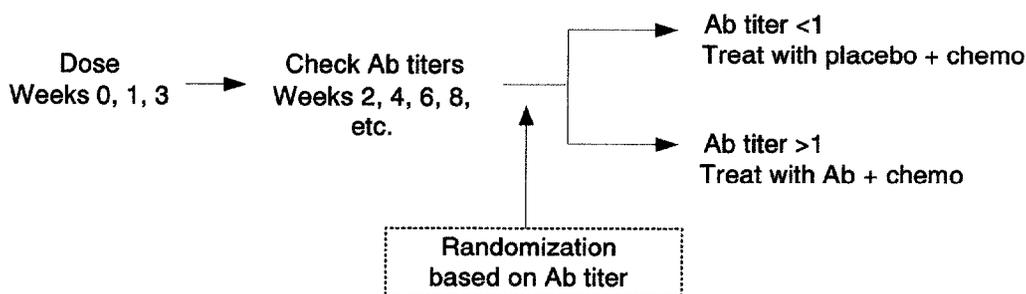


Figure 1. Alternative immunotherapeutic study design.

Variations on this design are possible, such as providing an initial immune challenge with the therapeutic cancer vaccine, and then randomizing based on the antibody titer only after patients are shown to be refractory to the standard-of-care chemotherapy. Unfortunately, it is difficult, if not impossible, to

demonstrate the clinical benefit of additional dosing in such study designs, because this would require demonstration of the benefit of primary dosing versus multiple follow-on doses of the vaccine. Moreover, in the case of therapeutic vaccines intended to treat cancer patients' with a short life expectancy (e.g., as in advanced pancreatic cancer) only a few patients are likely to receive more than three doses of the vaccine.

Because of the limitations noted for each proposed study design, the best design appears to be the traditional prospective, parallel-group design. However, in the case of cancer vaccines, in addition to the ITT analysis, other types of analyses should also be considered when evaluating the clinical benefit. Specifically, in addition to the direct comparison of active treatment and placebo or standard therapy, a preferred analysis that compares benefit in patients who are antibody titer positive with that of patients who are antibody titer negative should be considered. A prospective identification of antibody titer-positive patients for a preferred analysis should be valid as a primary efficacy endpoint because patients who do not generate an antibody titer effectively never received the drug and are therefore not expected to receive clinical benefit from the vaccine. An additional analysis to demonstrate the validity of the selection of the antibody titer-positive population would include comparison of the patients who received placebo with an alternative method of treatment group comparison or "imputational analysis" (see Cancer Vaccine Development Consideration #3 below).

Cancer Vaccine Development Consideration #3: Alternative Methods for Evaluating Treatment Comparisons

As the previous examples show, it is oftentimes impractical to identify potentially predictive markers that prospectively define immune-reactive patients (i.e., baseline covariates, such as demographics, baseline performance status, laboratory values). Imputational analysis provides an option to define subsets of "would be immune reactive" or "placebo immune reactive," and therefore, is a useful alternative. Future progress on using imputation of data and consideration of genomic and proteomic innovations should also be considered when looking at supporting efficacy findings in studies of cancer immunotherapeutics and vaccines.

Determination of which patients within the placebo arm of the study would have mounted an antibody titer is not possible without administering the drug to placebo patients (and thereby invalidating the placebo control). To improve the "comparability" of the placebo arm to antibody titer-positive patients, putative antibody titer-positive patients in the placebo arm can be identified by randomly selecting from the placebo population a subgroup of the placebo patients and randomly comparing the survival curves or other efficacy endpoints of these "placebo titer-positive patients" with the known antibody titer-positive patients' log-rank statistics. This process of random selection of subgroups of placebo patients and analysis is repeated many (e.g., 10,000) times to approximate the true distribution of the p-values of the comparison. If statistical evidence of a difference between the two treatment groups is present in a significantly large proportion of these simulated samples of the experiment, then it is plausible that these differences are due to treatment with the antibody-generating compound, even though the true set of "placebo titer-positive patients" in the control arm is unknown. The specific structure and parameters for the imputational analysis may be prospectively defined in the statistical analysis plan and developed in a dialogue with the FDA.

The imputational analysis proposed above provides a framework to identify parameters that may predict the immune responders in controlled studies of immunotherapeutics. In addition to positive-trending ITT and preferred analyses of subpopulations, the imputational analysis should provide sufficient evidence that the drug is efficacious. Accelerated approval of immunotherapeutics and cancer vaccines based on the proven efficacy using predefined imputational analysis together with the low risk of such treatment

provides an improved path for clinical development of such compounds. Based on these findings, Phase 4 studies may follow that can verify the efficacy in the selected population.

Accelerated approval with Phase 4 commitment is an attractive answer to the development challenges for therapeutic cancer vaccines that show significant benefit in subset populations and have positive risk-benefit ratios. Phase 4 protocols would allow the conduct of trials large enough to see clinical benefit in the ITT population, however, under the current review paradigm, acceptance of subanalyses and demonstration of efficacy in Phase 4 commitment protocols cannot be applied in the cases outlined because currently, Phase 4 studies are only initiated to confirm Phase 3 efficacy of surrogate endpoints.

In the interim, it may be valuable to assemble the FDA and various sponsors of therapeutic cancer vaccines with products in Phase 3 or Phase 4 development to exchange innovative approaches about the unique challenges faced by these products. Specifically, use of the statistical approach outlined above and other possible statistical or experimental design options could be discussed in a cooperative manner to help identify meaningful prospective parameters and possible surrogate endpoints with the aim to accelerate the development of promising therapies for these life-threatening diseases.

Highlight: An Example for Developing a Critical Therapy under Significant Manufacturing and Safety Data Constraints — Infant Botulism, BabyBIG[®], and the Case for Industry/FDA Cooperation

Infant botulism is a devastating disease that affects approximately 100 babies annually and for which no effective FDA-approved treatment was available until late 2003. Although a drug to treat this disease would clearly merit orphan drug designation, the development program undertaken by the California Department of Health Services (CDHS) faced multiple, possibly insurmountable challenges. The story of how the FDA and CDHS worked collaboratively to ultimately obtain licensure for a human antitoxin IgG product to treat this disease, BabyBIG, illustrates general strategies by which the FDA and industry can productively collaborate to increase the success rate of pharmaceutical development and potentially can serve as an example for future products.

Some of the challenges not unique to this product class or indication include the following:

- Developing a product with extremely limited sponsor resources
- Producing the biological product from a limited amount of starting material (plasma from toxoid-vaccinated donors)
- Extracting sufficient manufacturing data from only two lots of product (and for which certain manufacturing details differed)
- Recruiting from a limited patient pool
- Determining appropriate study endpoints
- Extracting sufficient safety data from one pivotal trial and one open-label study

From early in the research program, CDHS and FDA sought solutions proactively and collaboratively. CDHS strategies that fostered this environment of cooperation included the following:

- Presenting resource constraints to the FDA in respectful, nonargumentative, transparent, and rational ways
- Describing proposed solutions clearly in a pre-BLA meeting package so that the FDA was able to understand issues before the pre-BLA meeting; discussing at each opportunity thereafter during BLA review

- Providing timely responses to the FDA questions; ensuring submissions were well organized and easily navigated
- Demonstrating willingness to undertake additional manufacturing-related studies and postapproval commitments
- Negotiating labeling in a professional and data-driven fashion

These collaborative discussions and practices helped the FDA understand the challenges faced by the BabyBIG sponsor and determine ways to evaluate the product in the absence of the traditional quantity of manufacturing, safety, and efficacy data. Ultimately, through continued rounds of discussion and collaboration, the FDA was reassured of the integrity of not only the product's safety, efficacy, and potency, but also its ultimate availability for use in the marketplace. Final licensing approval was obtained shortly thereafter. BabyBIG approval not only satisfies a current need for infants, but significantly decreases the medical care costs associated with the treatment of these infants. Furthermore, the information collected from the development of BabyBIG could provide an important knowledge basis for treatment of botulism toxin in the unfortunate event of a possible bioterrorism incident in the future.

In summary, one of the biggest challenges to vaccine development is the lack of consistent or completely reliable predictors of the specific human immune response. The body's immune response is a complex combination of cellular reactions and signaling cascades. Yet few vaccinologists would disagree that unless a vaccine, prophylactic or therapeutic, mounts a specific immune response, clinical benefit is unlikely. As with the case of BabyBIG, innovators of therapeutic cancer vaccines and the FDA must continue to work together to find creative solutions to the unique challenges faced by this much-needed class of therapeutics. These challenges include defining endpoints that are achievable given the aggressiveness of the disease and the life expectancy of the patient population; consideration of appropriate therapy-specific trial design; and defining alternative analyses that are prospective and supportive of the ITT analysis. Failure to thoroughly review the issues surrounding the development of therapeutic cancer vaccines at best will lead to further delays in development of these new therapies and limitation of the available treatment options for cancer patients and at worst will lead to discouraging development where it otherwise might have been feasible.

FDA's Critical Path Initiative has the goal of identifying and prioritizing the most pressing development problems and areas that represent opportunities for rapid improvement and public health benefit. Oncology immunotherapeutics, and specifically therapeutic cancer vaccines, represent a class of promising therapies that often have benign safety profiles and that offer substantial benefit to appropriately identified patient populations. At this time, the sources of variability in human responses are not well understood and thus cannot be controlled. Bioinformatics, proteomics, and genomics hold the promise of better informed trial design (e.g., improved inclusion and exclusion criteria), improved selection of endpoints, and alternative analyses of clinical data. Expanded knowledge in these areas and its application in alternative data analyses using imputational analyses as outlined in this document will highly benefit and expedite the development of this much-needed class of compounds.

Cato Research appreciates the opportunity to provide comments on the Critical Path Initiative and looks forward to implementation of new development strategies designed to improve the viability of innovative new drugs in general.

Respectfully submitted,

Cato Research

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