BIOTECHNOLOGY INDUSTRY ORGANIZATION
1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

December 17, 2009

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA- 2009-D-0427

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the draft guidance *Clinical Considerations for Therapeutic Cancer Vaccines*.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

COMMENTS

The draft guidance states that dose levels used in toxicology studies should be based on dose levels that showed biological activity in proof of concept studies, and should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). The draft notes that 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. FDA states that it is important, therefore, for the sponsor to provide justification, with supporting scientific data, for the extrapolation modality used to determine the clinical starting dose and dosing scheme in the IND. The draft also notes that preclinical studies should incorporate a dosing schedule that mimics the intended schedule for the early phase clinical trial as closely as possible.

BIO requests that clarification of these statements be given in the following areas of the proposed guidance:

"the general mechanisms of action"

BIO suggests rephrasing this to read, "species-specific variation in immune activity".

"…should bracket and exceed clinical dose levels…"

We ask FDA to clarify that the method used to calculate a preclinical dose which exceeds the clinical dose should be the following: inject the maximum allowable volume of the clinical test vaccine into the appropriate nonclinical species. This will represent a calculable multiple over the anticipated human clinical dose on a units/kg body weight basis. This is the practice for other non-oncology vaccines. Bracketing below the clinical dose can be achieved typically by reducing the volume of the clinical test vaccine injected.

"…to identify a no-observed-adverse-effect-level (NOAEL)…".

BIO proposes that this statement be removed from the document.

"…should incorporate a dosing schedule that mimics the intended schedule for the early phase clinical trial as closely as possible."

BIO proposes changing this statement to read: *… incorporates a dosing schedule based on the immune response expected in the early phase clinical trial*.

In a majority of cases, a vaccine toxicological response is related to the generated immune response (in effect the drug) not the amount of vaccine delivered (in effect a pro-drug). If an observed toxicological effect is a consequence of the generated immune response this may be seen at any dose level, particularly upon repeated dosing and subsequent enhancement of the immune response. Therefore, while it is important to determine if immune response driven pathologies are a risk, a standard NOAEL approach assuming a dose response relationship may not be appropriate. Such pathologies may correlate with intensity of the immune response rather than the vaccine dose administered. For example, toxicities related to T cell avidity may be greater at lower vaccine doses compared with higher vaccine doses (Miller et al, 1996). The key to determining the risks of a therapeutic vaccine is a thorough understanding of the generated immune response and designing the safety programme appropriately.

Please do not hesitate to contact us for further information or clarification of our comments.

Sincerely

s/

Sara Radcliffe
Vice President, Science & Regulatory Affairs
The Biotechnology Industry Organization (BIO)