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**Coulter**
PHARMACEUTICAL

1524 '99 OCT 25 A9:17

October 22, 1999

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

**RE:** Docket No.99-18928: Draft Guidance for Industry: Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations (July 26, 1999).

Gentlemen:

Coulter Pharmaceutical is engaged in the development of novel drugs and therapies for the treatment of people with cancer. The company is developing a family of cancer therapeutics based upon two drug discovery programs: therapeutic antibodies and targeted oncologics. Our lead candidate is Bexxar™ (iodine I 131 tositumomab), which consists of a monoclonal antibody conjugated with a radioisotope.

We would like to take this opportunity to comment on the above referenced draft guidance. This draft guidance recognizes that monoclonal antibodies represent a unique class of biologics. It defines sameness on the basis of the sequence of amino acids within the CDR's of the monoclonal antibody. While the antigen binding properties of most/all antibodies are primarily determined by CDR sequences, some framework residues may play an important role in antigen binding.

An antibody product is usually defined by its antigen binding specificity and affinity as well as its isotype (therefore effector functions/half-life) or fragment (half-life) and species (non-human or human, humanized or chimeric). The isotype of the monoclonal antibody, or the fragment form of an antibody, are key determinants of its *in vivo* activity. Antibody products comprising the same V-regions but different C-regions may display very different *in vitro* and *in vivo* properties. Furthermore, where repeated antibody administrations are used for clinical studies, the utility and efficacy of a monoclonal antibody may be limited

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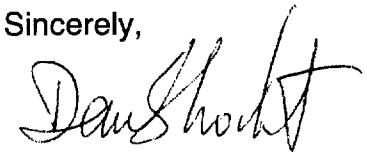
by a patient's immune response to the administered antibody; an antibody with a different DNA/protein sequence should not be cross-reactive with the neutralizing antibodies produced to the previously administered monoclonal antibody. Therefore, this second monoclonal antibody is a functionally distinct product.

We believe that the sameness should be defined both by the CDR-region sequence (with minor changes) and constant-region isotype or fragment form. The CDR-regions should be considered the primary determinants of binding specificity since humanization on different framework regions can be carried out to give antibodies with the same affinity and specificity. However, modifications can be made in the CDR regions without a significant change in binding specificity and affinity.

The broader issue of antibodies with different CDR sequences which bind to the same epitope on an antigen, or antibodies which bind to different epitopes but are functionally equivalent needs careful consideration. In the 'spirit' of orphan drug status, one may consider functional equivalence between antibodies to a given antigen as the key determinant. But, how is functional equivalence measured, *in vitro*, *in vivo* in animal models, or *in vivo* in clinical studies?

In conclusion, we believe that the FDA should convene a workshop of experts in the field to assist the agency in making this important scientific and policy decision. We suggest that FDA could profit from such outside expertise. The FDA should invite all stakeholders to participate in a conference to help the agency determine a means for distinguishing monoclonal antibody products. This would both broaden the expertise available to the agency, and give all stakeholders the opportunity to participate in the process, thus increasing the acceptance of the final guidance.

Sincerely,



Dan Shochat, Ph.D
Sr. Vice President and CSO

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