Docket No. FDA-2010-N-0621

CDER's Statement of Questions Presented

By letter dated February 23, 2011, Dr. Midthun directed counsel for Genentech, Inc. ("Genentech") and the Center for Drug Evaluation and Research ("CDER" or the "Center") (jointly "the parties") to prepare a joint statement of undisputed facts and disputed issues relating to the proposed withdrawal of the metastatic breast cancer ("MBC") indication for Avastin. After extensive consultation, the parties submitted their "Joint Statement of Undisputed Facts and Select Issues in Dispute" on April 7, 2011. However, the parties have been unable to agree on the central questions that must be answered to enable the Commissioner to determine whether withdrawal of the MBC indication is appropriate under governing law. Each party therefore decided to submit a separate document setting forth its understanding of those questions. CDER hereby submits its Statement of Questions Presented.

The breast cancer indication for Avastin was approved under the Agency's accelerated approval authority (section 506 of the Food, Drug, and Cosmetic Act ("the Act") and 21 CFR Part 601, Subpart E).[1] As a condition of the MBC approval, Genentech proposed and was required to submit data from post-marketing studies to "confirm the effect on the clinical endpoint" and "verify and describe [Avastin's] clinical benefit," pursuant to section 506(b)(2)(A)

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[1] The full indication appearing on Avastin's FDA approved labeling reads as follows.

Avastin is a vascular endothelial growth factor-specific angiogenesis inhibitor indicated for the treatment of:

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- Metastatic breast cancer, with paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.
  -Effectiveness based on improvement in progression-free survival. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
  -Not indicated for disease progression following anthracycline and taxane chemotherapy administered for metastatic disease.

of the Act and 21 CFR § 601.41, respectively.[2] Genentech submitted data from five clinical studies to support the MBC indication for Avastin. After extensive review, CDER concluded that the data: (1) fail to verify the clinical benefit of Avastin for the MBC indication; and (2) fail to demonstrate that Avastin is safe and effective for that use.

CDER therefore proposes to withdraw approval of the MBC indication for Avastin, pursuant to the withdrawal authority for accelerated approvals set forth in the Act and in 21 CFR § 601.43. CDER proposes to withdraw the indication because the postmarketing clinical studies failed to very clinical benefit within the meaning of 506(b)(3)(B) of the Act and 21 CFR § 601.43(a)(1) and because the totality of the data demonstrate that Avastin is not safe and effective under its conditions of use when used for its breast cancer indication within the meaning of sections 505(e)(1) and 506(b)(3)(C) of the Act and 21 CFR § 601.43(a)(6).

To determine whether CDER's proposal to withdraw approval of the MBC indication for Avastin is supportable, the Commissioner must determine:

1. Whether the clinical study data that Genentech submitted to the BLA and CDER reviewed verify the clinical benefit of Avastin for its MBC indication within the meaning of section 506(b)(3)(B) of the Act and 21 CFR § 601.43(a)(1).

    a. Whether the data from 5 MBC studies (E2100, AVF2119g, AVADO, RIBBON1, and RIBBON2), only one of which showed a meaningful treatment effect on progression free survival (PFS), demonstrate that Avastin provides a clinical benefit to patients with MBC.

[2] The February 22, 2008 approval letter for Avastin's MBC indication identified AVADO and RIBBON1, which were proposed by Genentech, as the studies that Genentech would be required to submit pursuant to the accelerated approval regulations under 21 CFR 601.40-46.

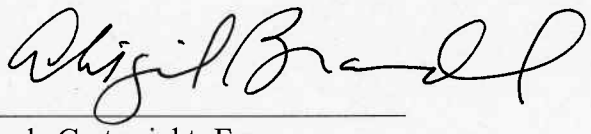
b. Whether the studies AVF2119g and RIBBON2, which were conducted in patients previously treated with chemotherapy for MBC, submitted by Genentech to the Avastin BLA and considered by CDER in deciding to pursue withdrawal, are relevant to this proceeding.

2. Whether the totality of the data submitted to the BLA and reviewed by CDER show that Avastin is safe and effective for its MBC indication, within the meaning of the Act and 21 CFR § 601.43(a)(6). Specifically, whether the minimal effect of Avastin on PFS and absence of a demonstrated effect on length of overall survival, when weighed against the serious adverse reactions attributable to the drug, result in a favorable benefit-risk profile for the MBC indication.

3. Whether CDER has appropriately exercised its authority by proposing to withdraw approval of the MBC indication, rather than allowing the indication to remain on the label while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit.

Although there are ancillary questions that will need to be addressed in this proceeding, these are the pivotal questions before the Commissioner. If the Commissioner concludes that the data do not verify clinical benefit or that the product is not safe and effective for the MBC indication, then withdrawal of approval for the MBC indication is appropriate under the accelerated approval regulations and the Act.

Respectfully submitted,



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