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March 10, 2011

BY EMAIL AND U.S. MAIL

Laurie Lenkel
Director, Office of the Ombudsman
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO 32, Room 4260
Silver Spring, Maryland 20993

Re: Docket No. FDA-2010-N-0621; Avastin®

Dear Ms. Lenkel:

I am writing on behalf of Genentech, Inc. ("Genentech") in response to the February 23, 2011 and March 3, 2011 letters from Karen Midthun, M.D., Presiding Officer, granting a hearing and addressing certain procedural issues in the above-referenced matter (Docket No. FDA-2010-N-0621). As Dr. Midthun has instructed, we will consult with CDER regarding the procedures proposed in Dr. Midthun's March 3 letter and provide comments at the same time as we submit a joint statement of agreed facts and disputed issues. I am writing now to raise two important preliminary matters regarding the hearing. The first relates to the advisory committee for the hearing, and the second to public participation at the hearing.

The Advisory Committee

We understand that the Presiding Officer has determined to use FDA's Oncologic Drugs Advisory Committee ("ODAC") for the hearing and to provide advice and recommendations to the Commissioner, and not to supplement the ODAC with additional expert consultants. In particular, the Presiding Officer has explained that she is electing not to add consultants because of concerns that experts in the field of breast cancer have already expressed a view on the issues raised by FDA's proposal to withdraw the approval of Avastin for metastatic breast cancer ("MBC"), and might be perceived as having conflicts of interest. Genentech appreciates these concerns, but we believe they apply equally to the ODAC.

All of the current ODAC members,[1] with the exception of Drs. William Kelly and Margaret Tempero, were present at the July 20, 2010 ODAC, which previously considered and voted to withdraw the approval of Avastin in MBC. Even though Genentech intends to present information at the hearing that was not considered by the ODAC, these ODAC members have already expressed a clear opinion on much of the data and voted against maintaining approval of the MBC indication. Moreover, a number of the ODAC members— including the Chair of the ODAC—have expressed their views in the media. For example, the ODAC Chair Dr. Wyndham Wilson was quoted by the Associated Press as stating: "We have definitive evidence that Avastin causes harmful side effects and we've now seen a number of well-done studies that show no advantage to lifespan."[2] Dr. Wilson later defended the ODAC's vote in various outlets such as the ASCO Post,[3] and was quoted in the Washington Post as stating that "[t]he vast majority opinion of the committee was that the drug was not doing very much, and what it was doing was more than offset by the negative. In our best judgment, we did not feel the drug was safe to give relative to its benefits."[4]

Other ODAC members have also expressed strong views in the media. For example, Dr. Patrick Loehrer was quoted in the New York Times as stating: "It just delays by another visit before [patients] get the news that their tumor progressed."[5] Dr. Mikkael Sekeres wrote in an op-ed in Oncology Times: "It almost goes without saying that differences in survival were negligible, and not significant."[6] These quotes and the prior ODAC vote on the continued approval of Avastin for MBC show that the ODAC will be participating in the new hearing having already expressed definite views on the issues under consideration. This raises a very real concern about whether the ODAC's participation will compromise the objectivity and fairness of the hearing. Furthermore, both the Federal

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[1] The current roster for the ODAC includes Chair Wyndham Wilson, M.D., Ralph Freedman, M.D., Ph.D., Jean Grem, M.D., F.A.C.P., William Kelly, D.O., Patrick Loehrer, Sr., M.D., Brent Logan, Ph.D., Mikkael Sekeres, M.D., M.S., Margaret Tempero, M.D., consumer representative Virginia Mason, R.N., and non-voting industry representative Gregory Curt, M.D.

[2] Matthew Perrone, *Experts Veto Avastin As A Breast Cancer Treatment*, Associated Press, July 20, 2010.

[3] *ODAC Voting Members Discuss Panel's Recommendation About Bevacizumab In Advanced Breast Cancer*, The ASCO Post, Sep. 1, 2010.

[4] Rob Stein, *FDA Considers Revoking Approval Of Avastin For Advanced Breast Cancer*, Washington Post, Aug. 16, 2010.

[5] Andrew Pollack, *Panel Urges F.D.A. To Revoke Approval Of Drug For Breast Cancer Treatment*, New York Times, July 21, 2010.

[6] Dr. Mikkael Sekeres, *Second Thoughts From Sekeres: Waiting for Godot: Why We Need Phase III Trials For Cancer Drugs*, Oncology Times, Nov. 2010.

Advisory Committee Act and FDA regulations require that an advisory committee be balanced in terms of the points of view represented.[7]

FDA's decision to invoke the separation of functions within the agency reflects a sensitivity to providing for a fair and impartial hearing on the important public health issues under consideration. Yet having the ODAC function as the advisory committee required under the regulations severely undercuts FDA's separation of functions because of the ODAC's prior intimate involvement on the issues. For example, the ODAC has specifically advised CDER on Avastin, and also worked closely with CDER in shaping CDER's broader approach to its accelerated approval program.

In light of these concerns, we ask that the Presiding Officer reconsider the use of the ODAC as the advisory committee for the hearing. If the Presiding Officer retains the ODAC, we would urge her to consider the use of consultants or temporary voting members to supplement the ODAC and provide advice to the Commissioner. Even though the parties will be able to call experts as witnesses at the hearing, the advisory committee plays a distinct and important role under the regulations and the hearing procedures the Presiding Officer has set out. For example, the ODAC will have the ability to question the presenting witnesses (as currently proposed, for one hour and thus greater than the 35 minutes proposed for each of Genentech and CDER), and (as currently proposed) there will be a half-day during the second day of the hearing dedicated to the ODAC's deliberations and advice. Accordingly, it is critical that the advisory committee itself have objectivity as well as the appropriate expertise. Adding temporary voting members can help serve both purposes, by including individuals who have not previously expressed views on the issues under consideration, and who also can provide important breast cancer expertise to the ODAC. We understand the Presiding Officer's concern that some experts in the field may have already voiced views on these issues, but we believe it should be possible to find experts who have not and who also would meet FDA's conflict of interest rules.

In this regard, we note that it is quite typical for the rosters for ODAC meetings to include both standing committee members and temporary voting members. All the rosters for ODAC meetings for the last two years included temporary voting members,

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[7] 5 U.S.C. app. § 5(b)(2); 21 C.F.R. § 14.40(f)(2); *see also* 21 C.F.R. § 14.1(b)(5) ("An advisory committee ... serves as a source of independent expertise and advice rather than as a representative of or advocate for any particular interest.")

and temporary voting members were added to the ODAC roster for both the July 20, 2010 and December 5, 2007 ODAC meetings discussing Avastin in MBC.[8]

Moreover, and separately, the procedures that the Presiding Officer utilizes for the hearing could help ensure a more impartial proceeding. The Presiding Officer has stated in correspondence to date that at least the morning of day two of the hearing will be reserved for the advisory committee to provide its advice and recommendations. It is not clear yet how precisely this portion of the hearing will be structured. In contrast to a typical advisory committee meeting, and in keeping with her role under the regulations governing the hearing, we suggest that the Presiding Officer should chair and direct the advisory committee portion of the hearing.

Additionally, on day one of the hearing the time allotted for questioning could be distributed in a more balanced manner than currently proposed. Given that the ODAC comes to the hearing essentially aligned with CDER, we view as skewed the current allocation of 35 minutes for questioning by each of CDER and Genentech and one hour of questioning by the ODAC (with the Presiding Officer). We thus propose that Genentech be given additional time for its questioning, with the ODAC potentially sharing its time for questions with CDER rather than with the Presiding Officer. Further, however the question period is divided, we view 35 minutes for our allotment as not sufficient, and believe each presenting witness should be available for questioning after his/her presentation. We will discuss these issues further in our consultation with CDER regarding the hearing procedures, but wanted to raise them now as a preliminary matter because they relate to the broader issue of the use of the ODAC.

Public Participation

The Presiding Officer has stated that members of the public will be permitted to submit their views to the hearing docket in writing, but will not be permitted to make oral presentations at the hearing. For the reasons stated below, Genentech respectfully requests that the hearing include an opportunity for interested members of the public to make oral presentations.

The governing regulations provide for public participation in the actual hearing, as follows: "The commissioner concludes, as a matter of discretion, that it is in the public interest to permit persons to present information and views at a public hearing on any

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[8] The meeting rosters for the December 5, 2007 and July 20, 2010 ODAC meetings included three and six temporary voting members, respectively. At the July 20, 2010 ODAC, two of the temporary voting members were the only members to have experience in breast cancer.

matter pending before the Food & Drug Administration."[9] Indeed, the regulations set out detailed procedures for public participation, such as requiring notice of the hearing, providing persons an opportunity to file a notice of participation, requiring prior notice of a hearing schedule with the time allotted to each participant, and requiring attempts to hear participants who are late.[10] Written submissions are also permitted under the regulations as an additional avenue for public opinion.[11] The provisions for written submissions and public participation at the hearing are separate, however, and indicate that the two are intended as complements, not as alternatives.

Genentech recognizes the logistical concerns that the Presiding Officer has raised and the desire to hold the hearing over a two-day timeframe. However, the regulations clearly envisage participation by the public, especially where, as here, the matter is of great public interest. Furthermore, the robust public response and numerous submissions to the public docket[12] (including a large number from MBC patients) demonstrate the strong public interest and the need for public participation in this matter. Genentech, therefore, respectfully requests that an effort be made to provide an opportunity for interested members of the public to make oral presentations, in addition to live presentations by Genentech and CDER.

* * *

Thank you for considering these issues. Genentech does not wish to complicate the planning for the hearing. At the same time, this is a novel proceeding with

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[9] 21 C.F.R. § 15.1(a).

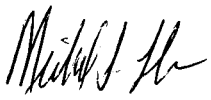
[10] 21 C.F.R. §§ 15.20, 15.21, 15.30.

[11] 21 C.F.R. § 15.25.

[12] As of March 4, 2011, nearly 350 comments, one including a petition with over 10,000 signatures, had been submitted to the docket.

real public health consequences. We thus feel compelled to raise our concerns regarding the ODAC and the lack of public participation at the hearing.

Respectfully submitted,



Michael S. Labson
Counsel for Genentech, Inc.

cc: Carla Cartwright, Office of the Chief Counsel, Food and Drug Administration
Donald Beers, Office of the Chief Counsel, Food and Drug Administration