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Chairman John D. Dingell
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Chairman Bart Stupak
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairmen Dingell and Stupak:

I am writing in response to your March 20, 2007 letter to Kevin Sharer, in which you posed four questions prompted by recent reports concerning Erythropoiesis-Stimulating Agents (ESAs). We appreciate the importance of this subject, and we are pleased to cooperate fully with the Committee's inquiry. We strongly believe that Amgen's ESAs, Aranesp® (darbepoetin alfa) and EPOGEN® (epoetin alfa) are safe and effective medicines when used in approved patient populations in accordance with FDA-labeled dosing recommendations, and we welcome the opportunity to answer your questions, as well as those that may be raised at the May 10, 2007 meeting of the FDA's Oncology Drugs Advisory Committee (ODAC), to which your letter refers. Our responses to your questions are set forth below, including those involving your concern as to direct-to-consumer (DTC) product marketing. (Amgen has not engaged in DTC product advertising on television or radio, or in print (*i.e.*, consumer magazines), since the launch of EPOGEN® in 1989 and Aranesp® in 2001.) We also have taken the necessary steps to satisfy the Committee's request to preserve all records identified in your March 20 letter.

1. **When did Amgen or any of its employees or consultants learn of the suspension of any EPO study (Phase II-IV) that was halted out of concern for the subjects in the study?**

We are aware of only three ESA studies since the May 2004 ODAC meeting that could fall within the ambit of this question. One of these (DAHANCA 10) is an investigator-initiated study involving the use of Amgen's Aranesp® at levels higher than those approved in the United

States. This study was terminated on November 28, 2006, because of the minimal likelihood of increased survivability in patients treated with Aranesp®. The second study is a Johnson & Johnson study (CHOIR), which likewise focused on off-label uses and which was terminated in May 2005. The third study is a Roche study concerning an unapproved Roche ESA. To the best of our knowledge, this study is ongoing, although Roche announced in February 2007 that it had temporarily suspended the recruitment of new patients into the study. We discuss these studies below.

To provide some context for the DAHANCA 10 study, it may be helpful to first note the four other studies (in addition to DAHANCA 10) that are part of Amgen's FDA-approved Aranesp® pharmacovigilance program, and provide a brief update as to the status of each. All five of these studies (including DAHANCA 10) were discussed at the May 2004 ODAC meeting. Four of these studies (DAHANCA 10, GELA, PREPARE, and ARA-PLUS) are investigator-initiated – that is, studies initiated, conducted, and controlled by independent investigators.[1] As is typical in the case of investigator-initiated studies, Amgen provides grants that assist in supporting the conduct of the trial as well as grants to support the purchase of Aranesp® for use in the trial. The fifth pharmacovigilance study (Amgen 20010145) was sponsored by Amgen using Amgen's clinical trial monitoring and compliance infrastructure.[2] DAHANCA 10 is the only one of these five trials that has been terminated.

DAHANCA 10. It is our understanding that the DAHANCA 10 study, conducted by the Danish Head and Neck Cancer Study Group, was designed to evaluate whether maintenance of hemoglobin concentrations at near normal levels (hemoglobin levels of 14.5 – 15.5 g/dl) with Aranesp® would improve the effect of radiotherapy in patients with head and neck cancer. This was an off-label use not approved in the United States.

On December 1, 2006, the study's principal investigator, Professor Jens Overgaard (Head of the Department of Experimental Clinical Oncology, Aarhus University Hospital; Aarhus, Denmark), emailed a copy of the Interim Analysis of DAHANCA 10 to Amgen, announcing the conclusions reached by the DAHANCA study group at a meeting on November 28, 2006. According to the Interim Analysis, the DAHANCA study group had decided at their November 28 meeting, based upon their collective analysis of the interim study data, that the trial should be terminated. The Interim Analysis indicated that the treatment with Aranesp® had been well tolerated by the patients in the study without causing excess major serious adverse events, with the preliminary analysis showing an approximate 10% difference in three-year locoregional failure, the primary endpoint of the study. The DAHANCA study group decided to

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[1] We discuss the DAHANCA 10 study below. The three other studies initiated, conducted, and controlled by independent investigators have advanced since the May 2004 ODAC review, but have not generated final results. The GELA study of non-Hodgkins lymphoma, being conducted in France and Belgium, has an expected clinical study report date of Q3 2010. Investigators reported interim data in December 2006, showing no negative impact on event-free or overall survival. The PREPARE study, a non-adjuvant study in Germany of patients with breast cancer, has an expected clinical study report date of Q4 2007; a previous analysis by the study's data safety monitoring board recommended that the study continue. The ARA-PLUS study, also being conducted in Germany, is an adjuvant study in breast cancer with a clinical report date of Q2 2011; one interim safety analysis recommended that this study likewise be continued.

[2] Amgen 20010145 is a study of small-cell lung cancer. Although Amgen 20010145 has a clinical study report date of Q4 2007, the study has reached the predetermined number of endpoints, and Amgen expects to be able to provide study results before the upcoming May 2007 ODAC meeting. There have been two interim analyses reviewed by the study's data safety monitoring board, which supported the study's continuation.

terminate the study because of the minimal likelihood that the Aranesp®–treated patients would have significantly better results with their radiotherapy treatment versus the placebo group. Amgen, however, still has not been provided the opportunity to review the underlying data or peer reviews.

Based upon our investigation to date, we believe that no Amgen officers, employees, or consultants knew before December 1, 2006, what the DAHANCA study group's data showed, or that the group had decided on November 28 to terminate the trial. On October 18, 2006, Amgen did learn from Professor Overgaard that he was temporarily stopping further *recruitment* of new patients. This decision, however, was not prompted by negative data from the DAHANCA 10 study, but rather by the publication at that time of pre-clinical research data on the potential expression of EPO-R in head and neck cancer by Michael Henke, *et al.*, in the Journal of Clinical Oncology (October 10, 2006),[3] which roughly coincided with the imminent approach of the DAHANCA 10 study's predetermined threshold number of primary endpoint events (150) for the planned interim analysis. Professor Overgaard specifically advised in his email that his temporary hold on recruiting *new* patients should not affect *existing* patients currently in treatment – and long-term follow-up of all enrolled patients continues.

Amgen understood from this email and a subsequent email the following day that Professor Overgaard was continuing to treat patients already enrolled in the DAHANCA 10 study with Aranesp® as before, while the DAHANCA investigators worked expeditiously to collect remaining data and perform the necessary interim analysis. The DAHANCA study group did not decide to terminate the study until November 28, 2006, after collecting and analyzing the data. Amgen did not learn of this decision until Professor Overgaard sent his December 1, 2006 email. In recent correspondence to Amgen, Professor Overgaard advised that no one, including the DAHANCA investigators, were aware of the results of the interim analysis prior to the morning of November 28, 2006, and he confirmed that nothing was communicated about these results to Amgen until December 1, 2006. Furthermore, he cautioned against over-interpretation of the DAHANCA 10 data; he specifically emphasized that the results to date merely show a very small likelihood of *increased* survival in patients treated with Aranesp®, rather than decreased survival.

Other companies' studies.

Since the May 2004 ODAC meeting, one ESA study not included in Amgen's pharmacovigilance program was terminated upon the recommendation of the study's data safety monitoring board. This clinical trial, Correction of Hemoglobin and Outcomes in Renal Insufficiency (referred to as the CHOIR study), was a cardiovascular study sponsored by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. According to Johnson & Johnson, the CHOIR study was conducted to understand whether anemic patients with chronic

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[3] The Henke article analyzed a subset of patients with head and neck cancer, from an earlier Henke trial. Professor Overgaard specifically noted to Amgen that it was "not clear" whether Henke's observations had relevance to his DAHANCA 10 study. He nevertheless elected to suspend further patient recruitment pending the upcoming interim DAHANCA 10 analysis out of an abundance of caution. It should be noted that the DAHANCA group had previously performed an interim analysis in the wake of the original Henke article and had elected as a result of that analysis to continue the DAHANCA 10 trial.

kidney disease (CKD) not on dialysis, when treated with PROCRIT® at off-label hemoglobin target levels, would have improved mortality and specific cardiovascular outcomes compared to patients treated in accordance with label hemoglobin levels. PROCRIT® (epoetin alpha) is sold by Ortho Biotech (a Johnson & Johnson subsidiary) under a license agreement with Amgen. Johnson & Johnson notified the FDA on May 27, 2005, that it had recently terminated the CHOIR study. Amgen learned of this development at that time.

Finally, a study involving an unapproved ESA for another company, Roche, has not been halted, but there has been a temporary suspension in recruitment. On February 23, 2007, Roche announced that it was temporarily suspending recruitment into its Phase II dose-finding study (NH19960) with Roche's drug Mircera (also referred to by Roche as "C.E.R.A.") but that the treatment of enrolled patients would continue. Roche's study focuses upon anemic patients with advanced non-small cell lung cancer receiving chemotherapy. The FDA has not approved the use of Mircera for any indication. Roche describes Mircera as an investigational anemia therapy for the treatment of renal anemia associated with CKD. Roche filed a Biologic License Application (BLA) with the FDA for Mircera on April 20, 2006, for the treatment of anemia associated with CKD, not oncology. On December 15, 2006, Roche announced that it had provided additional data to the FDA in support of its BLA and that, as a result, the FDA had granted Roche a three-month extension of the review period.

2. When did Amgen notify the FDA of such suspensions and who in the Agency was notified?

Amgen notified the FDA of the termination of the DAHANCA 10 study; the other companies notified the FDA as to the studies concerning their products.

With respect to DAHANCA 10: Amgen received written notification from the DAHANCA 10 study group of preliminary interim results of the DAHANCA 10 study on Friday, December 1, 2006. On Monday, December 4, Amgen (Erik Poulsen, Global Regulatory Leader – Aranesp® Oncology) left a voice message with the FDA (Monica L. Hughes, MS, Project Manager) regarding the termination of the DAHANCA 10 trial and alerting the FDA that a letter would follow. On Tuesday, December 5, Amgen (Erik Poulsen) provided formal written notification to Patricia Keegan, MD, Director of the FDA's Division of Biological Oncology Products (attention: Monica L. Hughes).

3. Please describe all discussions Amgen has had with the FDA or the Department of Health and Human Services (HHS) regarding direct to consumer advertising of Aranesp or Epogen since advising the Agency of any of the adverse events that are cautioned against in the black box warning announced last week.

In the wake of the reported results of the CHOIR, DAHANCA 10, and Amgen 103 studies, Amgen had numerous, often daily, communications with the FDA (via facsimile and teleconference) on a variety of safety issues related to ESAs. These communications culminated in the finalized, FDA-approved labeling (including black box warnings) issued for Aranesp® and

EPOGEN®/PROCRIT® on March 9, 2007. One issue addressed with the FDA during the course of the labeling discussions centered around promotional activity.

As a preliminary matter, Amgen has not engaged in direct-to-consumer (DTC) product advertising on television or radio, or in print (*i.e.*, consumer magazines), since the launch of EPOGEN® in 1989 and Aranesp® in 2001.[4] Amgen has historically communicated to patients, however, via Amgen-sponsored websites (*e.g.*, www.aranesp.com, www.epogen.com, www.chemotherapy.com) and through Amgen's distribution of product-related Patient Brochures. These types of communications were consistent with, and built upon, the FDA-approved Patient Package Inserts for EPOGEN® and Aranesp®.

Despite its historical forbearance from DTC advertising, during conference calls with the FDA and FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) on February 22 and 28, 2007, Amgen and FDA/DDMAC agreed that Amgen would voluntarily not run any DTC television, print, or radio advertising until after the May 10, 2007 ODAC meeting.[5] Amgen confirmed its discussions with DDMAC in letters dated March 14, March 22, and April 6, 2007. Furthermore, after the FDA issued the revised ESA labeling on March 9, 2007, Amgen promptly modified its product websites (www.aranesp.com and www.epogen.com), by uploading the new product labeling (Package Insert and Patient Package Insert) on both the Professional and Patient portions of the websites, and by removing outdated materials that did not reflect the new product labeling.

Although Amgen has never used the types of DTC advertising outlined above for its ESAs, Amgen did seek pre-clearance comments from DDMAC in May 2006 on a *proposed* DTC print advertisement for Aranesp® that had been slated to run in consumer magazines in 2007. The proposed advertisement focused on anemia due to the effects of concomitantly administered chemotherapy, an approved indication included in Amgen's FDA-approved Package Insert and Patient Package Inserts. DDMAC, in consultation with the FDA's Division of Biologic Oncologic Products, reviewed the proposed print advertisement and provided comments back to Amgen by fax dated December 6, 2006. Amgen incorporated these comments into a final version of this proposed advertisement, but this proposed advertisement has never run in any publications, and, in light of our February 2007 commitment to DDMAC, Amgen currently has no plans to run DTC advertising (TV, radio, or consumer print) for Aranesp® or EPOGEN®.

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[4] Direct-to-consumer (DTC) advertising should be distinguished from direct-to-professional advertising. Amgen has regularly run print advertisements in professional journals aimed at the healthcare professional audience. These publications for Aranesp® in the oncology setting have included the American Journal of Hematology/Oncology; Blood; Community Oncology; and the Journal of Clinical Oncology.

Subsequent to the FDA's final approval of revised labeling (including black box warnings) for Aranesp® and EPOGEN®/PROCRIT® on March 9, 2007, Amgen took additional steps to inform the healthcare community of these changes: On March 12, 2007, Amgen and Johnson & Johnson issued a joint, FDA-approved letter, describing the new labeling, which they then mailed to 66,000 health professionals. Amgen field representatives have also been proactively disseminating the new labels to healthcare professionals as part of their calls on providers to advise them of the new safety and risk information.

[5] The FDA publicly acknowledged and reported Amgen's commitment by posting it on the FDA website on March 9, 2007, the same day that the FDA issued the new ESA labels, announced the Public Health Advisory, and held a public press conference by telephone.

4. Please describe all promotions that Amgen undertakes that have the effect of relating the prescription of EPO products to the income of physicians or their practices.

Amgen does not believe that it undertakes promotions that have the effect of relating the prescription of EPO products to the income of physicians or their practices, particularly any "personal income incentives" as referenced in the Committee's press release of March 21, 2007. As is common in the industry, Amgen interacts with healthcare professionals in a variety of ways in the course of its business. Enclosed is a copy of Amgen's "Business Conduct Standards for Interactions with Healthcare Professionals," which govern the conduct of U.S. sales and marketing professionals, including product and reimbursement discussions.[6] Also, based on discussions with staff, we have not addressed competitive contracting issues (some of which are the subject of ongoing litigation).

Once again, Amgen welcomes the opportunity to address the Committee's questions in this area and pledges our continued cooperation with your inquiry. If you have further questions after reviewing these responses, please contact me.

Yours sincerely,

David Beier
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Global Government Affairs
Amgen Inc.

Enclosures

cc: The Honorable Joe Barton, Committee on Energy and Commerce
The Honorable Edward Whitfield, Committee on Energy and Commerce

[6] Specifically, for example, the standards state that "Field-Based Employees may never discuss how much money a Healthcare Professional can make on the difference between the Healthcare Professional's acquisition cost and reimbursement from Medicare or other third party payors (*e.g.*, 'spread,' 'profit,' 'return to practice,' or other similar concept)." U.S. Standard for Product and Reimbursement Discussions, § 4.1.