



Amgen  
555 13<sup>th</sup> Street, NW  
Suite 600 West  
Washington, DC 20004  
Direct : 202.585.9600

June 11, 2007

The Honorable Charles Grassley  
United States Senate Committee on Finance, Ranking Member  
135 Hart Senate Office Building  
Washington, DC 20510-1501

Dear Senator Grassley,

I am writing in response to your letter of May 16, 2007, which asked Amgen to brief your Committee staff on the issues and concerns that have been reported in the media over the last several weeks regarding the marketing and safety of Erythropoiesis Stimulating Agents (ESAs). We are scheduling such a briefing and will respond to all of the questions in your letter.

This letter specifically addresses the issue you raised related to Amgen's interactions with the Food and Drug Administration about safety data on oncology use of ESAs. It is important to us that you understand that Amgen has responded and will continue to respond to requests for such data in a timely and comprehensive way.

Amgen has marketed Aranesp® (darbepoetin alfa) since 2002 for use in treating anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. Amgen scientists developed Aranesp® and the other biologicals known as ESAs and have perhaps the world's most significant knowledge base and experience with this class of biologicals. We have conducted and sponsored numerous clinical trials on ESAs over the past 20 years, and have always taken very seriously any safety concern raised during those trials.

After FDA conducted an oncology advisory committee meeting regarding the safety of ESAs in 2004, Amgen entered into a post-marketing commitment with the agency under which we agreed to submit the results of five pharmacovigilance studies (one Amgen-sponsored and four investigator-sponsored) and a meta-analysis of those results. As discussed in more detail below, Amgen has completed the Amgen-sponsored '20010145' study and provided these data in full to FDA. Amgen has actively engaged with and supported the four investigator-sponsored studies and been diligent in providing study updates and data in a timely manner to the FDA. In addition, Amgen proactively notified healthcare practitioners about safety signals raised by a separate study of Aranesp® use in treating the anemia of cancer and submitted those data in full to FDA.

Again, we emphasize that Amgen is absolutely committed to the prompt communication of safety information to FDA. We make every effort to report this information rapidly and comprehensively, and will continue to do so.

## **Background**

Amgen currently markets Aranesp® for the treatment of anemia in patients with non-myeloid malignancies where the anemia is due to concomitantly administered chemotherapy.<sup>1</sup> The FDA approved Aranesp® in 2002 for this indication based on a Phase 3, double-blind, placebo-controlled, randomized clinical study in anemic patients with advanced, small cell or non-small cell lung cancer, receiving concurrent chemotherapy. This study established that Aranesp®, as compared to placebo, significantly reduced the proportion of patients requiring red blood cell transfusion.

The theoretical possibility that a growth factor product such as Aranesp® may have the potential to stimulate tumor growth has long been recognized. In fact, this risk was listed in the Precautions section of the approved Aranesp® label in 2002. Additionally, as a science-based company, Amgen is committed to developing additional information about the safety and efficacy of its products even after FDA approval. Thus, Amgen has undertaken a number of post-marketing studies of Aranesp®. This research has been conducted both by Amgen and by independent investigators, including cooperative groups around the world. As a general rule, investigator-sponsored studies are initiated and controlled by academic researchers who are independent of Amgen. We rely on these investigators for timely reporting of their results to us, so that we may then make that information available to FDA.

In 2004, after two studies conducted by other companies showed negative effects of ESAs on survival and tumor outcomes, FDA convened a meeting of its Oncologic Drugs Advisory Committee (ODAC) to review data available regarding ESAs. After rigorous analysis and discussion of these data, the Committee was unable to reach a definitive conclusion on the true implications of the data and recommended additional study of questions around these outcomes.

Consequently, pursuant to an agreement with FDA, Amgen committed to complete additional studies to explore whether, in fact, Aranesp® accelerates tumor growth and decreases patient survival. This group of studies – which we characterize as a pharmacovigilance program – includes four investigator-sponsored trials (FR-2003-3005, DE-2001-0033, DE-2002-0015, and SE-2002-9001) and one Amgen-sponsored trial (20010145).

### **Amgen's Reporting of Results to FDA**

On December 1, 2006, Amgen received notice of the halting of enrollment in an investigator-sponsored study, SE-2002-9001, that is part of the pharmacovigilance program. Known as DAHANCA 10, the study evaluated the effects of Aranesp® in patients with head and neck cancer receiving radiation therapy but not concurrent chemotherapy. After conducting an interim data analysis, the DAHANCA study group concluded that the trial would be highly unlikely to demonstrate improved outcomes with Aranesp® treatment. Therefore, consistent with international standards for the conduct of clinical trials, the group halted enrollment in the study on November 28, 2006. Long-term follow up for the study continues. Preliminary interim data showed that patients treated with Aranesp® (to experimental, high hemoglobin levels) had

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<sup>1</sup> Amgen also markets Aranesp® and EPOGEN® (Epoetin alfa) for treatment of anemia in patients with chronic renal failure on dialysis. This response does not address studies conducted for these other indications nor does it address studies of ESAs conducted by other companies.

increased locoregional tumor progression compared to patients in the control group with a trend toward decreased survival in the Aranesp®-treated patients.

Amgen received a report from the principal investigator of the DAHANCA study group on Friday, December 1, 2006, notifying the company of this decision. Amgen notified FDA of the termination of enrollment in the study on Monday, December 4, 2006, and submitted the preliminary information from the DAHANCA study group to FDA on December 6, 2006. Currently, the sponsors of DAHANCA 10 are in the process of completing data analysis. Amgen has been working with these investigators to facilitate their analysis.

Over the first week of January 2007, Amgen's senior management team began review of the preliminary results from an efficacy study that was not part of the Aranesp® pharmacovigilance program, Amgen 20010103 (Study 103). Study 103 was designed to establish the effectiveness of Aranesp® in patients with anemia of cancer, but failed to meet its primary endpoint of reducing red blood cell transfusions in the Aranesp® treatment group. In addition, although not designed to examine safety, study patients treated with Aranesp® experienced significantly shorter overall survival compared to patients on placebo. Amgen submitted these preliminary results to FDA as soon as the data sets were reviewed and, on January 26, 2007, proactively issued a "Dear Health Care Professional" letter informing the medical community of the Study 103 data. Primary electronic data sets for Study 103 were provided to FDA as soon as they were available for transfer in March 2007. In accordance with Amgen's policy on Public Disclosure of Clinical Trials and Clinical Trials Results, a summary of the results was also posted at [clinicaltrials.gov](http://clinicaltrials.gov) so that all interested parties could review the study findings.<sup>2</sup>

Concurrently, Amgen engaged in discussions with FDA about revisions to the Aranesp® label to incorporate this information. On Friday, March 9, 2007, Amgen and FDA agreed to add a boxed warning to the labels of Aranesp® and the other U.S. marketed ESAs (Procrit® and EPOGEN®) to emphasize safety information on appropriate dosing, cardiovascular and thromboembolic events, and tumor progression. Similar information had previously been included in the Warnings, Precautions, and Dosage and Administration sections of the products' labels. Amgen again reached out to the physician community with a "Dear Health Care Professional" letter on Monday, March 12, 2007, announcing these labeling revisions.

At that time, FDA also announced that it would reconvene the ODAC to discuss the data and seek additional advice from the Committee regarding the risk/benefit profile of ESAs in the oncology setting.<sup>3</sup> At the May 10, 2007 ODAC meeting, Amgen presented data from Study 103, as well as the results of the recently completed pharmacovigilance Study 145, a double-blind study in which anemic patients with small cell carcinoma of the lung were treated either with

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<sup>2</sup> This policy is available at [http://www.amgentrials.com/medpro\\_policy.cfm](http://www.amgentrials.com/medpro_policy.cfm).

<sup>3</sup> As part of the 2007 ODAC preparations, Amgen Study 20000161 (Study 161) was discussed. Initial results from Study 161 – presented to the 2004 ODAC – demonstrated statistically similar but directionally adverse overall survival and progression free survival for patients treated with Aranesp® and placebo. This was not unexpected given the study design which did not control for disease type. In April 2005, Amgen submitted to FDA a clinical study report from long-term patient follow up as a component of the extended dose file; here again, adverse survival data were well characterized. In addition to these regular updates on this study, in preparation for the May 10, 2007 ODAC meeting, FDA requested a full data set from the long term follow up from this study, which was promptly provided.

Aranesp® or placebo.<sup>4</sup> In Study 145, Aranesp® treatment had no significant effect on overall survival or tumor progression in these patients.<sup>5</sup>

Consistent with our post-marketing commitment with FDA, Amgen has not yet submitted complete data sets to FDA from the remaining studies that comprise the Aranesp® pharmacovigilance plan because the studies have not been completed. Studies FR-2003-3005 (GELA) and DE-2002-0015 (ARA-03) are ongoing and are projected to be complete in August 2010 and May 2011, respectively. Interim data from GELA were submitted to FDA and presented at the 2006 annual meeting of the American Society of Hematology in December 2006. An abstract reporting the second interim safety analysis of ARA-03 was submitted to FDA and was presented at the American Society of Clinical Oncology in May 2007.<sup>6</sup> Study DE-2001-0033 (PREPARE) has completed patient accrual, but follow-up continues. Due to logistical complications with the investigator, data collection has been stalled, and Amgen notified FDA of that fact in February 2007. Amgen is working with the parties involved to accelerate completion of the PREPARE data acquisition and analysis.

## Conclusion

As described above, Amgen has submitted to FDA all available data, including primary data, from post-marketing pharmacovigilance studies involving Aranesp® as well as from other studies that have raised safety concerns. As for the ongoing Aranesp® pharmacovigilance studies, Amgen is actively engaged with the independent investigators and has diligently provided study updates to FDA when those have become available. Interim data or analyses by the respective independent data monitoring committees for these ongoing studies have not revealed safety concerns or, alternatively, reasons to discontinue the trials.

Amgen is committed to the complete and timely analysis of those studies as soon as the data are available, and those results will then be made available both to FDA and to the public.

**Amgen strongly believes that ESAs, including Aranesp® and EPOGEN®, are safe and effective medicines when used in approved patient populations in accordance with FDA-approved prescribing information.** Comprehensive analyses of single patient level data, as well as study level data from randomized controlled trials, support a neutral impact of ESAs in chemotherapy-induced anemia on overall and progression-free survival.

Amgen is pleased to fully cooperate with your inquiry and looks forward to additional discussions in the coming weeks. This letter and the previous materials that we have provided to your staff, including Amgen's comments on the Center for Medicare and Medicaid Services'

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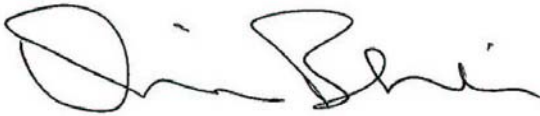
<sup>4</sup> Amgen informed FDA on March 21, 2007, that it would include 145 data in its presentation to ODAC but that the data would not be included in the briefing documents submitted before that meeting. On April 23, 2007, Amgen formally submitted to FDA the Flash Statistical Report of the data. An annotated study report along with primary data was submitted to FDA on April 27, 2007. Results of this study were also posted on clinicaltrials.gov.

<sup>5</sup> The termination of enrollment in DAHANCA 10 for futility also was acknowledged at the ODAC meeting, but full study results could not be presented as they are not yet available.

<sup>6</sup> Aranesp® had no significant effect on overall survival in this study.

Proposed Decision Memorandum for ESAs for Non-Renal Indications, respond to questions 1 through 3 of your May 16<sup>th</sup> letter. We will provide additional responses and documents to you by June 19, 2007.

Yours Sincerely,

A handwritten signature in black ink, appearing to read "David Beier". The signature is fluid and cursive, with a large initial "D" and "B".

David Beier  
Senior Vice President  
Global Government Affairs  
Amgen, Inc.