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June 1, 2007

Steve Phurrough, MD, MPA, CPE
Director, Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Mail Stop: C1-09-06
7500 Security Boulevard
Baltimore, Maryland 21244

Re: Proposed Decision Memorandum for Erythropoiesis Stimulating Agents for Non-Renal Disease Indications (CAG-00383N)

Dear Dr. Phurrough:

Amgen Inc. (Amgen) is a science-based company, committed to developing innovative products that treat grievous illnesses. The highest levels of patient safety are an important part of this commitment throughout the lifecycle of our products. We communicate proactively and regularly with the U.S. Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS) regarding the safety of our products, and Amgen is committed to working with CMS to provide objective, rigorous, and evidence-based information in response to the agency's Proposed Decision Memorandum (PDM) for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N) released on May 14, 2007.[1] Amgen scientists developed the breakthrough molecules known as ESAs and have perhaps the world's most significant knowledge base and experience with this class of biologicals.[2]

As we have shared with CMS previously, Amgen takes seriously the recent safety concerns. We are also attentive to the concerns of CMS regarding the appropriate use of this class of products. Based on our understanding of the important benefits associated with ESA use in oncology, we have prepared a detailed response to the proposed National Coverage Determination (NCD) and offer specific scientific and clinical recommendations for the agency's consideration in preparing a finalized NCD on ESAs. These recommendations are intended to help CMS balance understandable safety concerns with the need to provide appropriate access to ESAs, which serve an important and well-recognized supportive care role in many types of cancer.[3]

I. EXECUTIVE SUMMARY

Anemia—defined as a below-normal level of red blood cells, hemoglobin, or both—is a debilitating complication that is common in cancer patients receiving chemotherapy, patients with cancer not receiving chemotherapy, and patients with myelodysplastic syndrome. Individuals with cancer-related anemia may present with a range of symptoms—most frequently fatigue, but also potentially including dizziness, shortness of breath, palpitations, lack of endurance, and angina, among others.

ESA therapy revolutionized anemia management. For nearly 15 years, ESAs have been employed by physicians to reduce the burden of red blood cell transfusions in patients receiving myelosuppressive chemotherapy. Clinical studies make plain that, compared with placebo, ESA treatment reduces by half the number of transfusions in such patients and extends the time to first transfusion. In addition, ESA treatment helps alleviate the signs and symptoms of anemia, which provoke physicians to transfuse red blood cells, and clinical trials report improvements in patient-reported outcomes for chemotherapy patients.

While CMS has a legitimate role to play in determining coverage policy for ESAs under the authority granted to it by Congress (*i.e.*, to determine the uses that are "reasonable and necessary"), in finalizing a NCD for these products, we urge CMS to guide its decisions by several important principles, including:

- That the coverage policy should be based strictly on the principles of evidence-based medicine, avoiding a physiologic rationale as a basis for coverage restriction and also avoiding coverage parameters that have never been studied in clinical trials or utilized in clinical practice;
- That CMS should acknowledge the role of the FDA in its judicious evaluation of the safety profile of the ESAs, and avoid using coverage policy to play the role of the FDA by issuing prescribing instructions;
- That the agency's decisions should reflect the paramount importance of the physician's role in delivering optimal cancer treatment for his or her patients;
- That the agency's actions should be made in full compliance with relevant laws, regulations, and past CMS statements on the development of coverage policies; and
- That the agency should ensure that the coverage process is open and transparent to all stakeholders.

Importantly, CMS has proposed broad coverage restrictions to the FDA-approved indication for ESAs in chemotherapy-induced anemia (CIA),[4] as well as broad restrictions to off-label uses. However, there is an absence of compelling clinical evidence in CIA patients on which to base these restrictions. The underlying logic of the PDM, which restricts coverage for ESAs in CIA in addition to off-label uses, appears to be based on the following three suppositions:

1. That safety signals observed in isolated off-label, experimental, or investigational uses should be extrapolated to ESA therapy in CIA and that these isolated studies are apparently judged to be of greater weight than the entire body of relevant data in CIA patients.

2. That the hypothesis that erythropoietin (EPO) receptors (EPO-R) may be expressed on tumors is valid, that these receptors—interacting with ESAs—could perhaps promote tumor growth, and that this unproven phenomenon would prove deleterious to cancer patients.
3. That a hemoglobin initiation level not to exceed 9.0 g/dL will minimize any risks while maintaining patient benefit.

In response to the first supposition, Amgen encourages CMS not to extrapolate the safety signals in off-label and experimental conditions to CIA based on individual studies, but rather to rely on a robust analysis of all available evidence to guide coverage policy.

The reasons that the approach adopted in the PDM is scientifically and clinically unjustified are summarized as follows:

- CMS can be confident that Amgen has been diligent in our pharmacovigilance, has supplied all available data to the FDA in a timely manner, and has proactively shared these data with health care professionals. The entire body of relevant data is included in the analyses contained herein.
- Robust analyses of CIA studies, including both study-level and patient-level meta-analyses, support a neutral impact of ESAs on survival.
- Although subgroup analyses point to decreased overall survival in ESA-treated patients with head and neck cancer undergoing radiotherapy, and in patients with anemia of cancer (AOC) who have active cancer not receiving or planning to receive chemotherapy or radiation therapy, these findings should not be extrapolated to the broad population of CIA patients.
- Several ongoing studies will continue to inform CMS, health care providers, and patients about the safety of ESAs.
- Several prominent medical societies and experts have also questioned the evidence base underlying the PDM.

In response to the second supposition, Amgen urges CMS to complete a careful, critical assessment of the clinical literature and evidence-base regarding EPO-R.

Such an assessment leads to a conclusion that there is no definitive evidence of EPO receptor involvement in tumor progression for the following reasons:

- While published papers provide data seemingly consistent with the hypothesis of EPO-R involvement in tumor progression, examination of the evidence shows it to be either flawed or circumstantial. This view has been confirmed by independent reviews of the literature, and is shared by several experts in the fields of oncology and immunohistochemistry.
- Several additional facts, which help support this view, are as follows:
    - EPO-R is not expressed at significant levels in human cancer cells, and EPO itself does not stimulate tumor growth.
    - The EPO-R gene does not behave as an oncogene.
    - There exist no satisfactory antibody reagents for detecting EPO-R, and the most commonly used EPO-R polyclonal antibody (*i.e.*, Santa Cruz C-20) was shown to detect heat shock protein HSP70, not EPO-R, in tumor samples.

- Experiments designed to detect cell surface EPO-R on tumor cell lines by measuring binding of radio-labeled EPO showed no evidence of EPO binding, and therefore no evidence that EPO-R is present on these cells.

In response to the third supposition, Amgen notes that the agency's proposed policy of initiating therapy at 9.0 g/dL in each month is not supported by scientific evidence.

Importantly, CMS has not provided any clinical or scientific rationale for setting an implicit hemoglobin upper limit at 9.0 g/dL (*i.e.*, initiation at 9.0 g/dL in each month) when the recently revised FDA label is not to exceed 12.0 g/dL.

Key Points on Initiation Level

- Almost all randomized clinical trials (RCTs) have initiated ESA therapy when the hemoglobin level is less than 11.0 g/dL. As a result, evidence-based clinical practice guidelines have recommended the initiation of ESA therapy in cancer patients when the hemoglobin level is less than 11.0 g/dL.
- In placebo-controlled trials, when ESA-treated patients initiate therapy at hemoglobin < 9.0 g/dL, 68 percent receive at least one transfusion; however, if the hemoglobin is between 10.0 and 11.0 g/dL, only 26 percent receive at least one transfusion. Thus, the agency's proposed policy would increase the percentage of patients who receive at least one transfusion.
- A meta-analysis of studies with an average hemoglobin level between 10.0 to 12.0 g/dL at baseline showed neutral outcomes with respect to overall survival (odds ratio, 0.86; 95 percent CI 0.69 – 1.08).
- Comparison of strategies for early intervention (generally, initiation of therapy at approximately 12 g/dL) and later intervention (generally, initiation of therapy when hemoglobin level drops below 10 g/dL) have been evaluated in a number of RCTs. A meta-analysis of these studies has demonstrated an approximate 50 percent reduction in the risk of transfusion favoring the early intervention approach (relative risk, 0.55, 95 percent CI 0.42 – 0.73).

Key Points on Hemoglobin Target Level

- Most of the RCTs that define the efficacy and safety of the ESAs targeted hemoglobin levels of 11.0 to 13.0 g/dL, with dose withholding at a minimum of 13.0 g/dL. These data represent the highest level of evidence upon which CMS typically bases coverage policies.
- Current evidence-based clinical practice guidelines (*i.e.*, American Society of Hematology [ASH]/ American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Networks (NCCN), European Organisation for Research and Treatment of Cancer [EORTC]) recommend targeting hemoglobin levels in the range of 11.0 to 13.0 g/dL.
- The recent FDA label change, in response to safety findings, includes a change from a target hemoglobin of 10.0 to 12.0 g/dL to a hemoglobin limit of 12.0 g/dL. **The recent FDA Oncology Drugs Advisory Committee (ODAC) panel voted, based on an analysis of existing data, that this level not be changed.**

- When survival outcomes are evaluated through meta-analysis in CIA, the hemoglobin threshold of 12.0 g/dL to 13.0 g/dL is not associated with an increase in mortality, with an odds ratio for overall survival of 0.87 (95 percent CI, 0.54, 1.38).
- Finally, in a recent Agency for Healthcare Research and Quality (AHRQ) meta-analysis of ESA safety, the relative risk of venous thromboembolism (VTE) does not vary when hemoglobin thresholds range from > 13.0 g/dL to 16.0 (Seidenfeld et al., 2006).
- While Amgen does not recommend that physicians target a hemoglobin level > 12.0 g/dL in anemic cancer patients, clinicians must practically manage hemoglobin targets and variability. To manage patients effectively, physicians need discretion to determine, for the individual patient, whether to reduce the dose or withhold the dose when the hemoglobin level temporarily exceeds 12.0 g/dL.

CMS has proposed a limit of 12 weeks per year for ESA treatment. This timeframe is without support in the clinical evidence and should be re-evaluated carefully in light of the best available data.

Chemotherapy regimens in cancer patients are frequently prolonged, and may last beyond 12 weeks. Moreover, patients experience a variable number of courses of chemotherapy in a year depending on tumor type, extent of disease and response to therapy. As such, the agency's proposal could inadvertently discriminate against Medicare beneficiaries who are prescribed chemotherapy regimens in excess of 12 weeks or who require multiple courses in a year. There is insufficient evidence to support this recommendation.

Moreover—as Amgen has commented previously and ASH has recommended—the duration of ESA therapy might need to be up to 90 days after completion of chemotherapy with longer durations depending on individual patient circumstances due to the myelosuppressive effects of chemotherapy.

Overview of Amgen's Recommendations

While there is little scientific basis to support many of the coverage restrictions proposed by CMS, there are aspects of the policy that are clinically and scientifically reasonable, and where Amgen and CMS share common views. Amgen agrees with several of the agency's non-coverage recommendations provided that specific clarifications (noted below in italics) are made, as detailed in Table 1.

Table 1: Overview of Amgen's Recommendations on Eight Areas of Agreement with the PDM

Proposal to Restrict Coverage in Eight Areas	Amgen Recommendation
1. Anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis 2. Anemia of myeloid cancers, *specifically acute myeloid leukemia (AML) and chronic myeloid leukemia (CML)* 3. Anemia associated with the treatment of myeloid cancers or erythroid cancers 4. Anemia associated with *primary treatment with* radiotherapy 5. Prophylactic use to prevent chemotherapy-induced anemia *in patients who have never suffered from CIA* 6. Prophylactic use to reduce tumor hypoxia *in non-anemic patients* 7. Patients with erythropoietin-type resistance due to neutralizing antibodies 8. Anemia due to cancer treatment if patients have uncontrolled hypertension	Consider Finalizing These 8 Proposed Coverage Limitations

Note: The italicized text represents specific clarifications that would make the proposed policy clearer.

In light of the clinical evidence, Amgen recommends that CMS reconsider a series of proposed coverage restrictions, as noted in Table 2.

Table 2: Overview of Amgen's Recommendations on 10 Restrictions for CMS to Reconsider Based on Clinical Evidence

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
1. Use with anti-angiogenic and anti-epidermal growth factor receptor (EGFR) monoclonal antibody therapies	• ESAs do not stimulate angiogenesis based on a comprehensive review of the literature and Amgen's experimental results • The PDM appears to have blended the results from two separate and unrelated studies: (1) the PACCE study of Vectibix™ (panitumumab) in colon cancer patients and (2) the study of darbepoetin alfa in patients with AOC (Amgen Study 20010103)	• Because this recommendation is not based on any clinical evidence, it should not be finalized

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
2. Anemia of cancer (AOC)	• Anemia of cancer represents a heterogeneous group of patients with solid and hematologic tumors in various stages of disease • There is published evidence of benefit from controlled clinical trials, without evidence of detrimental survival outcomes, in certain subgroups of patients receiving ESAs for AOC • We urge caution in extrapolating the safety finding in a specific subgroup of patients with active cancer not receiving or planning to receive chemotherapy or radiation therapy, to all AOC patients	• CMS should not provide coverage in AOC patients with active cancer not receiving or planning to receive chemotherapy or radiation therapy • CMS should provide coverage for other patients with AOC
3. Patients with thrombotic episodes related to malignancy	• There is insufficient evidence of increased relative risk in patients with prior thrombosis • ESA use in patients with thrombotic episodes is not a contraindication or a warning in the prescribing information	• Because this recommendation is not based on clinical evidence, it should not be finalized
4. Myelodysplastic syndrome (MDS)	• A systematic review of 59 studies (2,106 patients) with epoetin alfa and single arm studies of darbepoetin alfa support the safety and efficacy of ESAs in treatment of anemia associated with MDS (Ross et al., 2007) • Without ESA therapy, many MDS patients must undergo chronic red blood cell transfusions, carrying substantial risks, such as iron overload	• The restriction is unwarranted based on the available scientific evidence, and should not be finalized

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
5. Limits on hemoglobin level for ESA initiation and hemoglobin target	• The PDM blends initiation threshold and target hemoglobin level, and ESAs have never been studied with an initiation level of hemoglobin < 9.0 g/dL • Scientific evidence suggests that the greatest avoidance of transfusion occurs when ESAs are initiated at hemoglobin < 11.0 g/dL • There is practical evidence of a target hemoglobin level, allowing physician flexibility in managing individual patients who require a dose reduction rather than a dose withholding at hemoglobin > 12.0 g/dL	• CMS should implement an initiation level of hemoglobin < 11.0 g/dL, which is evidence-based • CMS should consider the need for physician discretion to dose reduce rather than withhold when hemoglobin exceeds 12.0 g/dL during chemotherapy
6. Limits on duration of ESA therapy	• Chemotherapy regimens in cancer patients are frequently prolonged and last beyond 12 weeks, and the number of courses of chemotherapy in a year is highly variable	• Duration of therapy should be individualized for the particular patient • Because this recommendation is not based on clinical evidence, it should not be finalized
7. Limits on ESA dosing	• ESAs are dosed to achieve hemoglobin targets, and there is no known association between ESA dose and suboptimal outcomes • FDA label specifies to use lowest dose necessary to achieve hemoglobin objectives, and the dose and hemoglobin levels cannot be managed independently	• Because this recommendation is not based on clinical evidence, it should not be finalized
8. Limits on dose adjustments	• The criteria in the PDM are not predictive of response based on published literature	• Because this recommendation is not based on clinical evidence, it should not be finalized • CMS should allow for dose titration and continued product use based on the prescribing information

Proposal to Restrict Coverage in 10 Areas	Review of Clinical Evidence	Coverage Recommendation
9. Limits on patients with weight gain and fluid retention	• This proposal is not founded in scientific evidence	• Because this recommendation is not based on clinical evidence, it should not be finalized
10. Limits on ESA use within clinical research programs	• In CIA, the evidence supports a positive benefit-to-risk profile when used according to the prescribing information and a neutral risk on survival and tumor progression • Well-described risks and patient-monitoring recommendations are included in the FDA-approved product labeling	• Such a restriction for an FDA-approved indication would be inappropriate and unprecedented for any Medicare covered drug or biological • It is not justified given the multitude of published evidence supporting ESA use • Therefore, this consideration should not be finalized

To support our recommendations, Amgen offers comments addressing the following areas:

II. ANALYSIS OF THE CLINICAL AND SCIENTIFIC BASIS OF THE PDM

CMS has proposed broad coverage restrictions to the FDA-approved indication for ESAs in CIA. However, there are no compelling clinical data in CIA patients on which to base these restrictions.

The underlying logic of the PDM, which proposes dramatic coverage restrictions in the FDA-approved indication of CIA,[6] appears to rest on three suppositions. These suppositions are as follows:

1. That safety signals observed in isolated off-label, experimental, or investigational uses should be extrapolated to ESA therapy in CIA and that these isolated studies are apparently judged to be of greater weight than the entire body of relevant data in CIA patients.
2. That the hypothesis that EPO receptors (EPO-R) may be expressed on tumors is valid, that these receptors—interacting with ESAs—could perhaps promote tumor growth, and that this unproven phenomenon would prove deleterious to cancer patients.
3. That a hemoglobin initiation level not to exceed 9.0 g/dL will minimize any risks while maintaining patient benefit.

Below, we discuss these suppositions in turn.

Response to Supposition 1: **CMS should not extrapolate the safety signals in off-label and experimental uses and patient populations to CIA based on individual studies, but should rather rely on a robust analysis of all available evidence to guide coverage policy.**

The reasons that the approach adopted in the PDM is scientifically and clinically unjustified are summarized below:

A. CMS can be confident that the entire body of relevant data is included in these analyses and that Amgen has been completely transparent with the FDA and CMS. There are 14 studies listed by CMS as "terminated, suspended, or otherwise not completed", the implication being that data are not available for analysis or have been omitted from analyses. In fact, summary data are available for 11 of these studies and all of the available studies have been included in the study level meta-analyses. These analyses, therefore, provide a comprehensive assessment of the safety of ESAs in cancer patients and patients treated for CIA, in particular.
B. These robust and comprehensive analyses of RCTs in CIA, including both study-level and patient-level meta-analyses, support a neutral impact of ESAs on overall survival and progression-free survival. These analyses strongly support Medicare coverage of ESAs in CIA.
C. The 14 studies identified by the FDA as having "adequate follow-up" reflect a heterogeneous mixture of studies on-label, off-label and experimental uses. However, meta-analyses of these trials support the conclusions from Amgen's robust, comprehensive meta-analyses and provide no evidence of adverse survival outcomes in patients receiving ESAs in CIA.

D. Combined analyses of all relevant data, including data from studies in off-label uses, have identified subgroups of patients for whom the totality of data does and does not indicate a potential survival risk. These analyses point to an ESA-associated mortality risk in patients with head and neck cancer undergoing radiotherapy, and in patients with AOC who have active cancer not receiving or planning to receive chemotherapy or radiation therapy. Within CIA, some individual studies have raised safety signals, but others have not, and the weight of evidence across all CIA studies does not indicate that mortality is affected overall, in solid tumors (including breast cancer and lung cancer), or lymphoproliferative diseases.
E. While ongoing studies will continue to inform CMS and other stakeholders about the safety of ESAs, the currently available body of evidence strongly supports coverage in CIA.
F. Amgen is not alone in questioning the supposition that CMS should extrapolate the safety signals from a subset of individual, experimental studies to all patients with the proposed coverage restrictions in CIA.

For each of the points summarized above, we provide a detailed discussion below.

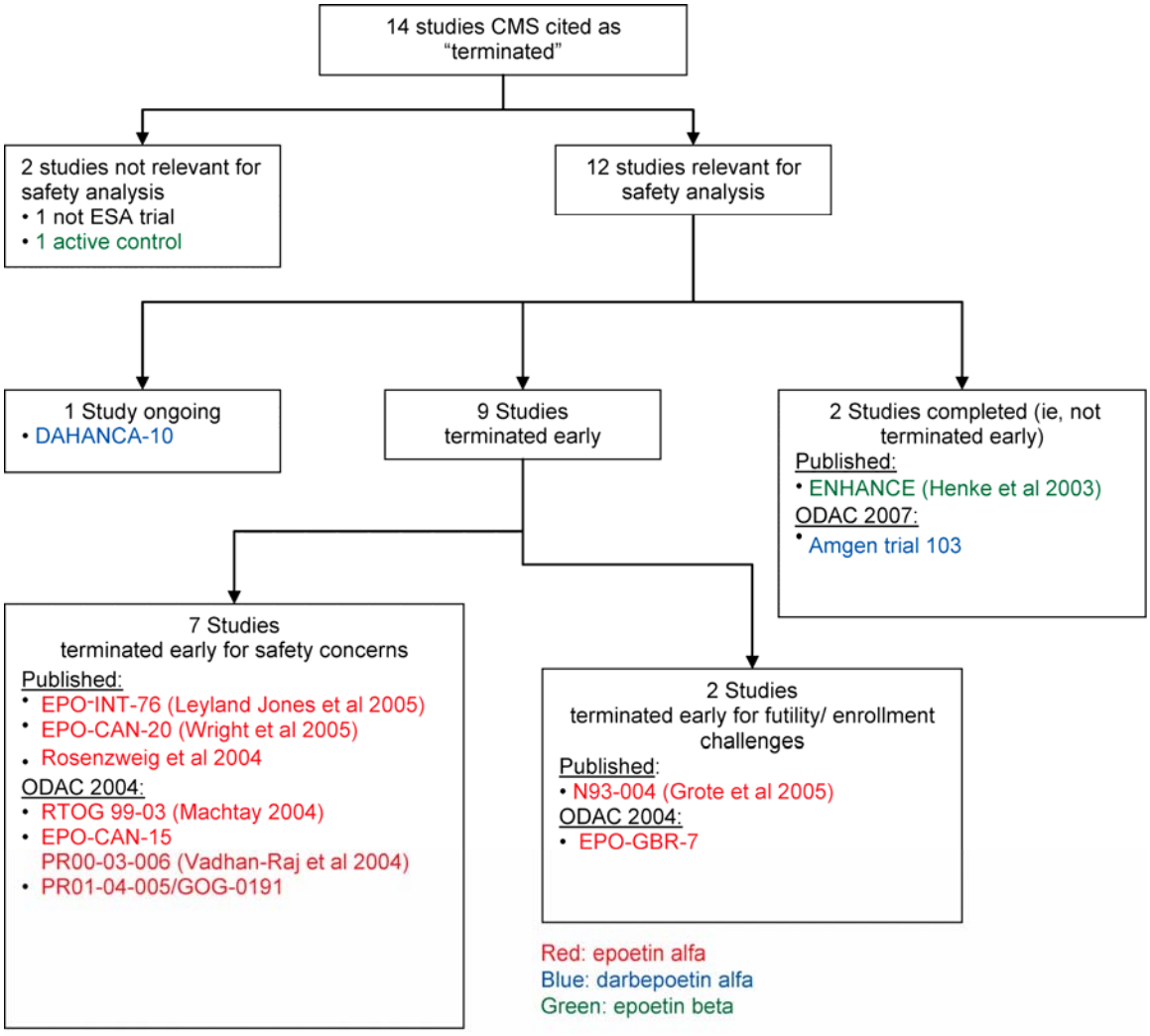
A. *CMS can be confident that Amgen has been fully transparent and that all the relevant individual studies are included in this analysis.*

Based on the results of the individual studies that have raised safety concerns, Amgen has taken appropriate steps to safeguard patient safety by updating product labeling and broadly communicating the results of these studies as they have become available. Amgen has been fully compliant and transparent with regard to its participation in ODAC meetings and provided the FDA with full electronic datasets of its studies to permit FDA analysis of the data. With respect to Amgen's pharmacovigilance program that arose out of the 2004 ODAC meeting, Amgen has completed the Amgen-sponsored '20010145' study (which provided data earlier than was expected) and provided these data to the FDA (available at ClinicalStudyResults.org). Amgen has actively engaged with and supported the 4 investigator initiated studies and been diligent in the provision of study updates and data in a timely manner to the FDA.[7]

There are 14 studies listed by CMS as "terminated, suspended, or otherwise not completed" (Chart 1 and Table 3). Data from 11 of the 14 studies were, in fact, included in the study level meta-analyses provided to FDA, ODAC, and CMS. Of the three remaining studies, one (DAHANCA-10) is still ongoing, one used an active comparator study (the Roche epoetin beta study: Hirsch et al., 2007), and one study was apparently cited in error. It should be noted that ten of the studies that were listed as missing by CMS were in fact disclosed and analyzed at the 2004 ODAC and again at the 2007 ODAC. These same ten studies are also included in the most recently published meta-analysis by the independent Cochrane study group (Bohlius et al., 2006b).

We summarize below the key points of each of the studies that CMS cited.

Chart 1: Studies Referenced by CMS in the PDM as "Terminated, Suspended, or Otherwise Not Completed"



In summary, Amgen has taken the results of all individual studies that have raised concerns seriously, has acted in a timely manner to ensure patient safety, has included the results of all of these studies in its analyses, and has been diligent in the generation and provision of data to agencies to further understand the safety concerns that have been raised.

B. *Robust and comprehensive analyses of RCTs in CIA, including both study-level and patient-level meta-analyses, support a neutral impact of ESAs on overall survival and progression-free survival. These analyses strongly support Medicare coverage of ESAs in CIA.*

As previously indicated, thorough analysis of safety signals requires that a three-level approach to available data be taken, as follows:

- assessment of individual study data,
- meta-analysis of patient level data from multiple studies, and
- meta-analysis of study level data.

Amgen has engaged in analysis at all three of these levels in its assessment of safety of ESAs in oncology patients. Amgen conducted meta-analyses using both the odds ratio (for study-level analyses) and the hazard ratio (for patient-level analyses). Amgen presents the results of these meta-analyses using a random-effects model as this approach incorporates an assessment of variability between trials.[8] For the odds and hazard ratios, when the 95 percent confidence intervals include unity, no statistical significant differences between groups can be concluded.

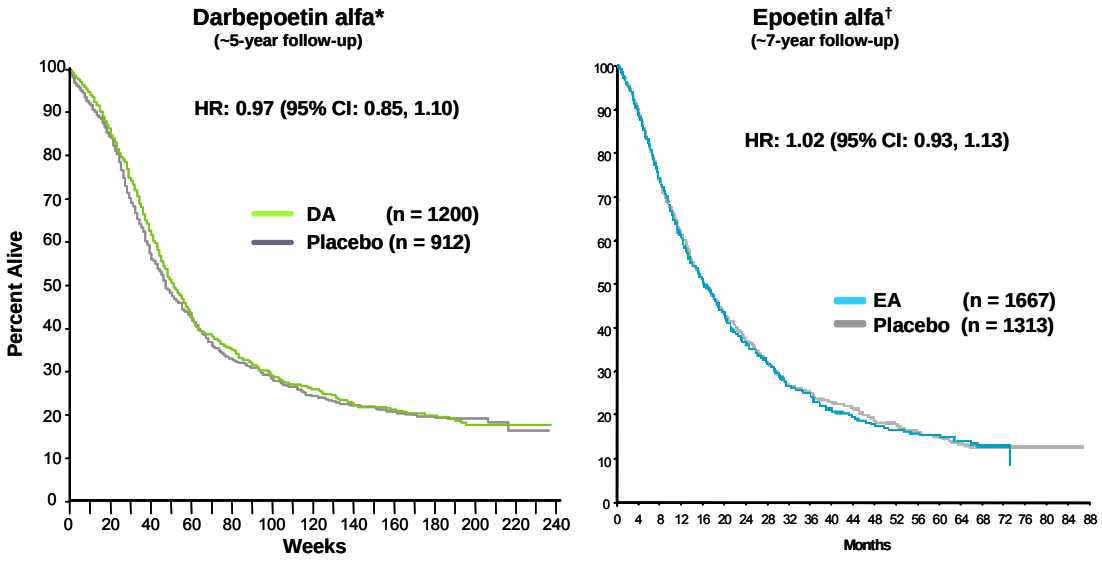
The FDA recognizes patient-level integrated analyses as key data in regulatory filings to support safety (21 CFR 314, ICH E9). Such evidence is considered the highest level on the hierarchy of evidence (Seidenfeld et al., 2006; Harris et al., 2001). For time-dependent endpoints such as time to death, these analyses provide the most complete and rigorous description of the data. For these reasons, analyses of randomized controlled trial data conducted at the level of individual patients should rank the highest in evaluation of the safety of ESAs, and any coverage policy that CMS adopts in CIA should be based primarily on this evidence. Study-level meta-analyses also play an important role in evaluating the evidence base. While not as rigorous as patient-level analyses, appropriately conducted and analyzed study-level analyses contribute greatly to the overall safety assessment, as has recently been described with regard to the safety assessment of rosiglitazone-associated cardiac events (Nissen and Wolski, 2007). However, critical to the validity of any meta-analyses are the criteria for study selection with the exclusion of any randomized trials carefully justified. Any analyses that are performed where controlled randomized trials are not included (*e.g.*, due to time period, design or other reasons) need to be carefully justified and performed as a sensitivity analyses to a more comprehensive analysis of all the evidence.

Table 3: Biostatistical Perspective on the Importance of Meta-analyses

Susan Ellenberg, Former FDA Biostatistician and Current Professor of Biostatistics and Associate Dean for Clinical Research at the University of Pennsylvania
"Some argue that you get the most reliable answers from meta-analysis, because you are putting together all of the information from randomized studies… but you never quite know how people selected the studies that went into meta-analyses." (Cancer Letter, June 1, 2007)

A robust analysis of studies using individual patient-level data, including all placebo-controlled studies, demonstrates that ESA treatment poses no increased risk on overall survival or progression-free survival in patients with CIA. Kaplan-Meier plots for darbepoetin alfa and epoetin alfa studies are shown in Charts 2 and 3, respectively.

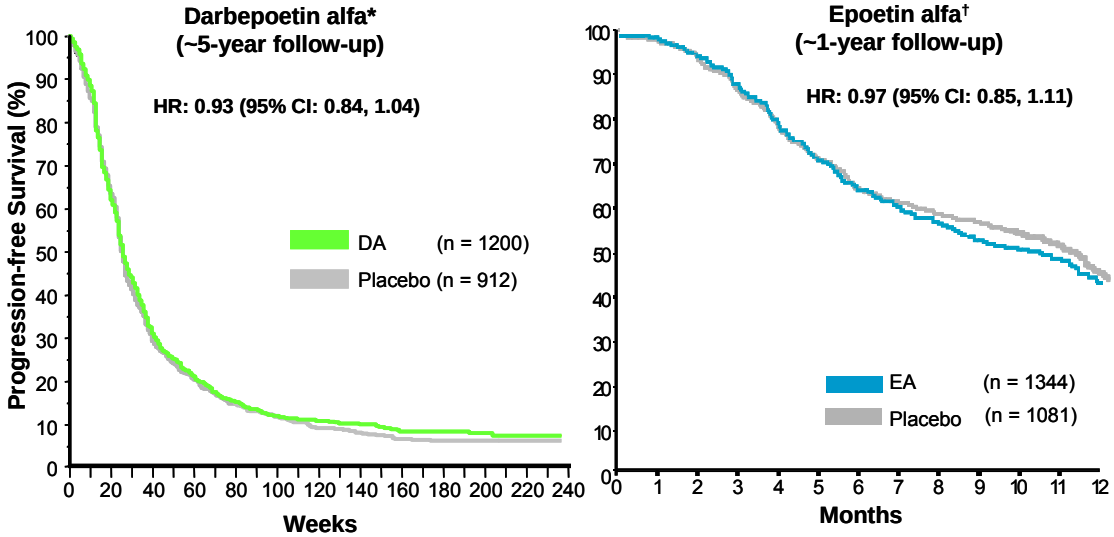
Chart 2: No Impact on Overall Survival in Placebo-controlled CIA Studies



*** 6 Randomized, placebo-controlled darbepoetin alfa CIA studies**
† 11 Randomized, placebo-controlled Epoetin alfa in CIA studies (including BEST)

Presented at ODAC 2007

Chart 3: No Impact on Investigator-determined Progression-free Survival In Placebo-controlled CIA Studies



The median time (95% CI) to progression-free survival including long term follow up in weeks was 26 (25, 28) for darboepoetin alfa and 26 (24, 27) for placebo.

*** 6 Randomized Placebo-controlled Darbepoetin alfa CIA Studies**

† 11 Randomized Placebo-controlled Epoetin alfa CIA Studies

In fact, no study in CIA has demonstrated an adverse effect of ESAs on tumor progression, as demonstrated in Table 4.

Table 4: No Study in CIA Patients Reported Adverse Progression Outcomes

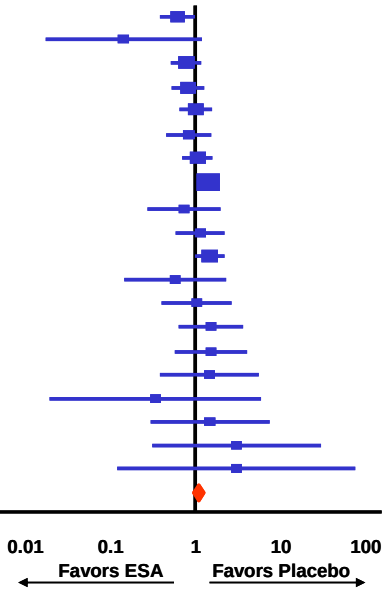
Study	Total (N)s	Tumor	Response	HR, RR, or %ESA & % Control
Aapro et al., 2006 (BRAVE)	463	Metastatic breast	PFS	HR: 1.07 (0.89-1.3)
Blohmer et al., 2004	257	Cervical	RFS	15% & 24%
Grote et al., 2005	224	SCLC	PD (after 3 cycles)	7% & 8%
Leyland-Jones et al., 2005 (BEST; EPO-INT-76)	939	Breast	PD (final)	42% & 46%
			PFS	RR: 1.0 (p=0.98)
Möbus et al., 2007	658	Breast	5-year DFS (p=0.89)	72% & 71%
Strauss et al., 2005	74	Cervical	PD	RR: 1.08 (0.62-1.87)
Wilkinson et al., 2006	173	Ovarian	PD	11% & 2%
Amgen Study 20010145	597	SCLC	PFS	HR: 1.02 (0.86 – 1.21)

PD = disease progression; PFS = progression-free survival; DFS = disease-free survival;
RFS = relapse-free survival

Finally, when an appropriate study-level meta-analysis is conducted of all CIA ESA studies (both published and unpublished), the findings of the patient-level meta-analysis are confirmed. As summarized on the following pages, this analysis is robust, as the same finding of a neutral impact on survival is shown when only placebo-controlled studies are included (Chart 4); when all studies with non-ESA controls are included (Chart 5); and when solid, lymphoproliferative, or mixed tumor populations are analyzed (Table 5).

Chart 4: Combined Study-level Analysis of Overall Survival in Placebo-Controlled CIA Studies

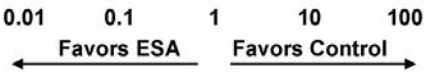
Study Name	OR	95% CI	
Vansteenkiste Amgen	0.62	0.38	1.01
Dammacco	0.14	0.02	1.21
AMG145 with follow up	0.79	0.52	1.21
Littlewood	0.83	0.53	1.30
Witzig 2005	1.02	0.65	1.59
Taylor 2005	0.84	0.45	1.59
Osterborg 2005	1.08	0.69	1.67
Leyland-Jones	1.42	1.07	1.90
Henry 1995	0.75	0.27	2.03
INT-47	1.15	0.59	2.26
Hedenus 2003 Amgen	1.48	0.97	2.27
Kotasek 2003	0.59	0.15	2.35
Case	1.05	0.40	2.74
Grote 2005	1.54	0.64	3.72
Rose	1.54	0.58	4.12
INT-3	1.48	0.39	5.65
P-174	0.34	0.02	5.97
INT-I	1.48	0.29	7.51
Razzouk 2006 update	3.06	0.31	29.83
O'Shaughnessy 2005	3.06	0.12	77.16
Random Effects Model	1.04	0.88	1.22



Meta Analysis Using log OR including INT-47, $I^2 = 16.2$.
Sensitivity analysis excluding O'Shaughnessy and Razzouk has a Random Effects Model OR of 1.03 (95% CI: 0.92, 1.20)
3 studies did not report any deaths.

Chart 5: Meta-analysis of Death for All CIA Studies

Study Name	OR	95% CI	
Vansteenkiste Amgen	0.62	0.38	1.01
Oberhoff	0.35	0.12	1.04
Dammacco	0.14	0.02	1.21
AMG145 with follow up	0.79	0.52	1.21
Littlewood	0.83	0.53	1.30
Blohmer revised	0.67	0.33	1.34
Aapro 2006	0.98	0.65	1.48
Witzig 2005	1.02	0.65	1.59
Taylor 2005	0.84	0.45	1.59
Chang 2005	0.88	0.49	1.60
Osterborg 2005	1.08	0.69	1.67
Moebus	1.15	0.77	1.71
EPO-GER-022	1.02	0.60	1.75
Savonije 2005	1.15	0.71	1.86
Leyland-Jones	1.42	1.07	1.90
Henry 1995	0.75	0.27	2.03
INT-47	1.15	0.59	2.26
Hedenus 2003 Amgen	1.48	0.97	2.27
Kotasek 2003	0.59	0.15	2.35
Osterborg 96 Roche	1.10	0.50	2.44
Coiffer	0.97	0.35	2.66
Case	1.05	0.40	2.74
Del Mastro 1997	0.31	0.03	3.17
Grote 2005	1.54	0.64	3.72
Rose	1.54	0.58	4.12
Ten Bokkel Roche	0.75	0.13	4.28
Thatcher combined	1.03	0.24	4.31
Cazzola Roche	0.49	0.04	5.56
INT-3	1.48	0.39	5.65
P-174	0.34	0.02	5.97
Bamias	1.83	0.51	6.55
INT-I	1.48	0.29	7.51
Dunphy_1999	0.31	0.01	8.28
Razzouk 2006 update	3.06	0.31	29.83
Wilkinson 2006	3.57	0.18	70.31
O'Shaughnessy 2005	3.06	0.12	77.16
Random Effects Model	1.03	0.93	1.15



Meta Analysis using log OR, $I^2 = 0$. Sensitivity analysis excluding Razzouk, O'Shaunassay, Wilkinson, and INT-47 has a Random Effects Model OR: 1.02 (95% CI 0.92, 1.14)
Three studies did not report any deaths (Hedenus, Cascinu, and Kurz) but were randomized CIA studies.

Table 5: Combined Study Level Analysis of Overall Survival in CIA Studies by Tumor Type

Tumor Type	Random Effects OR (95% CI)s	I^2
Solid (21 Studies)	1.00 (0.86, 1.16)	7.4%
Mixed (8 Studies)	0.96 (0.75, 1.24)	0%
Hematologic (7 Studies)	1.18 (0.87, 1.60)	8.7%

C. *The 14 studies identified by the FDA as having "adequate follow-up" reflect a heterogeneous mixture of studies on-label, off-label and experimental uses. However, meta-analyses of these trials support the conclusions from Amgen's robust, comprehensive meta-analyses and provide no evidence of adverse survival outcomes in patients receiving ESAs in CIA.*

There have been six individual studies in which significant safety signals with ESAs in cancer patients have been observed (listed in Table 6) and results from these studies led to the ODAC meetings in 2004 and 2007. Amgen takes the safety signals generated by individual studies very seriously. The recent safety concerns have arisen primarily in the off-label and experimental population of patients with active cancer not receiving chemotherapy or radiotherapy and many have limitations regarding their conduct, interpretation or generalizability. While there are limitations in the individual trials and no consistent evidence of a detrimental effect in independent studies despite similar trials in the same population (*e.g.*, Leyland-Jones et al., 2005 and Aapro et al., 2006 in newly diagnosed metastatic breast cancer patients), these concerns require a scientifically rigorous and objective review of all the relevant evidence across current licensed and unlicensed indications. It is critical that the results of these studies are appropriately integrated into the total body of evidence that exists for ESA use in oncology before conclusions can be drawn.

Table 6: Review of Studies that Have Raised Safety Concerns for ESA Use

Study	Population	Primary Objective	Hemoglobin Target (g/dL)	Overall Survival	Comments/Limitations
Trials of ESAs in combination with chemotherapy Total # of controlled trials in setting: 39 Total number of controlled trials with possible negative signals regarding overall survival: 2					
BEST (Leyland Jones et al., 2005)	Metastatic breast	12-month overall survival	12-14	HR=1.37 (95% CI: 1.07, 1.74) p=0.012	• Conducted above current recommended use of ESAs • No impact on PFS observed (HR=1.00 [95% CI: 0.85, 1.18] p=0.98)
Amgen Study 20000161 (Hedenus et al., 2003)	Lympho-proliferative disease	Hemoglobin response	≤ 13-14 (women) ≤ 13-15 (men)	HR=1.36 (95% CI: 1.02, 1.82)	• No robust evidence of significant survival difference (alternate methods [*e.g.*, odds ratio or relative risk], alternate study populations [ITT vs as treated] and unadjusted analyses are all neutral) • Heterogeneous population enrolled with significant imbalances favoring placebo within key stratum • No impact on PFS observed (RR=1.01 [95% CI: 0.79, 1.29])
Trials of ESAs without either radiotherapy or chemotherapy Total # of controlled trials in setting: 9 Total number of controlled trials with possible negative signals regarding overall survival: 2					
Amgen Study 20010103 (Glaspy et al., 2007)	Mixed tumors	Reduction of occurrences of transfusion	12-13	HR=1.22 (95% CI: 1.03, 1.45) p=0.022	• Heterogeneous population enrolled with significant imbalances within strata • No robust evidence of significant survival difference (analyses adjusted for imbalances in known prognostic factors are neutral)
Wright et al., 2007	NSCLC	QOL	12-14	HR=1.84 (95% CI: 1.01, 3.35) p=0.04	• Terminated early because of safety issues (70 of 300 patients enrolled) • Data on 62 patients presented at ODAC 2004
Trials of ESAs in combination with radiotherapy Total # of controlled trials in setting: 7 Total number of controlled trials with possible negative signals regarding overall survival: 2					
ENHANCE (Henke et al., 2003)	Head and neck cancer	Effect of high hemoglobin on locoregional progression-free survival	> 14 (women) > 15 (men)	RR=1.39 (95% CI: 1.05, 1.84), p=0.02	• Significant number of protocol violations • Inconsistent findings across study populations and strata (per protocol analysis indicated no difference in survival)
DAHANCA-10 (provisional interim data)	Head and neck cancer	Loco-regional control	14-15.5	No significant difference in overall survival (p=0.08)	• Only very limited summary data from interim analysis available on website • ~ 10% difference in 3 year loco-regional control in favor of control group (p=0.01)

Two studies (one study in breast cancer patients receiving chemotherapy [BEST, EPO-INT-76; Leyland-Jones et al., 2005] and one in head and neck cancer patients treated with radiotherapy [ENHANCE, MF4449; Henke et al., 2003]) first raised safety concerns that resulted in the 2004 ODAC meeting on ESAs in cancer. Two other studies in the six

studies listed above were also discussed at that meeting (Amgen Study 20000161 and Wright et al., 2007). Amgen Study 20000161 was an anemia treatment study in patients with a range of lymphoproliferative diseases. The interim results from the long-term follow-up was reported at the 2004 ODAC with a hazard ratio (HR) for overall survival (OS) of 1.33 (95 percent CI: 0.95, 1.86) (Amgen Inc., ODAC Briefing Book 2004). The final long-term follow-up data, adjusting for stratification factors, now report an HR for OS of 1.36 (95 percent CI: 1.02, 1.82) (Amgen Inc., ODAC Briefing Book 2007). Analyses unadjusted for baseline factors or utilizing the intention to treat (ITT) dataset are non-significant for survival, but with similar HRs to the adjusted analysis. Important baseline imbalances in factors known to be prognostic for disease outcomes were observed within individual strata. Progression-free survival (PFS) data from this study have remained neutral over the same time period (final long-term PFS HR=1.01 [95 percent CI: 0.79, 1.29]).

Two studies that have raised additional safety concerns with ESAs have become available since the 2004 ODAC. One study in head and neck cancer patients receiving radiotherapy is still ongoing and no data have been published or presented (DAHANCA-10). The other study, Amgen Study 20010103, was a placebo-controlled study in patients with active cancer not receiving or planned to receive chemo- or radiotherapy (Glaspy et al., 2007). The study enrolled a heterogeneous patient population and had a number of baseline imbalances in known prognostic factors for survival; for these reasons, it is difficult to draw definitive conclusions from the study. The results of this study have been fully disclosed to regulatory agencies, investigators and the broader clinical and scientific community.

Importantly, other data pertaining to the question of the impact of ESAs on survival have also become available in this timeframe including the BRAVE study (Aapro et al., 2006) (in 463 metastatic breast cancer patients receiving chemotherapy) and the Amgen Study 20010145 (available at ClinicalStudyResults.org) (in 597 patients with small cell lung cancer [SCLC] receiving chemotherapy). Both of these studies suggest a neutral impact of ESAs on survival in CIA. All of these data (and updated survival data for several other studies) have been included in the analyses Amgen has presented to FDA and CMS (Amgen Inc., ODAC Briefing Book, 2007).

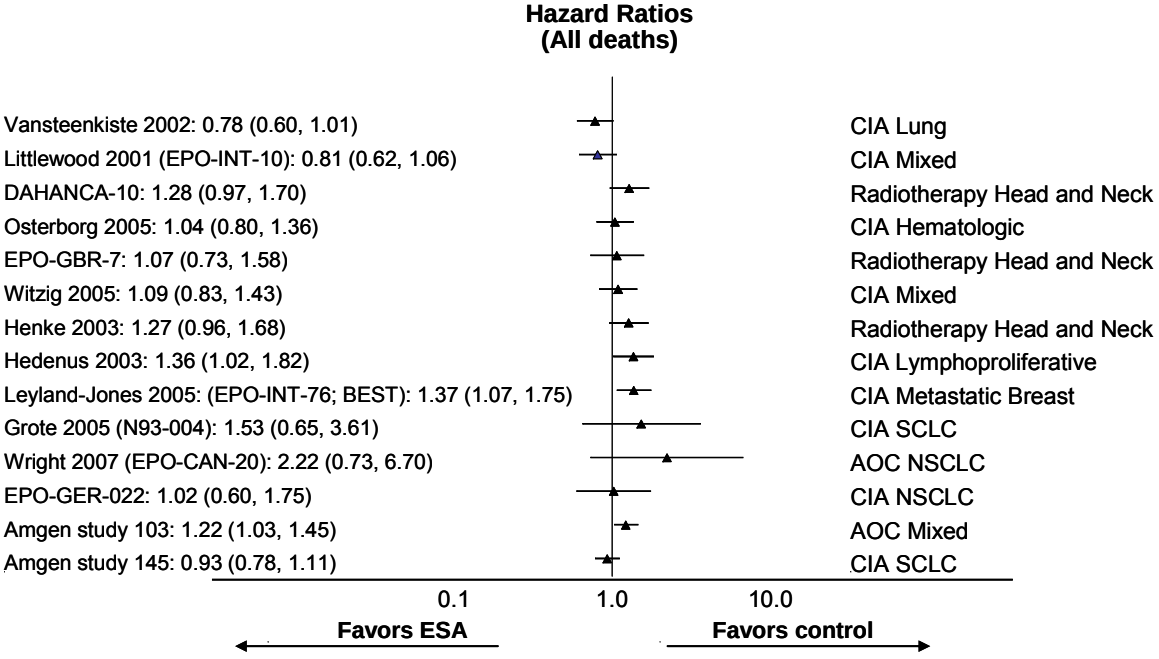
At the 2007 ODAC, the FDA presented an overview of data from individual studies they deemed of adequate design to inform the question of safety and overall survival. The FDA presentation summarized 14 trials, 9 trials evaluating the combination of ESAs with chemotherapy, 3 trials of ESAs in combination with radiotherapy and 2 trials evaluating ESAs in patients not receiving either chemotherapy or radiotherapy. The extrapolation of this dataset to CIA and the summary discussed by the FDA at ODAC is based on several assumptions that need to be thoughtfully considered as it relates to the need for CMS to limit coverage in CIA.

The criteria for the FDA summary were phase 3 studies with adequate follow-up (undefined further). However, the justification for these criteria is unclear and the application of their criteria inconsistent, with important limitations in the justification and presentation of these study data:

- Studies of ESA use in different patient populations (*e.g.*, CIA, AOC, radiotherapy) and indications for treatment (*e.g.*, anemia treatment, anemia prevention, and targeting high hemoglobin levels to hyper-oxygenate tumors) were mixed together without appropriate assessment of heterogeneity and exploration of sources of heterogeneity.
- The FDA included all studies they considered to have adequate long-term follow-up, yet 3 important studies were not included. These 3 studies (Möbus et al., 2007; Aapro et al., 2006 [BRAVE], and Chang et al., 2005 [EPO-CAN-17]) all demonstrated neutral survival outcomes in over 1000 breast cancer patients followed for two to five years.
- The FDA analysis included only studies with long-term follow-up (Chart 6). It is unclear, however, what criteria the FDA adopted in identifying the 14 studies included in their analysis presented at ODAC, except that they are "phase 3 studies" with "adequate follow-up". However, it is apparent that adverse survival outcomes were observed in the BEST (Leyland-Jones et al., 2005) and Amgen Study 20010103 (Glaspy et al., 2007) studies within a 4 month period. While longer-term follow-up is desirable, controlled studies with shorter duration of follow-up should at least be identified and included in the analysis to understand if such studies confirm or refute the finding of early mortality in cancer patients treated with ESAs. Moreover, in assessing mortality it is critical to count every death equally, whether it occurs early in a study or during follow-up after the study-specific treatment period has completed, since patient survival is a completely objective assessment from the first day of study throughout follow-up to the last patient contact. Omitting studies from the analysis that did not meet an arbitrary period of follow-up risks unnecessarily limits the available evidence base with which to inform the risk assessment.

In order to provide an objective, comprehensive assessment of ESA safety in cancer patients, Amgen has engaged in analysis of individual study data, meta-analysis of patient-level data from multiple studies, and meta-analysis of study level data in its assessment of safety of ESAs in oncology patients. Additionally, Amgen has performed an additional meta-analysis using the studies selected as "appropriate" by FDA to evaluate the consistency of our findings.

Chart 6: FDA Summary Presented at ODAC was Not Comprehensive: Survival Summary Is Limited to Studies with Longer Follow-up and Combines Populations Without Sub-group Analysis



Amgen's Analysis: Overall HR: Random Effect 1.10 (0.97, 1.25)

FDA did not perform a formal meta-analysis of these 14 trials. When a meta-analysis is performed on these trials, evidence of significant heterogeneity is observed overall with an apparent difference in conclusions drawn between studies of ESAs in patients receiving chemotherapy and those studies evaluating ESAs outside of the chemotherapy setting. In the meta-analysis of the studies receiving ESAs and chemotherapy, there was no evidence of any detrimental outcome on survival observed (HR, 1.04, 95 percent CI 0.87 – 1.24; I^2 = 56.5 percent). This finding is consistent with the meta-analysis of all chemotherapy trials (n=39) regardless of length of follow-up (Table 7).

Some evidence of a detrimental outcome is observed in the group of studies evaluating ESAs outside of the chemotherapy setting, however, these data are difficult to interpret due to the small number of trials (n=5) and the weighting of the ENHANCE study (approximately 20 percent; Henke et al., 2003) and Amgen Study 20010103 (approximately 50 percent) in the meta-analytic estimate for this study group. Again, this finding is consistent with the use of meta-analysis of all non-chemotherapy trials (n=17) regardless of length of follow-up.

Table 7: Meta-analysis of 14 Studies Deemed as Having "Adequate Follow-up" by the FDA

	Odds Ratio (95% CI)	Hazard ratio (95% CI)
All Chemotherapy studies (n = 9)	1.04 (0.85, 1.28) Heterogeneity, p=0.06, I^2=46%	1.04 (0.87, 1.24) Heterogeneity, p=0.02, I^2=56.5%
Non-CIA studies with "adequate follow-up" (n = 5)	Cannot be calculated; no information on DAHANCA-10*	1.23 (1.09, 1.39) Heterogeneity, p=0.79, I^2=0%
All studies with "adequate follow-up" (n=14)	Cannot be calculated; no information on DAHANCA-10*	1.10 (0.97, 1.25) Heterogeneity, p=0.02, I^2=50%

* For the DAHANCA-10 study, odds ratio calculation requires knowledge of the number of deaths in each treatment group, which was not reported on the DAHANCA website. For the calculation of hazard ratios for DAHANCA-10, an approximation (Parmar et al., 1998) was based on the reported total number of deaths and the p-value on treatment difference. Judging from the explanation given at ODAC by the FDA regarding its derivation of the hazard ratio for DAHANCA-10, it appeared that FDA adopted a similar approach for the approximation. Random effects model estimates presented.

As described, three important studies that appear to meet the FDA inclusion criteria for analysis, all in breast cancer patients receiving chemotherapy, were not included by FDA in their summary of phase 3 trials with "adequate long-term follow-up." All of these trials demonstrate neutral survival outcomes for ESAs, supporting the conclusions drawn from the meta-analyses of CIA studies (Table 8).

Table 8: Three Additional Studies Deemed to Have "Adequate Follow-up" per FDA Criteria

Overall Survival	Tumor Type	Treatment (n)	HR or OR for OS	95% CI	Follow-up
Aapro et al., 2006 (BRAVE)	Metastatic breast cancer	Chemotherapy (non-anemic patients) (n = 463)	1.07 HR	0.87–1.33	Study duration: 24 weeks + 18 month follow-up
Möbus et al., 2007	High risk adjuvant breast cancer	Chemotherapy (n=658)	1.15 OR	0.77-1.71	Median follow-up: 62 months
Chang et al., 2005 (EPO-CAN-17)	Adjuvant (80%) and metastatic (20%) breast cancer	Chemotherapy (n=354)	0.94 HR	0.55 - 1.60	Survival data collection: 2 years

Therefore, if CMS chooses to extrapolate the recent safety findings from individual studies to CIA, performing a comprehensive analysis would conclude that the risk is neutral. When considered in the context of the available evidence base relevant to an assessment of risk, these individual study conclusions should not provide greater weight

to CMS than the rigorous combined analysis of the entire relevant evidence base – particularly within CIA, the licensed indication.

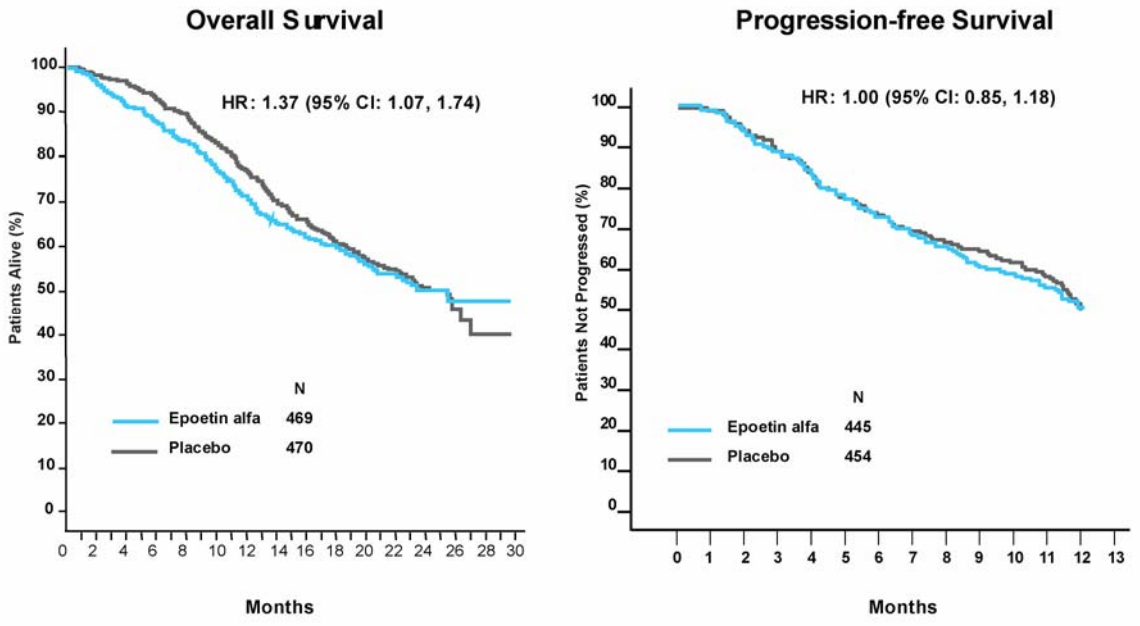
D. *Combined meta-analyses of all relevant data have identified subgroups of patients where the totality of data does and does not indicate a potential survival risk. Within CIA, some individual studies have raised safety signals, but others have not and the weight of evidence across all CIA studies does not indicate that mortality is affected overall, in solid tumors (including breast cancer and lung cancer), or in lymphoproliferative diseases. The study-level meta-analyses point to an ESA-associated mortality risk in patients with AOC who have active cancer not receiving or planning to receive chemotherapy or radiation therapy and in patients with head and neck cancer undergoing radiotherapy treated to a hemoglobin level ≥ 12.0 g/dL.*

Amgen has performed study-level meta-analyses of randomized placebo- or non-ESA-controlled clinical trials. In the analysis of all 55 placebo- or non-ESA controlled studies (12,678 patients), there was an overall neutral survival risk; (OR 1.08; 95 percent CI 0.98 – 1.18). There was also an overall neutral effect on survival among the 39 studies in which chemotherapy was administered (OR 1.03, 95 percent CI 0.93 – 1.15).

Breast Cancer

Within the CIA studies, data from the BEST study has raised concerns about tumor progression and survival (Leyland-Jones et al., 2005). The overall survival and progression-free survival results from the final report of this study are shown in Chart 7.

Chart 7: BEST Study Overall Survival and Time to Disease Progression



CMS is appropriately concerned about the adverse survival signal in this trial, and Amgen shares this concern. The approach to ESA therapy in BEST was to institute early and aggressive intervention with ESAs. Of 939 patients enrolled, 64 percent had

hemoglobin ≥ 12.0 g/dL and 80 percent had hemoglobin ≥ 11.0 g/dL when epoetin alfa was initiated (Ortho Biotech ODAC Briefing Book 2004). While the interim results indicated an increase risk of death and disease progression, the final study report for BEST showed that there was no statistically significant difference in either tumor response or disease progression whereas the negative signal with respect to death remained.

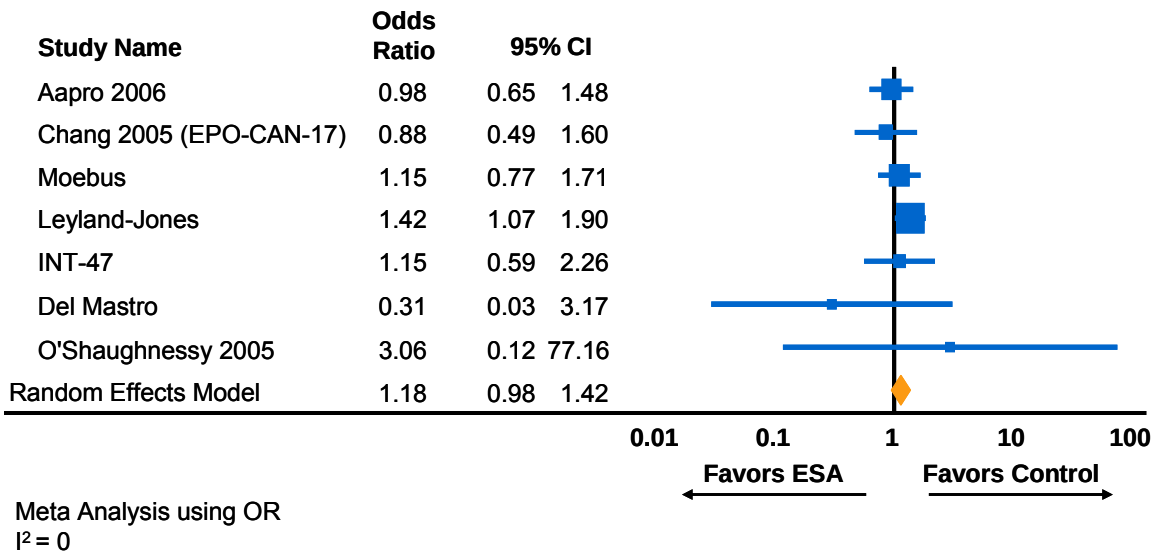
It is important to recognize that BEST is the only breast cancer study of 7 randomized studies of ESAs in breast cancer that has shown a negative survival signal. It is therefore important to compare the results of BEST to other trials in breast cancer patients that have similar study design characteristics. Three other non-ESA-controlled breast cancer studies (representing 1,475 patients) also collected long-term follow-up information (Aapro et al., 2006, Möbus et al., 2007, Chang et al., 2005). Three additional non-ESA-controlled studies (including 376 patients) did not collect follow-up information but did report deaths. These six studies, as well as the BEST study, are summarized in Table 9. In all studies other than BEST, the ESA groups had neutral survival risks relative to the control group. This clinical finding is consistent with the lack of preclinical evidence that pharmacologic concentrations of EPO act as a growth factor for breast cancer cells. Aapro, et al., 2006 is closed to enrollment and has presented its 18-month follow-up data. Möbus, et al., 2007 is an on-going adjuvant chemotherapy study and has presented data through a median of 62 months of follow-up. In addition, there are three other on-going studies (PREPARE, ARA-Plus, and EPO-ANE-3010) that have not released data related to survival to date. Data from these five on-going studies will provide additional important data to assess risk in this patient population when they are completed.

Table 9: Summary of Studies of Breast Cancer Studies Evaluating Tumor Progression

	Tumor Type	Treatment (n)	HR or OR for OS	95% CI	Follow-up
Studies with negative signal					
Leyland Jones et al., 2005) (INT-76; BEST)	Metastatic	Chemotherapy (non-anemic patients) (n=939)	HR: 1.37 (12 month survival)	1.07 – 1.74	Median follow-up: 52 weeks
Studies with neutral signal					
Aapro et al., 2006 (BRAVE)	Metastatic	Chemotherapy (non-anemic patients) (n=463)	HR: 1.07	0.87 – 1.33	Study duration 24 weeks + 18 month follow-up
Möbus et al., 2007	High-risk adjuvant	Chemotherapy (n=658)	OR: 1.15	0.77 – 1.71	Median follow-up: 62 months
Chang, et al., 2005 (EPO-CAN-17)	Adjuvant (80%) and metastatic (20%)	Chemotherapy (n=354)	HR: 0.94	0.55 – 1.60	Survival data collection: 2 years
Pronzato, et al., 2002 (EPO-INT-47)	All stages	Chemotherapy (n=220)	OR: 1.15	0.59 – 2.26	N/A
Del Mastro, et al., 1997	Stage II	Accelerated adjuvant chemotherapy (n=62)	OR: 0.31	0.03 – 3.17	N/A
O'Shaughnessy, et al., 2005	Stages I – III	Adjuvant or neoadjuvant chemotherapy (n=94)	OR: 3.06	0.12 – 77.16	N/A

When the study-level data from these seven breast cancer studies are meta-analyzed (see Chart 8), there was an overall neutral risk despite the large contribution (weighted at about 40 percent of the overall result) of the BEST study results (OR 1.18 [95 percent CI: 0.98, 1.42; I^2 = 0 percent]).

Chart 8: Survival is Risk-neutral in Breast Cancer Studies

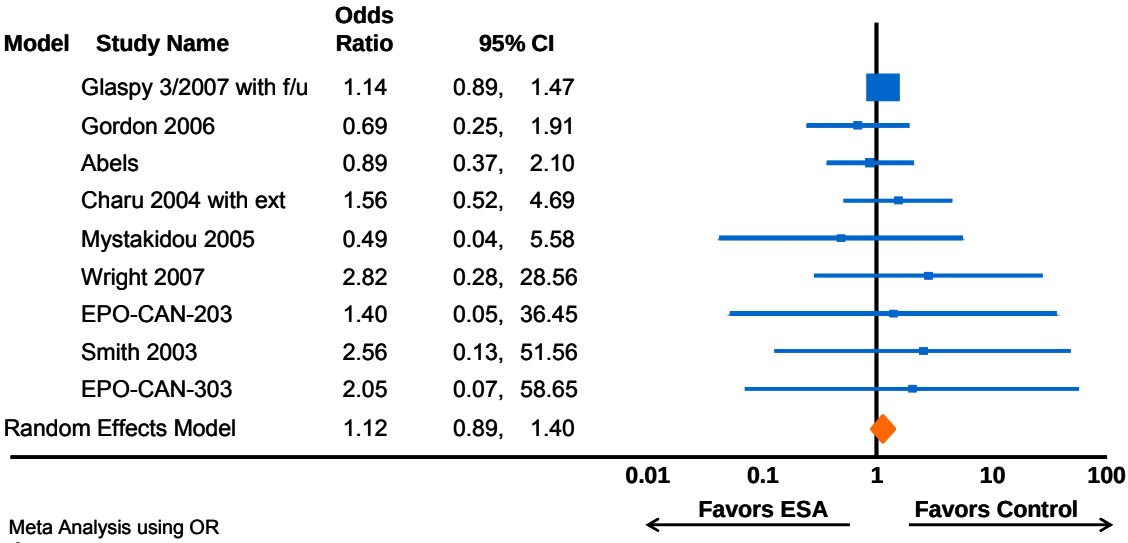


Note: Cochrane report + Amgen data on-file; INT-47 refers to Pronzanto et al., 2002

Anemia of Cancer

In the area of AOC, the studies of concern for adverse safety signals for ESAs are the Amgen 20010103 study (Glaspy et al., 2007) and the EPO-CAN-20 study (Wright et al., 2005). Both of these studies indicate increased risk of mortality in ESA-treated patients with active cancer who have exhausted all options and are not receiving or planning to receive chemotherapy or radiation therapy. It is worthwhile to note that while the HR for OS in the Amgen 20010103 study of 1.22 (95 percent CI of 1.03 to 1.45) favored the placebo group, the HR was reduced when post-hoc analyses were adjusted for baseline imbalances in known prognostic factors (HR: 1.15, with a 95 percent CI of 0.96 to 1.37). While the meta-analysis across all anemia of cancer studies indicates that the mortality risk may be neutral (HR:1.12; 95 percent CI: 0.89, 1.40), the setting represents a very heterogeneous patient group, and the increased risk in patients with active cancer not receiving nor planning to receive chemotherapy should be considered in coverage policy determination (Chart 9).

Chart 9: Combined Analysis of Overall Survival in AOC Studies is Risk-neutral, However, There is a Potential Increased Risk in Patients with Active Cancer Neither Receiving nor Planning to Receive Further Chemotherapy*



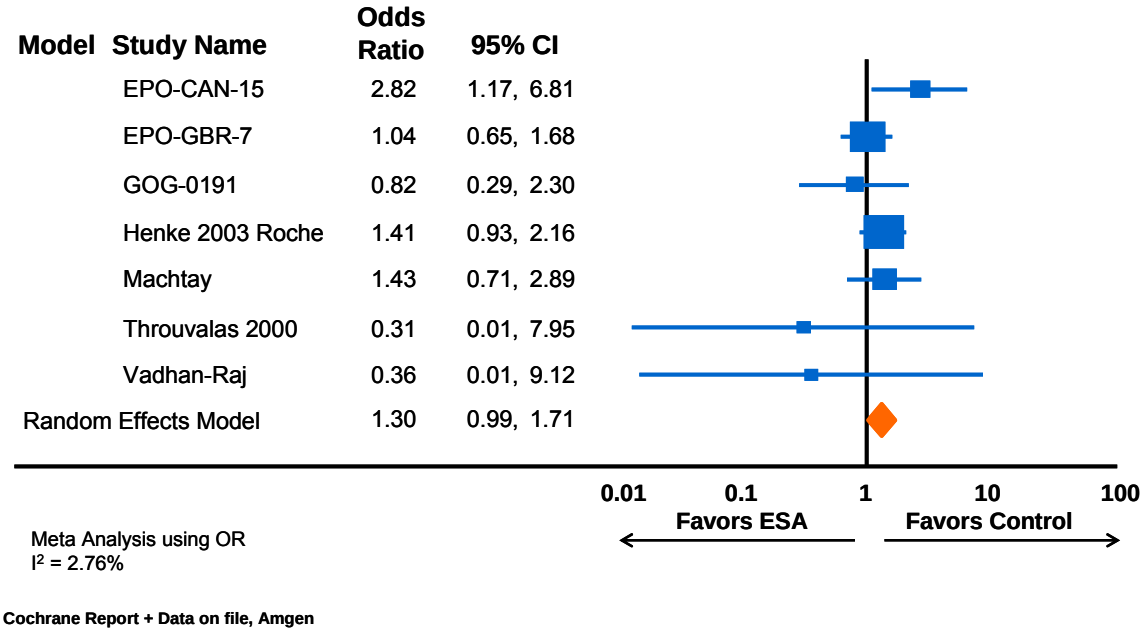
Meta Analysis using OR
$I^2 = 0\%$
* Glapsy et al, AACR 2007 presentation of an earlier interim analysis

Cochrane Report + Data on file, Amgen

Radiotherapy Studies Treating to a Hemoglobin ≥ 12.0 g/dL

In radiotherapy studies, particularly for head and neck cancer studies where higher hemoglobin levels (*e.g.*, ≥ 12.0 g/dL) were targeted in an attempt to potentiate radiation effects on tumors through hyper-oxygenation, there may be an increased risk of mortality, as shown in Chart 10 (OR 1.30 ; 95 percent CI 0.99 –1.71).

Chart 10: Radiotherapy Studies Treating to Hemoglobin Levels Greater than 12.0 g/dL Show Increased Risk



Cochrane Report + Data on file, Amgen

E. *While ongoing studies will continue to inform CMS and other stakeholders about the safety of ESAs, the currently available body of evidence strongly supports coverage in CIA.*

A study-level meta-analysis of 39 CIA placebo- or non-ESA-controlled ESA studies (including 9652 patients) demonstrated a neutral impact on survival (1.03 95 percent CI 0.93 –1.15). The available data strongly support coverage in CIA.

The ongoing studies include the use of darbepoetin alfa in breast cancer patients undergoing neoadjuvant chemotherapy (PREPARE; Möbus et al., 2007; DE-2001-0033) or the use of darbepoetin alfa in breast cancer patients undergoing adjuvant chemotherapy (ARA-Plus; Warm et al., 2007; DE-2002-0015), in patients with non-Hodgkin's lymphoma treated with chemotherapy (Delarue et al., 2006), the use of epoetin alfa in metastatic breast cancer treated with chemotherapy (EPO-ANE-3010; Ortho Biotech ODAC Briefing Book 2004), and the previously described Möbus and Aapro studies (Möbus et al., 2007; Aapro et al., 2006). Together, these studies will generate safety data in more than 4800 patients.

In those settings outside CIA where data exist to demonstrate risk of adverse outcomes, coverage can appropriately be restricted based on the data. These data from experimental populations should not be broadly extrapolated to CIA patients in an evidence-based and scientifically rigorous coverage decision.

F. *Amgen is not alone in questioning the supposition that CMS should extrapolate the safety signals from individual studies to all patients with the proposed coverage restrictions.*

Many aspects of the PDM are not supported by the clinical evidence and are in conflict with well-established clinical practice guidelines; therefore, the CMS proposal would be inconsistent with standard of care if finalized as proposed.

CMS determines whether an item or service is reasonable and necessary for the diagnosis or treatment of an illness or injury by relying on clinical evidence and evidence-based medicine (EBM).[9] Further, the agency has drafted guidelines to establish a framework for the evaluation process. In this guidance, CMS states that National Coverage Assessments (NCA) "decisions call for the best scientific and clinical evidence available concerning the effectiveness of various medical diagnostic procedures and therapies, and the highest attainable level of expertise to evaluate such evidence" (Table 10).[10]

Table 10: Definition of EBM Cited Publicly by CMS

EBM: Definition
"Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research."[11]

Amgen supports the use of this approach by CMS as it provides an appropriate scientific framework for the review of data to inform decision-making. However, in this PDM, the agency appears to have deviated from its own standards, as the PDM recommends an approach that is inconsistent with how the products were studied in well-designed randomized controlled trials, and relies upon a pathophysiologic rationale to support its proposed coverage restrictions in CIA.

As noted earlier, CMS has selectively relied upon evidence in the PDM but has highlighted certain evidence and cited details of particular medical specialty guidelines that support its position. However, in some instances, CMS does not mention these same societies' overall conclusions and recommendations for ESAs. The selective inclusion of data is inappropriate for a scientifically rigorous, evidence-based analysis that serves as a basis for a product coverage decision, and Amgen encourages CMS to conduct a more thorough review of the complete evidence base for these products before finalizing its policy.

The conclusions that CMS reaches in its review of the evidence outlined in the PDM diverge from the opinions of experienced clinical oncologists. For this reason, many experts in the field of oncology have already shared concerns with CMS. Examples of their comments are provided in Table 11.

Table 11: Reactions from Clinical Oncology Experts to the Proposed NCD

American Society of Clinical Oncology (ASCO) *The ESA coverage proposals "have no scientific basis and are in direct conflict with both published scientific evidence and expert opinion…"* (ASCO Statement to CMS) *American Society of Hematology (ASH)* *"The Society is deeply concerned that CMS's proposed coverage decision inappropriately restricts use of ESAs because a number of the proposals are not supported by scientific data, rely on poor quality data, or are in conflict with expert scientific analysis…"* (ASH Statement to CMS) *Dr. S. Gail Eckhardt, Chair, FDA's ODAC* *"I was shocked to see how the CMS restrictions go way beyond the scientific evidence that indicates what's actually proven beneficial or non-beneficial…"* (Eckhardt, Cancer Letter, May 18, 2007)

ASCO and ASH are leading science-based organizations focused on cancer care in the U.S., and their guidance should be carefully considered in determining the scientific and clinical evidence that CMS should weigh most critically before issuing its final decision.

Response to Supposition 2: **In the PDM, CMS appears to rely largely on a hypothesis about the putative role of EPO-R in tumor growth; however, the principal evidence cited by CMS on EPO-R does not stand up to even casual scrutiny and, thus, cannot serve as a reliable basis for an evidence-based coverage policy.**

EPO stimulates the formation of red blood cells by binding to and activating EPO-R, which is found on the surface of red blood cell progenitors. ESAs share this same mechanism of action to stimulate red blood cell formation. Some of the agency's suppositions about EPO-R that were included in the PDM appear to be largely based on two unsubstantiated hypotheses: (1) that ESAs promote tumor growth, and (2) that they do so through interaction with an EPO receptor present on tumor cells.

These hypotheses have been extensively studied by investigators around the world since concerns about ESAs and tumor promotion were discussed at the May 2004 meeting of the ODAC to review ESAs (Amgen Inc., ODAC Briefing Book 2004). Based on a comprehensive analysis of the evidence in numerous preclinical and clinical studies (Sinclair et al., 2007; Osterborg et al., 2007) Amgen believes there is no definitive evidence of EPO-R involvement in tumor progression, and no reliable evidence that the EPO-R is present on cancer cells.

The weight of the evidence shows that the EPO-R is not encoded by an oncogene (*i.e.,* a gene that causes transformation of normal cells into cancerous cells). There are multiple lines of evidence supporting this conclusion. For example, the EPO-R, even when expressed as an activated mutant protein, does not stimulate cancer cell growth.

An additional line of evidence comes from an analysis of levels of EPO-R mRNA, the direct precursor of the EPO-R protein. When the levels of EPO-R mRNA are directly compared in normal versus cancer cells, there is no difference between them. This evidence clearly refutes the notion that the EPO-R provides an important advantage to cancer cells.

Several published studies have purported to show that the EPO-R plays a role in tumor cell signaling, proliferation, migration or survival. However, these studies lacked critical controls, and often employed concentrations of ESA up to 1,000 times greater than the maximum concentrations achieved in patients. A very important element of the evidence that has seemed to support this unsubstantiated hypothesis is the purported detection of EPO-R on cancer cells, which relies upon antibodies against the EPO-R. However, most antibodies employed in these studies are non-specific, and bind to multiple proteins of different sizes rather than the EPO-R. In fact, the most widely used polyclonal antibody marketed to detect EPO-R actually detects heat shock protein 70 (HSP70) instead. Unlike EPO-R, HSP70 has long been known to be an important factor in predicting prognosis in cancer patients. Thus, the reports suggesting that EPO-R is expressed on tumor cells have actually been examining HSP70 (in addition to other proteins). There is no compelling evidence that the EPO-R itself is expressed on the surfaces of tumor cells, as detailed in Appendix A.

In summary, Amgen believes that there is no definitive evidence demonstrating any of the following:

- a link between EPO-R and involvement in tumor progression,
- the presence of EPO-R on cancer cells, and
- cancer cells responding to EPO signals.

Eminent scientific experts in the field have drawn the same conclusions (Brown et al., 2007; Osterborg et al., 2007; Constantinescu, 2007). Finally, we note in Table 12 the agency's own position on the importance of relying on high quality evidence for Medicare coverage decisions.

Table 12: CMS Perspective on the Importance of Basing Coverage on EBM Methods

Why CMS Bases Coverage on EBM
CMS notes that a rigorous EBM-driven framework helps guide researchers and payers because "lower quality studies are more likely to be wrong" and "deductions from basic biology and pathophysiology may be unreliable." (CMS, 2005)

Response to Supposition 3: **The agency's proposed policy of initiating therapy at a hemoglobin level of 9.0 g/dL in each month is not supported by scientific evidence and does not recognize current standards of clinical care.**

The proposed policy appears to blend two critical clinical concepts necessary for the effective care of anemic cancer patients: (1) when to start therapy and (2) when to withhold therapy based on the hemoglobin level (*i.e.*, the threshold hemoglobin level). Clinical care requires that clinicians initiate therapy to prevent transfusion, a decision made based on signs and symptoms of anemia and the myelosuppressive effects of chemotherapy administration. Once therapy is initiated, a target hemoglobin level is chosen, as clinicians cannot precisely control ESA response. Dose adjustment rules are clearly articulated in the revised FDA label to guide clinicians about how to titrate the ESA to achieve the desired hemoglobin levels, which should not exceed a threshold level of 12.0 g/dL.

The proposed policy of initiating ESA therapy at hemoglobin < 9.0 g/dL and then waiting for the hemoglobin level to drop below 9.0 g/dL in each month essentially sets the hemoglobin target range at 9.0 g/dL. There is simply no evidence to support this practice, and more importantly, there is no clinical experience of this practice in the clinical trials that have established the safety and efficacy of the ESA class.

Scientific evidence suggests that most transfusions are prevented when ESAs are initiated at a hemoglobin level between 10.0 and 11.0 g/dL.

In the United States, the lower limits of normal hemoglobin values are 12.5 g/dL for adult females and 13.5 g/dL for adult males. When patients become anemic due to the effects of myelosuppressive chemotherapy, the hemoglobin level may fall precipitously. ESAs can take from 4 to 6 weeks to have their intended effect (Aranesp® prescribing information, 2007); thus, waiting until the hemoglobin falls to below 10.0 g/dL will expose cancer patients to more severe and prolonged anemia symptoms, as the hemoglobin will likely fall further before the ESA takes effect. Therefore, defining the hemoglobin value to initiate therapy is critical.

- First, almost all randomized clinical trials have initiated ESA therapy when the hemoglobin level is less than 11.0 g/dL. As a result, evidence-based clinical practice guidelines have recommended the initiation of ESA therapy in cancer patients when the hemoglobin level is less than 11.0 g/dL.
- In placebo-controlled trials, when ESA-treated patients initiate therapy at hemoglobin < 9.0 g/dL, 68 percent receive at least one transfusion; however, if the hemoglobin is between 10.0 and 11.0 g/dL, only 26 percent receive at least one transfusion. Thus, the agency's proposed policy would significantly increase the percentage of patients who receive at least one transfusion. Importantly, the treatment effect regarding the reduction in red blood cell transfusions between ESA-treated patients and patients who received placebo is similar (*i.e.*, comparable hazard ratios) when hemoglobin is between 9.0 and 10.0 g/dL or when hemoglobin is between 10.0 and 11.0 g/dL (Table 13).

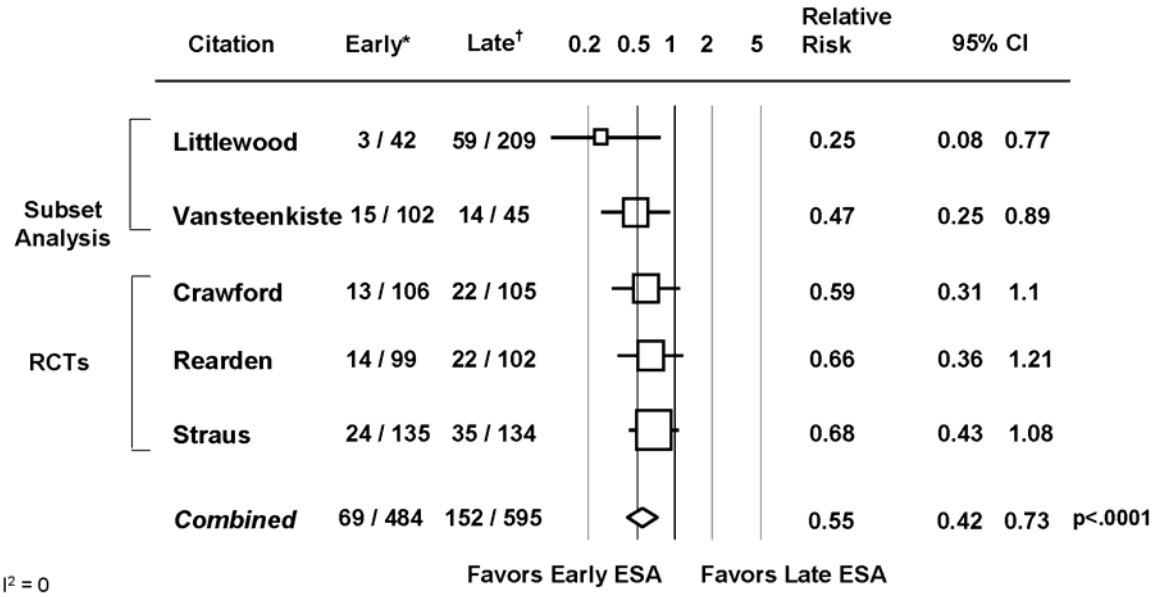
- Comparison of strategies for early intervention (generally initiation of therapy at approximately 12.0 g/dL) and later intervention (generally, initiation of therapy when hemoglobin level drops below 10.0 g/dL) have been evaluated in a number of RCTs. A meta-analysis of these studies has demonstrated an approximate 50 percent reduction in the risk of transfusion favoring the early intervention approach (relative risk, 0.55, 95 percent CI 0.42 – 0.73). This indicates that a 27 to 58 percent reduction in transfusions may be achievable when ESAs are used earlier (Chart 11).
- The hemoglobin initiation levels proposed by CMS will significantly reduce the effectiveness of ESAs in preventing transfusion, as the risk of transfusion when the hemoglobin level is < 9.0 g/dL is 68 percent.
- A meta-analysis of studies with an average hemoglobin level at baseline between 10 and 12.0 g/dL showed neutral outcomes with respect to overall survival (odds ratio, 0.86; 95 percent CI 0.69 – 1.08) (Amgen data on file).
- Finally, the current FDA label does not include an initiation threshold, and CMS has not provided any clinical or scientific rationale for including this as a basis for coverage policy.

Table 13: Initiation of ESA at Hemoglobin > 11.0 g/dL
Results in Lowest Absolute Transfusion Risk and Lowest Hazard Ratio

	Patients receiving transfusion (%, N)				
Baseline Hb	**Darbepoetin alfa (n = 822)**		**Placebo (n = 819)**		**HR (95% CI)**
Missing	**27%**	(6/22)	**65%**	(20/31)	
< 9 g/dL	**68%**	(65/96)	**83%**	(66/80)	**0.68 (0.48, 0.97)**
9 - < 10 g/dL	**35%**	(51/144)	**61%**	(103/170)	**0.52 (0.37, 0.72)**
10 - < 11 g/dL	**26%**	(56/212)	**41%**	(99/239)	**0.58 (0.42, 0.81)**
≥ 11 g/dL	**14%**	(49/348)	**35%**	(104/299)	**0.38 (0.27, 0.53)**
Total	**28%**	(227/822)	**47%**	(392/819)	

Amgen data on file

Chart 11: Higher Hemoglobin Initiation Results in an Approximately 50 Percent Relative Risk Reduction of Transfusions (Adapted from Lyman and Glaspy, 2006)



$I^2 = 0$

* Early intervention is generally initiation of ESA therapy at Hb levels of approximately 12 g/dL.
† Late intervention is generally initiation of ESA therapy when the Hb levels drop to ≤ 10 g/dL.

CMS has not provided any clinical or scientific rationale for setting an implicit hemoglobin upper limit at 9.0 g/dL (i.e., initiation at < 9.0 g/dL in each month) when the recently revised FDA label states that hemoglobin is not to exceed 12.0 g/dL.

The goal of ESA treatment is to reduce and eliminate symptoms of anemia, by raising hemoglobin values and avoiding red blood cell transfusions. Treating anemia by raising hemoglobin levels using ESA therapy has also been shown to improve fatigue, energy, and other domains of health-related QOL in anemic patients with cancer (Glaspy et al., 1997; Demetri et al., 1998; Gabrilove et al., 2001; Littlewood et al., 2001; Hedenus et al., 2002, Vansteenkiste et al., 2002; Osterborg et al., 2002). Therefore, the clinical goals of therapy should reflect the range of important health benefits achieved through transfusion avoidance and improved symptoms and consider the individual patient-specific needs.

- Most of the RCTs conducted to define the efficacy and safety of the ESAs targeted hemoglobin levels of 11.0 to 13.0 g/dL, with dose withholding hemoglobin threshold greater than or equal to 13.0 g/dL. A few of the initial registration trials of darbepoetin alfa in CIA actually withheld treatment at higher hemoglobin levels of 14.0 to 15.0 g/dL, and no additional risk was identified in long-term follow-up. Thus, the evidence base that exists to inform CMS coverage policy of the improved net health outcomes of ESA therapy comprises studies where the protocol specified that patient hemoglobin levels be managed in this manner. This represents the highest level of evidence upon which CMS bases its coverage policies.[12]

- Current evidence-based clinical practice guidelines recommend targeting hemoglobin levels in the range of 11.0 to 13.0 g/dL, with ASH/ASCO recommending maintaining hemoglobin near 12.0 g/dL (Lichtin et al., 2005); NCCN recommending maintaining hemoglobin between 11.0 to 12.0 g/dL for the longest duration during therapy (Rodgers et al., 2007) and EORTC recommending a target hemoglobin range of 12.0 to 13.0 g/dL (Bokemeyer et al., 2006). These recommendations are based on trials that have demonstrated that anemia correction aimed at reaching a target hemoglobin of 11.0 to 12.0 g/dL maximizes health benefits, avoidance of red blood cell transfusions and improving symptoms and QOL (Glaspy et al., 1997; Demetri et al., 1998; Vahdan-Raj et al., 2003, Lyman and Glaspy 2006; Crawford et al., 2002).
- The recent FDA label change, in response to safety findings, includes a change from a target hemoglobin of 10.0 and 12.0 g/dL to a hemoglobin limit of 12.0 g/dL. **The recent FDA ODAC panel voted that this level should not be changed in further label revisions based on a review of existing data.**
- When survival outcomes are evaluated through meta-analysis in CIA, the hemoglobin thresholds of 12.0 g/dL to 13.0 g/dL are not associated with an increase in mortality, with an odds ratio for overall survival of 0.87 (95 percent CI: 0.54-1.38). (Amgen data on file).
- Finally, in a recent AHRQ meta-analysis of ESA safety, the relative risk of VTE does not vary when hemoglobin thresholds range from > 13.0 g/dL to 16.0 g/dL (Seidenfeld et al., 2006).

A hemoglobin limit of 12.0 g/dL is currently in the FDA-approved label for both marketed ESAs. However, the ability of physicians to effectively manage hemoglobin within target and threshold values is particularly important, given the variability in hemoglobin during repeated cycles of chemotherapy. If a patient experiences a single, transient, hemoglobin concentration > 12.0 g/dL, providers need discretion to determine for the individual patient whether to reduce the dose or withhold the dose. Moreover, in some patients, the abrupt withdrawal of ESA treatment in response to a single hemoglobin level > 12.0 g/dL may not represent optimal management. Many individual factors must be considered in this decision, including the underlying comorbidities, the severity of anemia symptoms, degree of ongoing myelosuppression imposed by the chemotherapy regimen, and the timing of the hemoglobin level assessment relative to the planned dosing of chemotherapy and ESA regimen being employed.

There are several reasons a physician may determine it is appropriate and necessary medical care to administer a reduced dose of ESA to a patient with a hemoglobin level greater than 12.0 g/dL rather than to withhold the dose. Some examples include the following:

- Imminent myelosuppressive chemotherapy in a patient who, based on previous experience, is predicted to have a significant subsequent decline in hemoglobin levels, resulting in significant anemia symptoms, or the need for transfusion.
- Significant anemia symptoms at hemoglobin levels at or near 12.0 g/dL.
- Prolonged duration of planned chemotherapy with expected cumulative myelotoxicity.
- Comorbid illnesses, such as impaired cardiac or pulmonary disease, associated with low physiologic tolerance for anemia.

Importantly, Amgen does not recommend that physicians target a hemoglobin > 12.0 g/dL in anemic cancer patients. However, we recognize the practical importance of a target hemoglobin level, allowing appropriate physician flexibility in the management of individual patients, as opposed to a limit for the purposes of coverage or payment. CMS should also recognize that based on current data there is no evidence to suggest that ESA doses are administered frequently to cancer patients with hemoglobin > 12.0 g/dL. In fact, a recent analysis of one of the largest electronic medical record (EMR) databases in oncology, representing more than 13,069 CIA patients, found that 96.5 percent of all patients receiving ESAs had a hemoglobin level < 12.0 g/dL at the time of administration.[13] Moreover, a recent chart audit showed 94 percent of patients with CIA receiving ESAs had a hemoglobin under 12.0 g/dL at ESA administration.[14]

If CMS simply limits coverage or payment to hemoglobin values < 12.0 g/dL, physicians may believe that they do not have the discretion to adequately treat patients with hemoglobin levels between 11.0 g/dL and 12.0 g/dL, the range where patient benefit is optimized.

Finally, CMS will soon be able to more effectively monitor the care delivered to cancer patients with anemia. Based on the recently passed Tax Relief and Health Care Act of 2006 (TRHCA), CMS will develop a system to collect hemoglobin levels in cancer patients, beginning in 2008.[15] At that time, data may be adequately compiled and analyzed to determine the need to introduce hemoglobin levels into medical review or claims processing guidelines.

III. BENEFITS OF ESA TREATMENT

In issuing the PDM, CMS appears not to weigh fully the well-documented benefits of ESA treatment, which include increased hemoglobin levels and avoidance of transfusion. Additionally, clinical studies report improvement in patient-reported outcomes (PROs) in patients undergoing cancer treatment with chemotherapy.

ESAs demonstrate clear benefit in terms of avoidance of red blood cell transfusions required to treat signs and symptoms of anemia. Indeed, objective evidence of red blood cell transfusion reduction served as the basis for registration of ESAs in the treatment of CIA. Systematic reviews of randomized clinical studies through meta-analysis show that ESAs significantly increase the likelihood of hemoglobin response by more than three-fold, reduce the risk of transfusion by 36 to 59 percent (Bohlius et al., 2006b; Seidenfeld et al., 2006; Ross et al., 2006) and improve PROs based on the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) (Cella et al., 2002) and Linear Analog Scale Assessment (LASA) tools (Farrar et al., 2001), instruments that assess a patient's functionality, weakness/energy/tiredness, and ability to engage in daily activities. While these studies make use of clinical instruments that may not meet today's FDA standards for the registration of PROs in product labeling, the impact of ESA therapy on these PROs should not be discounted. Importantly, the clinical trials in the above-referenced meta-analysis included a large proportion of patients aged 65 and older, providing important evidence of benefit relevant to the Medicare beneficiary population.

Additionally, with ESA treatment, more consistent hemoglobin levels are maintained, helping to prevent the anemia from recurring. Following a transfusion, hemoglobin levels rise only temporarily, and patients may require multiple transfusions to treat the anemia as their hemoglobin levels inevitably decline.

Analysis of four randomized placebo-controlled Phase 3 clinical trials in CIA shows that starting ESA treatment at lower hemoglobin levels is associated with higher risk of transfusion. Among patients randomized to ESA treatment, 68 percent of all patients had at least one transfusion when the baseline hemoglobin was < 9.0 g/dL. In contrast, 35 percent of patients had at least one transfusion when baseline hemoglobin was between 9.0 and < 10.0 g/dL (Amgen data on file).

Further, shifting medical practice away from ESAs to transfusion will impose a significant burden on cancer patients and the health care delivery system. Access to transfusion is limited and cumbersome for the greater than 80 percent of cancer patients receiving chemotherapy in the community clinic. This was noted at the recent ODAC meeting on May 10, 2007 (Table 14).

Table 14: Reaction from Clinical Oncology Expert at ODAC 2007

Roy Beveridge, MD; Medical Oncologist at US Oncology
"Resorting to transfusion in this cancer population is very problematic in today's world. There are the obvious safety issues that have been discussed earlier today. There is a taxing of the limited supply of blood that we have. But there is also a very significant taxing of the delivery system. I was actually at Fairfax Hospital this morning before I came here. It opens at 6 am in the morning. It closes 13 hours later. It's open 7 days a week. The next time that we can schedule a blood transfusion if one wanted to do it today would be 13 days from now. The system is very saturated." (Beveridge, 2007)

If the PDM is finalized without changes, these patients would be forced by CMS to travel from the clinic to a hospital to receive transfusions.

An actual transfusion typically takes more than four hours to administer, requires specialized equipment and trained personnel, and, in some cases, must be done before chemotherapy can be given. This is an important fact because the typical transfused patient receives over five units of red blood cells from different donors, and some cancer patients are transfused much more than this.

Additionally, CMS may not have fully considered the following important issue: the inability of red blood cell transfusions to maintain patient hemoglobin at appropriate levels unless patients are subjected to chronic hypertransfusion. On the other hand, clinical evidence strongly supports the finding that prevention of transfusion and improvements in PROs are optimized when ESAs are used to target hemoglobin levels between 11.0 and 12.0 g/dL (Crawford et al., 2002). CMS should recognize that the safety of red blood cell transfusions in these patients has not been rigorously tested at these levels.

The real risks of red blood cell transfusions are significant and may not have been fully considered by CMS at the time the agency released the PDM.

CMS should consider the following risks before finalizing a policy that could have a significant impact on the safety and health of the beneficiaries that the agency serves:

- Transfusions are a proven transmission route for serious infections. The human immunodeficiency virus (HIV) and hepatitis virus plagued the blood supply for years before they were recognized and testing developed (Dodd et al., 2003). Further, current testing procedures and technologies for detecting these and other viruses before they enter the U.S. blood supply are not perfect (Busch et al., 2003; Busch et al., 2005).
- Simply put, the blood supply is, at best, safe until the next pathogen emerges. The question is not whether a new pathogen will emerge but when. As characterized by the Centers for Disease Control and Prevention, "numerous pathogens have emerged in the United States and worldwide with the potential to affect the safety of the blood supply." (Chamberland et al., 1998).

- Transfusion Related Acute Lung Injury (TRALI) is the leading cause of transfusion-related death according to the FDA and could occur at frequencies exceeding 1 in 10,000 patients (Bux and Sachs, 2007).
- Bacterial contamination has resulted in 1 in 10 transfusion-related deaths in the US (Kuehnert et al., 2001).
- Febrile reactions (*e.g.*, sweating, rapid heart rate, nausea, or headache) occur in 5 to 10 percent of patients receiving transfusion because of antibodies in the transfused blood (King et al., 2004).
- Potentially fatal hemolytic reactions and graft versus host disease are rare, but the associated sequelae are very serious (Sazama et al., 1990; Linden et al., 1997).
- Clerical errors resulting in a person's receiving the wrong blood occur every 1 in 14,000 to 18,000 transfusion and are often fatal (Goodnough et al., 1999; Williamson et al., 1999).
- Iron overload occurs in patients who must receive repeated and prolonged transfusion, such as in MDS (Franchini and Veneri, 2004).

Further, the U.S. blood supply does not meet current clinical needs. Notably, the U.S. Department of Health and Human Services' Advisory Committee on Blood Safety and Availability (ACBSA) noted in its most recent (2005) report on blood availability that "the mean number of days of unmet nonsurgical blood need increased significantly from 2.1 days in 2001 to 19.27 days in 2004 ($p<0.001$)." (Whitaker et al., 2006). Such shortages lead to substantial problems for the health care system and Medicare beneficiaries, including the cancellation of vital surgical procedures. Therefore, CMS must carefully evaluate the impact of its proposed coverage policy on the U.S. blood supply. We recommend that the agency consult with the ACBSA to understand what effects the proposed coverage policy would have on an already limited national blood supply.

IV. ANALYSIS OF THE POLICY IMPLICATIONS OF THE PROPOSED NON-COVERED AND COVERED CLINICAL INDICATIONS

Some of the agency's proposals appear to be clinically appropriate, and we recommend that CMS consider finalizing certain proposed non-covered indications.

CMS has proposed to consider the following eight uses of ESAs as non-covered:

1. Anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
2. Anemia of myeloid cancers, *specifically AML and CML*
3. Anemia associated with the treatment of myeloid cancers or erythroid cancers
4. Anemia associated with *primary treatment with* radiotherapy
5. Prophylactic use to prevent chemotherapy-induced anemia *in patients who have never suffered from CIA*
6. Prophylactic use to reduce tumor hypoxia *in non-anemic patients*
7. Patients with erythropoietin-type resistance due to neutralizing antibodies
8. Anemia due to cancer treatment if patients have uncontrolled hypertension

We note that the italicized text above represents specific clarifications that would make the proposed policy clearer.

Recommendation: **Amgen recommends that CMS finalize these restrictions with the clarifications noted in italics. In our view, these uses are not supported by the current clinical evidence and there is no significant use of ESAs in current practice for these settings. As clinical evidence may evolve over time, we suggest that CMS review data on these clinical conditions periodically to reassess the appropriateness of non-coverage.**

Below, we review the proposed covered and non-covered indications outlined in the PDM.

Some of the proposed non-covered indications are overly restrictive, when viewed against the available clinical evidence, and should <u>not</u> be implemented.

In the cases below, we review the instances in which the clinical data do not support the agency's proposed non-coverage determination and review the clinical evidence that supports coverage.

<u>Anemia of Cancer Not Related to Cancer Treatment</u>

In the PDM, CMS has proposed non-coverage of ESAs for all patients with AOC. This proposal does not appropriately recognize that there is published evidence of benefit from controlled clinical trials, without evidence of detrimental survival outcomes, in

certain subgroups of patients receiving ESAs for AOC. For this reason, CMS should not restrict coverage for the entire patient population.

In response to the NCA for ESAs, Amgen previously has recommended that CMS consider restricting coverage in a specified subpopulation of AOC patients until further data clarify the benefit-to-risk profile in these patients. Specifically, we noted that the agency should consider restricting coverage in the subgroup of AOC patients with active cancer not receiving or planning to receive additional chemotherapy or radiation therapy with a poor prognosis, as these are the patients for whom evidence suggests that the benefit-to-risk profile could be negative and is at best neutral. Data from a recent clinical study of this patient population suggest that coverage for these patients may not be warranted at this time (Glaspy et al., 2007).

Recommendation: **For these reasons, Amgen recommends that CMS not finalize the coverage exclusion for all AOC patients. Instead, CMS should consider restricting coverage for ESAs in only a subset of patients with AOC who have active disease and are not receiving or planning to receive chemotherapy or radiation therapy.**

Patients with Treatment Regimens Including Anti-angiogenic Drugs and Monoclonal / Polyclonal Antibodies Directed Against the Epidermal Growth Factor Receptor

CMS proposes to implement a coverage restriction of ESAs for all patients with cancer-related anemia who are receiving anticancer therapy with biologic agents such as Avastin® (bevacizumab), Erbitux® (cetuximab), and Vectibix™. The CMS proposal appears to be based on three points:

1. A "colon cancer study" showing that patients treated with the anti-EGF-R monoclonal antibody, Vectibix™, and an ESA experienced decreased survival within 16 weeks;
2. A single study that used a chimeric receptor (*i.e.*, extracellular EGFR and intracellular EPO-R) transfected into a hematopoietic cell line to study the EPO-R signaling pathway in hemoglobin synthesis; (Wakao et al., 1997); and
3. Preclinical studies suggesting a possible role for EPO-R signaling in angiogenesis (Ribatti et al., 2007a; Ribatti et al., 2007b; Batra et al., 2003; Yasuda et al., 1998; Yasuda et al., 2002).

Point 1 references research that does not appear to exist. This point appears to result from blending the results from two separate studies: a study of Vectibix™ in colon cancer patients (Amgen press release for PACCE, March 22, 2007) and a study of darbepoetin alfa in patients with anemia of cancer (Amgen press release for Study 20010103, April 16, 2007). Point 1, therefore, has no basis in evidence.

Point 2 cites an irrelevant study. The cited study demonstrated that the Stat5 protein is important for erythropoietin to stimulate hemoglobin synthesis. It does not bear on the question of whether ESAs will interfere with EGFR signaling (Wakao et al., 1997).

Point 3 represents speculation. This point has no supporting preclinical data and no relevant clinical data. The evidence cited included a letter to the editor (Ribatti et al.,

2002) speculating that angiogenesis stimulated by EPO may have contributed to the emergence of AML in an MDS patient as described in a case report (Bunworaste et al., 2001). The emergence of AML in patients with MDS is not uncommon, but angiogenesis is not believed to play a role in this pathologic evolution (Lundberg et al., 2006; Keith et al., 2007).

The ability of EPO itself to stimulate angiogenesis is highly speculative. The PDM cited a recent study (Zwezdaryk et al., 2007) using mesenchymal stem cells (MSCs) to show that erythropoietin elicited a pro-angiogenic response. However, the role of MSCs in tumor angiogenesis has not been well established; the study used the MAB307 antibody that does not specifically detect EPO-R; and a superphysiological concentration of erythropoietin (40-80 U/ml, 40-160-fold higher than levels achievable in clinical ESA therapy) was applied. Thus, the relevance of the findings from this study is unclear. Finally, EPO, even at huge concentrations, has no angiogenic activity in a rat corneal angiogenesis model, (Amgen Inc., ODAC Briefing Book 2007) which represents the most sensitive assay devised.

Recommendation: **For these reasons, Amgen recommends that CMS not exclude coverage for patients who are also receiving antiangiogenic and anti-EGFR therapies. The agency's recommendation against use of ESAs with EGFR inhibitors or antiangiogenic agents lacks a scientific foundation. For the vast majority of patients, EGFR inhibitors and antiangiogenic agents are administered in combination with myelosuppressive regimens, for which anemia is a known and well-characterized complication. Therefore, the proposed restrictions should be reconsidered in order to protect a patient population with a demonstrated clinical need for ESA therapy.**

<u>Patients with Thrombotic Episodes Related to Malignancy</u>

In the PDM, CMS proposed to exclude coverage of ESAs for all patients with a history of thrombotic episodes related to malignancy. Patients exposed to ESAs have an increased risk of thrombotic vascular events (TVEs), reported by the Cochrane group as a relative risk of 1.67 (95 percent CI: 1.35, 2.06). This risk is well-described in the FDA-approved labels for ESAs. The absolute increase in the rate of TVEs is about two to three percent. Integrated analysis of all placebo-controlled randomized studies of darbepoetin alfa showed a relative risk of 1.57 (95 percent CI: 1.10, 2.26), similar to that reported by the Cochrane study level meta-analysis of all randomized controlled trials of ESA.

Importantly, the integrated analysis also demonstrated that the actual TVE rate was five percent in the placebo group, and eight percent in the darbepoetin alfa group. The increase in the rate of TVE remains at about three percent (absolute difference) regardless of whether patients had a prior history of TVE or not. In placebo-controlled CIA studies of darbepoetin alfa, for patients without a prior history of a TVE, the rate of TVE is 4.3 percent in the placebo patients and 7.3 percent in the darbepoetin alfa-treated patients; for patients with a history of prior TVE, the rate of TVE is 15.8 percent

in the placebo patients, and 18.9 percent in darbepoetin alfa-treated patients, thus indicating about a three percent increase above baseline with ESA therapy regardless of whether patients had a history of TVE (Amgen data on file). These clinical data suggest a lack of interaction between ESA treatment and prior TVE in terms of ongoing TVE risk, and therefore there is no scientific basis to recommend against the use of ESAs in patients with a history of prior TVE. Finally, ESA use in patients with thrombotic episodes is not a contraindication or a warning in the prescribing information for these products.

Recommendation: **For these reasons, Amgen recommends that CMS not exclude coverage for patients who have had thrombotic episodes related to malignancy. The agency's recommendation against use of ESAs in this sub-population lacks a scientific foundation, as the clinical evidence shows a lack of interaction between ESA treatment and prior TVE in terms of ongoing TVE risk.**

Treatment of MDS

CMS proposes non-coverage of ESAs for all patients with MDS, a chronic bone marrow disorder most frequent in patients over 65 years of age that leads to chronic anemia and transfusion dependence in the absence of ESA therapy (Balducci et al., 2006). Finalizing this proposal would reject the body of evidence that supports the benefit conferred by ESA treatment in this setting, without evidence of detrimental survival outcomes. Further, the proposal is contrary to the agency's own Physicians Quality Reporting Initiative (PQRI) mandated by Congress under TRHCA. Under PQRI, CMS recognizes MDS as a condition for which ESA treatment plays a valuable role and encourages physicians to report iron store levels in patients receiving ESA therapy (Available at: http://www.cms.hhs.gov/PQRI/Downloads/PQRIMeasuresList.pdf).

Further, while large, placebo-controlled randomized studies are not available, numerous clinical trials have been conducted with ESAs in MDS patients, and the extensive published evidence (Balducci et al., 2006; Casadevall et al., 2004; Hellstrom-Lindberg et al., 1995; Kurtin et al., 2006; Negrin et al., 1996; Spiriti et al., 2005) supports the efficacy of ESAs in reducing transfusions in MDS patients. Amgen summarized these data in our submission to CMS on April 13, 2007. This body of evidence has been recognized in the compendium-listed acceptance for MDS and in evidence-based guidelines (Greenberg et al., 2007).

With regard to safety in MDS patients, Jadersten and colleagues (Jadersten et al., 2005) reported the long-term outcome of 129 MDS patients treated with epoetin alfa and granulocyte-colony stimulating factor (G-CSF) who were followed for up to 45 months. Erythroid response rate was 39 percent and median response duration 23 months (range, 3-116 months or more). Complete responders showed longer response duration than partial responders (29 versus 12 months, P = 0.006). There was no difference in survival (odds ratio [OR], 0.9; 95 percent CI: 0.7,1.2; P= 0.55) or risk of AML evolution (OR, 1.3; 95 percent CI: 0.7-2.2; P= 0.40) between the ESA-treated patients in comparison to untreated patients selected from the IPSS database using multivariate Cox regression, adjusting for major prognostic variables.

Additionally, a matched case-control study of transfusion-dependent MDS patients treated with ESAs and a granulocyte-colony stimulating factor (n=123) compared to control MDS patients (n=240) showed that 41 percent of ESA-treated patients achieved transfusion independence (Jadersten et al., 2006). Multivariate Cox regression analysis showed that treated patients with (historical) transfusion need of less than 2 units of red blood cells per month had a survival benefit, with HR 0.57 ($p = 0.015$), while no difference in survival was observed in patients with higher transfusion need ($p = 0.36$). There was no significant impact on risk of leukemic transformation in patients with either a low ($p = 0.75$) or high ($p = 0.21$) transfusion need. These retrospective analyses support the use of ESAs to reduce transfusion dependence in MDS patients. This population is particularly vulnerable given the risk of allo-immunization from repeated transfusions.

A systematic review of 59 ESA studies (2106 patients) including 4 RCTs support the safety and efficacy of ESAs in the treatment of anemia associated with MDS (Ross et al., 2007).

In the May 10, 2007, meeting of the FDA's ODAC, numerous participants recognized MDS as a condition that warrants Medicare coverage. In comment at the ODAC meeting, the Director of the FDA's Office of Oncology Drug Products noted the need to separate MDS from other clinical conditions, as noted in Table 15.

Table 15: FDA Statement on Need to Have Distinct Separation between MDS and Other Clinical Conditions for Coverage Purposes

Dr. Richard Pazdur, Director, Office of Oncology Drug Products, FDA
"Those are two different things. I do not want them [MDS patients] to get swept away with this. We will discuss this with our colleagues at CMS to make sure that does not occur." (Pazdur, 2007)

Recommendation: **For these reasons, Amgen recommends that CMS not exclude coverage for MDS. Given the well-recognized role of ESA therapy in MDS and the available clinical evidence that supports the use of ESA, CMS should not restrict coverage to Medicare beneficiaries for this indication.**

V. PROPOSED COVERAGE LIMITATIONS

The proposed restriction to limit coverage for patients with hemoglobin levels less than 9.0 g/dL is not based in the clinical evidence.

In this aspect of the PDM, CMS has blended the two following important but distinct clinical issues: (1) when to initiate ESA therapy and (2) when to withhold ESA treatment based on hemoglobin levels.

CMS states that the ESA should only be used when the hemoglobin falls below 9.0 g/dL, during each month for patients without known cardiovascular disease. Such a restriction is a serious concern because it is not based on the evidence of clinical efficacy of ESAs from randomized controlled trials. Most patients in randomized controlled trials had hemoglobin levels > 9.0 g/dL at study entry. For Amgen-sponsored darbepoetin alfa studies involving more than 10,000 patients, 88 percent had baseline hemoglobin of 9.0 g/dL or higher. The limitations as proposed by CMS will effectively set a hemoglobin target of 9.0 g/dL, a level that will negate the goal of avoiding transfusion with ESA therapy. This limitation is inconsistent with the FDA approved product label, and is in conflict with the current practice guidelines from major professional societies. This limitation also confuses two important aspects of optimal ESA treatment (*i.e.,* the hemoglobin level at which to initiate treatment, and the hemoglobin level to target once ESA treatment begins). For the purpose of avoiding transfusion and alleviating the signs and symptoms of anemia, it is important to set an initiation level at which the risk of transfusion is low. After initiation of therapy, the dose of ESAs should then be adjusted to achieve a target hemoglobin that is optimal to keep the patient free from the risk of transfusion as well as the signs and symptoms of anemia. Clinical trials to assess ESAs have been conducted with explicit levels of hemoglobin for initiation, and a clear guidance on dose adjustment to achieve and maintain a hemoglobin level considered appropriate for the well being of the patients.

This proposed restriction appears to be based on the cited “tradition” and critical care model of reserving transfusion for patients with hemoglobin levels less than 7 or 8 g/dL, and does not consider the current practice regarding transfusions in patients treated in the community-based outpatient clinic for CIA. Such evidence is available from clinical trials, community practice surveys, and claims database analyses. These analyses show that the hemoglobin level before transfusion varies over a wide range, but is consistent across multiple data sources. In the five randomized, phase 3 trials of darbepoetin alfa in CIA, 71 percent of the transfusions received by ESA-treated patients were preceded by a hemoglobin of < 9.0 g/dL. These results were similar to the 80 percent rate observed for two Amgen-sponsored, retrospective, observational studies.

These data clearly show that physicians prescribe red blood cell transfusions to treat the signs and symptoms of anemia, rather than relying on arbitrary hemoglobin level transfusion triggers. If CMS restricts ESA use with a 9.0 g/dL initiation level (which would also become the target level), it would lead to the replacement of ESA use with red blood cell transfusions for most patients.

The current product label for ESAs recommends that a hemoglobin level of no higher than 12.0 g/dL be used to avoid transfusion. This is a critical element in the current revised FDA label, which reflects a conservative approach, as most randomized clinical trials specified a target hemoglobin of 13.0 g/dL or higher and prior to the recently modified label, ESA treatment in cancer uses was withheld at 13.0 g/dL whereas now withholding occurs at 12.0 g/dL. The importance of this approach has been validated as the appropriate restriction by the recent ODAC panel, who recommended against a change in the labeled hemoglobin limit of 12.0 g/dL, which is essential to achieve the goals of transfusion avoidance. Under the proposed coverage restrictions, an arbitrary upper threshold for ESA therapy is set at a hemoglobin level of 9.0 g/dL, which will lead to transfusion in most patients *before* they can be qualified for ESA therapy, practically rendering the ESA ineffective in the FDA-defined primary objective of therapy— to reduce the risk of receiving a red blood cell transfusion (Aranesp® [darbepoetin alfa] prescribing information, Amgen). CMS should not implement a policy that conflicts with the ESA product label and the ODAC recommendation.

Recommendation: **For these reasons, Amgen recommends that CMS include no initiation limit for ESAs. However, if CMS decides to implement an initiation threshold, we recommend a threshold of 11.0 g/dL and to allow treatment until a patient's hemoglobin reaches 12.0 g/dL. CMS should consider the need for physician discretion to dose reduce rather than withhold when hemoglobin exceeds 12.0 g/dL during chemotherapy.**

CMS has proposed a timeframe of 12 weeks per year for ESA treatment. This limit is without support in the clinical evidence and should be re-evaluated carefully in light of the best available data.

Chemotherapy regimens in cancer patients are frequently prolonged and last beyond 12 weeks. For instance, in the adjuvant setting, colorectal cancer and breast cancer patients are typically treated with chemotherapy for six months. For patients with metastatic cancer, chemotherapy regimens are commonly administered until disease progression, at which time the second-line treatment may begin, and multiple lines of chemotherapy are often administered with the total treatment duration well over 12 weeks for patients who survive beyond 12 months. Clearly, the number of courses of chemotherapy in a year is highly variable depending on tumor type, extent of disease and response to therapy. Based on data from the Tandem Cancer audit (Amgen, data on file) the duration of chemotherapy is outlined in Table 16 for common tumor types.

Table 16: Common Cancer Types and Treatment Durations

Cancer Type	Average Chemotherapy Duration
Colorectal Cancer	23 weeks
Breast Cancer	16 weeks
Hodgkin's Disease	24 weeks
Non-Hodgkin's Lymphoma	20 weeks
Non-Small Cell Lung Cancer	17 weeks
Small Cell Lung Cancer	18 weeks
Ovarian Cancer	22 weeks
Prostate Cancer	26 weeks

Tandem Cancer Audit, Amgen data on file

Thus, it is clear that anemia in patients receiving myelosuppressive chemotherapy commonly lasts more than 12 weeks. As such, this proposal would inadvertently discriminate against Medicare beneficiaries who are prescribed chemotherapy regimens in excess of 12 weeks.

Further, patients with cancer are at risk of developing anemia not only when they are receiving myelosuppressive chemotherapy but also for a variable time period after the completion of their chemotherapy. The time necessary for bone marrow recovery after cessation of chemotherapy varies widely based on individual patient factors such as age, type of chemotherapy, type of disease, and effects of the chemotherapy on renal endocrine function. Additionally, expert medical societies, including ASH, have recommended that the duration of ESA therapy might need to be up to 90 days after completion of chemotherapy with longer durations depending on individual patient circumstances (ASH Statement to CMS).

For all of these reasons, a specific recommendation regarding the maximum duration of ESA treatment should not be made, as any time limit would be, quite simply, arbitrary.

Recommendation: **For these reasons, Amgen recommends that CMS include no time limit for ESA treatment given the wide variations in treatment regimens for chemotherapy courses and need for multiples cycles and lines in cases of progression. Further, for purposes of coverage policy, CMS should define CIA as (1) patients with cancer and anemia who are receiving concomitant chemotherapy and (2) patients with anemia who have completed myelosuppressive chemotherapy within the prior three months.**

CMS has proposed a coverage limit of 126,000 units for epoetin alfa and 630 mcg for darbepoetin alfa per four week period. This proposal is not supported by the clinical evidence and should be reconsidered.

This proposed restriction is inconsistent with the FDA-approved dosing regimen for ESAs. The ESAs are titratable drugs used to achieve specific hemoglobin levels. The starting doses and dose adjustment guidelines are clearly delineated in the product label and clinical practice guidelines. Further, the currently proposed coverage policy appears to be drafted to carefully control hemoglobin initiation and target levels. As such, restricting the dosing as well would not result in effective clinical care.

Moreover, the FDA-approved labeling for darbepoetin alfa states that one of the product's dosing regimens allows for administration at a dose of 500 mcg every three weeks (*i.e.,* up to 1,000 mcg per six weeks unless there are dose reductions). Limiting the total dose of darbepoetin alfa to 630 mcg per 4 weeks will limit the ability for physicians to effectively manage anemia in patients who may require a higher than average dose to respond and disadvantage patients who are prescribed every-three-week dosing given with their chemotherapy regimens. Similarly, the labeled dose of epoetin alfa is 40,000 U per week and the product label recommends an increase to 60,000 U per week (*i.e.*, 360,000 U per six weeks), if patients who do not have satisfactory response after 4 weeks of therapy.

Recommendation: **For these reasons, we recommend that CMS not limit the doses for ESAs. If the agency chooses a dose limit, we recommend that CMS use the maximum approved doses for ESAs, per their product labels, in the finalized NCD. Additionally, CMS should adjust the timeframe to six weeks (versus four) because one ESA can be dosed on a three-week basis. Therefore, the maximum allowed doses should be 1,000 mcg per six weeks for darbepoetin alfa and 360,000 U per six weeks for epoetin alfa.**

In the PDM, CMS has proposed to limit access to ESAs if there is evidence of poor drug response (i.e., hemoglobin rise < 1.0 g/dL or hematocrit rise < 3 percent) after 4 weeks of treatment. This proposal lacks necessary scientific support.

Patients considered to be hypo-responsive, in the absence of other factors such as intestinal bleeding or functional iron deficiency, have typically been administered increased doses of ESAs after either 4 or 6 weeks, an approach used in the majority of licensing studies which have demonstrated positive risk/benefit for ESAs and have formed the basis of the current FDA label (Witzig et al., 2005; Vansteenkiste et al., 2002, Hedenus et al., 2002). In this regard it is important to note that although hemoglobin changes (as opposed to a bona fide clinical response) can be seen in as little as 2 weeks, the median time to a rise in hemoglobin of > 1.0 g/dL is 28 days (Amgen data on file). The current FDA label of Aranesp states "Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment" and refers the reader to the dosage and administration section. For weekly administration, this section recommends that if a patient has an inadequate initial response to therapy (defined as a less than 1.0 g/dL increase in 6 weeks) the weekly dose should be increased as

opposed to recommending cessation of therapy (Aranesp® prescribing information). Additionally, the NCCN clinical practice guidelines recommend discontinuation of ESA treatment only if no response is observed after 8 to 12 weeks of therapy (Rodgers et al., 2007). While different dose titration rules have been used in different studies, these dose titration rules have not been demonstrated to be valid predictors of clinical benefit, or surrogates for possible risk. In clinical trials the formal protocol-specified assessment of hemoglobin response to ESAs is typically performed after 8, 12, or 16 weeks of treatment. Amgen believes that an evaluation of hypo-responsiveness or non-response should be based on the clinical assessment based on the individualized treatment goals for a particular patient rather than on a broad laboratory based assessment that is inconsistent with current guidelines on clinical trial evidence.

Recommendation: **For these reasons, Amgen recommends that CMS not include a specified time limit to assess ESA therapy response in the final policy. If the agency chooses to implement such a policy, we recommend that it be in line with the product label and clinical practice guidelines by extending the coverage parameters for an adequate trial of therapy to 12 weeks of therapy (instead of four).**

In the PDM, CMS has proposed restrictions on the administration of ESAs if there is a rapid rise in hemoglobin greater than 1.0 g/dl or hematocrit greater than 3 percent after 2 weeks of treatment.

A potential safety concern with erythropoietic therapy is that rapid increases in hemoglobin or high hemoglobin concentrations may be associated with an increased rate of cardiovascular or thromboembolic adverse events. Using the data from previous Aranesp studies, a Cox Proportional-Hazard time-dependent analysis was conducted to examine the association between the rate of rise in hemoglobin and the risk of thromboembolic events. The time at-risk following a hemoglobin concentration of ≥ 1.0 g/dL within a 2-week period was not associated with an increased risk of a thromboembolic event, although similar analyses of patients who had an increase in hemoglobin concentration of ≥ 2.0 g/dL within a 28-day period suggested that the increase may be associated with an increased risk for thromboembolic events (Amgen ODAC Briefing Book 2004). Although early studies of darbepoetin alfa in the oncology setting did not use dose titration rules to address rapidly rising hemoglobin concentrations, based on the data indicating the potential for increased risk of thromboembolic events with a 2.0 g/dL increase in 28 days and the lack of clinical need to increase hemoglobin more rapidly, a precautionary approach was adopted in the US package insert (Aranesp® prescribing information). The current label information recommends a dose reduction for patients with a ≥ 1.0-g/dL increase in hemoglobin within 14 days.

However, the CMS recommendation to withhold therapy from patients with a > 1.0 g/dL increase in hemoglobin within 14 days is not based on evidence from clinical trials and will have an important negative impact on the benefit derived from ESA therapy in the cancer setting. Hydration therapy, chemotherapy, individual patient factors, and variation in laboratory values in patients with cancer theoretically make significant contributions to the natural variability in hemoglobin concentrations during the course of

each chemotherapy cycle. These factors may result in a significant rate of "false positives" when applying the 1.0 g/dL increase within 14 days rule, even in the absence of erythropoietic therapy. In fact, due to the natural variability of hemoglobin in cancer patients receiving chemotherapy in an analysis of placebo-controlled trials, the number of placebo-treated patients who had a > 1.0 g/dL increase in hemoglobin over 14 days was estimated to be 52% (excluding the effect of transfusions).

Given the inherent variability of hemoglobin concentrations and the lack of evidence suggesting an association between thrombotic events and a 1.0-g/dL increase in hemoglobin concentration within 14 days, a recommendation regarding cessation of therapy based on this algorithm is inappropriate for patients with cancer who are receiving chemotherapy. Coverage policy should adhere to the FDA-approved dosing recommendation and current treatment guidelines which recommend a dose reduction if a patient achieves a rapid rise in hemoglobin.

Recommendation: **Therefore, Amgen recommends that CMS not include a specified time limit in this regard as part of the final policy. If the agency chooses to implement such a policy, we recommend that CMS revise its proposed NCD and implement a policy in line with prescribing information, by requiring a dose reduction of 40 percent for an approved ESA when the levels of hemoglobin increase by more than 1.0 g/dL in a two-week period.**

The agency has also proposed to restrict access to continued administration of ESAs if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment.

We find no evidence to support this proposed restriction.

Recommendation: **Therefore, Amgen recommends that CMS cite specific data to support this proposal or explain how such a situation would constitute a medical problem. Otherwise, CMS should remove it from the finalized NCD.**

VI. DISCUSSION OF LIMITATION OF COVERAGE TO ONLY BENEFICIARIES ENROLLED IN CLINICAL RESEARCH PROGRAMS

The agency commented that it is considering limiting coverage of ESAs to only those beneficiaries enrolled in clinical research studies.

The implication of the agency's reference in the PDM to tying coverage to clinical studies is that the benefit-to-risk profile of ESAs in cancer patients does not support *any* use of an ESA outside of a purely investigative setting. As we have described throughout this document, the weight of evidence supports a neutral risk of adverse survival outcomes in CIA.

The hierarchy and weight of evidence already established for ESAs makes this type of restriction unnecessary. ESAs have been well studied, and appropriate analyses of the data are extremely reassuring. If the only mechanism for Medicare beneficiaries to access FDA labeled indications for ESA were in a clinical research study, beneficiaries who could not participate in such trials (*e.g.,* because of lack of trials in their locality) would lack treatments available to other beneficiaries who are fortunate enough to live near a clinical research site. This situation could prove common in rural areas and could appear to some as geographic discrimination. Furthermore, the great majority of community oncologists are not investigators. Limiting ESA access to investigational use would deny ESA access to many patients, leaving them with red blood cell transfusions as the only treatment option for anemia management.

Such a requirement for a Medicare Part B covered drug or biological would also be unprecedented and extraordinary, as CMS has never before imposed such a coverage limitation on any class of marketed products that has been used in clinical practice for nearly 20 years. To make cancer care the first area to have this type of experimental restriction is unwise and could pose a significant potential for worsening patient outcomes in anemia management.

For off-label uses, we suggest that CMS consider consultation with a broad group of stakeholders in the oncology community (*i.e.,* national medical societies, guideline organizations, community oncology groups, clinical and academic experts, patient groups, and manufacturers) to determine whether there are important questions that could be addressed in the context of ongoing clinical research.

Recommendation: **For these reasons, Amgen recommends that CMS not implement a coverage restriction that would limit Medicare beneficiary access to ESAs only if they participate in a clinical research study.**

* * * *

Amgen appreciates the opportunity to share this information with CMS. We believe that our submission will help provide useful data for CMS to consider as its staff work to finalize an NCD for ESAs in non-renal disease indications (CAG-00383N). If you would like any further information, please contact me personally by phone at (805) 447-0787 or by email at jofman@amgen.com. Alternatively, you may contact Sarah Wells Kocsis in Amgen's Global Government Affairs office at (202) 585-9713 or by email wellss@amgen.com. Thank you for your attention to these important matters.

Regards,

Joshua J. Ofman MD, MSHS
Vice President
Global Coverage and Reimbursement
Global Health Economics

Attachment: Appendix A (Review of the Science on the Hypothesis about the Putative Role of EPO-R in Tumor Growth)

cc: Barry Straube, MD, Director, Office of Clinical Standards and Quality (OCSQ), Chief Medical Officer, CMS
Louis Jacques, MD, Director, Division of Items and Devices, Coverage and Analysis Group (CAG), CMS
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ENDNOTES

1. *See* "Proposed Decision Memorandum for Erythropoiesis Stimulating Agents for Non-Renal Disease Indications (CAG-00383N)." Available at http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=203 (Accessed May 14, 2007).
2. We note that the class of biologicals known as ESAs includes Amgen's products, Aranesp® (darbepoetin alfa) and EPOGEN® (epoetin alfa). These biologicals have been studied for more than 15 years in a variety of clinical uses. Aranesp® and EPOGEN® have improved anemia management in approximately 4 million patients worldwide. Amgen was the first to clone the gene encoding erythropoietin and is the sponsor of the epoetin alfa Biologics License Application. In the United States, epoetin alfa is marketed under the trade names EPOGEN® and Procrit®. Amgen clinically developed, manufactures, markets, and distributes EPOGEN® for the treatment of anemia associated with chronic renal failure in patients who are receiving dialysis. While Amgen manufactures both Procrit® and EPOGEN®, Ortho Biotech Products, L.P., a subsidiary of Johnson & Johnson (J&J), is responsible for the clinical development, marketing, and distribution of Procrit® in the United States under license from Amgen.
3. In the PDM, CMS discusses and requests information about the benefits and risks of ESAs across a variety of cancer and cancer-related clinical conditions for which these products are currently used in clinical practice. We note that Amgen only markets and promotes its ESA products with their FDA-approved product labels. However, in response to the agency's specific request for information, we provide a robust summary of the evidence in labeled and non-labeled indications for ESAs.
4. We note that the labeled indications for ESAs include the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. For the sake of clarity and brevity, we have termed any study that evaluated ESAs in combination with chemotherapy as "chemotherapy-induced anemia" or "CIA."
5. As disclosed in Amgen's Form 10-K and noted in CMS' request, Amgen has received an informal inquiry from the SEC regarding the DAHANCA-10 study. Amgen intends to cooperate fully with the SEC inquiry.
6. We note that the labeled indications for ESAs include the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. For the sake of clarity and brevity, we refer to this indication in our submission using the clinically accepted reference "chemotherapy-induced anemia" or "CIA."
7. As disclosed in Amgen's Form 10-K and noted in CMS' request, Amgen has received an informal inquiry from the SEC regarding the DAHANCA-10 study. Amgen intends to cooperate fully with the SEC inquiry.
8. There are two commonly used meta-analysis models: the fixed-effects model and the random-effects model. Fixed-effects models assume that the true effect of treatment is the same in every study. This assumption implies that the observed differences among study results are due solely to chance. Random effect-models assume that the treatment effects are not identical in all studies, but follow some distribution. In general, random-effect models are preferred because they acknowledge heterogeneity from study-to-study. When heterogeneity is suspected, random-effects models are preferable to fixed-effects models as they explicitly incorporate the added

variability. For this reason, results of the random-effects model will be presented. It is important to consider the consistency of results between studies included in a meta-analysis. One statistic for quantifying inconsistency is the inconsistency statistic, I^2, which describes the percentage of the variability is due to heterogeneity rather than sampling error (chance) (Higgins et al., 2003.) I^2 can range from 0 percent to 100 percent; values > 50 percent indicate a moderate to high level of heterogeneity. Tests for heterogeneity are commonly used to decide on methods for combining studies and for concluding consistency or inconsistency of findings. When $I^2 = 0$, then the results of the fixed-effects model equals that for the random-effects model. However, the confidence interval calculated for the random-effects model may be slightly wider than for the fixed-effects model.

9. *See* 1862(a)(1)(A) of the Social Security Act.
10. See "Factors CMS Considers in Commissioning External Technology Assessments" (http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=7). The principles of evidence-based medicine should be used to derive coverage positions, avoiding the broad extrapolation of clinical and safety data beyond the defined patient groups studied.
11. S. Phurrough. "Medicare Coverage Decisions: Balancing Competing Demands." National Health Policy Conference Presentation (Feb. 2, 2005). Available at http://www.academyhealth.org/nhpc/2005/phurrough.pdf.)
12. "CMS considers whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses." *See* CMS. "Decision Memo for Anticancer Chemotherapy for Colorectal Cancer (CAG-00179N), Appendix B, General Methodological Principles of Study Design (Section VI of the Decision Memorandum)." Available at http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=90 (Accessed March 14, 2007).
13. Luo W, et al. Adherence to guidelines for use of erythropoiesis stimulating proteins in patients with chemotherapy-induced anemia: Trends from Electronic Medical Records. Abstract submitted to *International Society for Pharmacoeconomics and Outcomes Research. Value in Health*. 2007;in press.
14. Anemia Insights, Time frame: 1/1/04-3/31/06. Data on file at Amgen.
15. *See* Section 110 (Reporting of Anemia Quality Indicators for Medicare Part B Cancer Anti-Anemia Drugs) of TRHCA.

Note to June 11 version:
This version incorporates corrections to minor typographical errors in text and tables; these corrections do not substantively change the content or meaning of this document. A full listing of these corrections is available from Amgen on request [Contact Ashley Koss, 805 313-6151, akoss@amgen.com].

Appendix A

Review of the Science on the Putative Role of EPO-R in Tumor Growth

June 1, 2007

Amgen recognizes the critical importance of the question of the potential role of the erythropoietin (EPO) receptor (EPO-R) in human tumors and is concerned that the agency's review of the scientific evidence has led to a proposed coverage policy that is not science-based and would needlessly restrict access to ESAs for the vast majority of Medicare beneficiaries who could safely benefit from these important medicines.

Careful, critical assessment of the complete literature and evidence base leads to only one conclusion, namely, that EPO-R and EPO play no discernable role in the development or progression of human tumors. While there are indeed published papers that provide data which at first blush appear consistent with the hypothesis of EPO-R involvement in tumor progression, more recent studies make plain that EPO-R is not expressed at significant levels in human cancer cells, and that EPO does not stimulate tumor growth.

We note the following:

- The EPO-R gene is not significantly amplified or overexpressed in solid tumors (Sinclair et al 2005). Hence the EPO-R gene does not behave as an oncogene in this respect. Expression of constitutively active forms of EPO-R does not transform non-hematopoietic cells (Longmore and Lodish, 1991).
- Conditions in humans that have hyperactivating mutations of EPO-R (truncations) or overexpress EPO (Chuvash Polycythemia) result in erythrocytosis and not increased tumor incidence (Arcasoy et al., 2002; Gordeuk et al., 2004; de la Chapelle et al., 1993).
- While the EPO-R gene is transcribed in most tissues and cell lines at low to moderate levels (Sinclair et al 2005), high level transcription of EPO-R is restricted to known EPO responsive erythroid precursor cells (Ulich et al.,1991; Ashihara et al.,1997; Billia et al., 2001)
- In addition, steady-state levels of EPO-R mRNA mirror those seen in normal tissues from which the tumor originates (Winter et al, 2005; Feldman et al 2006; Sinclair et al., 2005). Hence there is no evidence that augmented expression of EPO-R mRNA confers a survival advantage.
- Detection of EPO-R protein on the surfaces of cells is technically challenging because no satisfactory antibody reagents for detecting EPO-R exist. Indeed the most commonly used "anti-EPO-R" polyclonal antibody (*i.e.,* Santa Cruz C-20) was shown to detect heat shock protein HSP70 (Elliott et al 2006, Brown et al 2007; Ragione et al, 2007), in tumor cell lines and samples. Hence there are no well-founded data to suggest that cancer cells express immunologically detectable EPO-R molecules on their cell surface.

- Gold-standard experiments designed and conducted to detect cell surface EPO-R on tumor cell lines by measuring binding of radiolabeled EPO showed no evidence of EPO binding, and therefore no evidence that EPO-R is present on the surface of these cells, even though EPO-R protein was synthesized (Sinclair et al., 2005; LaMontagne et al., 2006). A few studies have reported surface EpoR expression on tumor lines using EPO binding studies (Westenfelder and Baranowski, 2000; Masuda et al., 1993; Okuno et al., 1990; Um et al., 2007) but receptor number or affinity was very low where measured, raising questions about the significance of the findings. In contrast, the same experimental method easily detects high affinity binding of EPO in normal red blood cell progenitor cells from human bone marrow (Fraser et al., 1988; Sawada et al., 1988; Broudy et al.,1991).
- Many groups have reported that tumor cell lines do not proliferate in response to ESAs (Mundt et al, 1992; Pedrazzoli et al, 1992a; Berdel et al, 1991; Rosti et al, 1993; Westphal et al, 2002; Liu et al, 2004; Dunlop et al, 2006; Rossler et al, 2004; LaMontagne et al, 2006; Gewirtz et al, 2006; Abdalla et al, 2005; poster abstract). Those in vitro studies that claim a response report modest (*i.e.,* 1.15- to 4.0-fold) effects on proliferation that are similar to background experimental noise, and only after exposure to high levels of EPO, far beyond those that can be attained in patients (Takeshita et al, 2000; Acs et al, 2001; Westenfelder and Baranowski, 2000; Feldman et al, 2006; Lai et al, 2005; Ogilvie et al, 2000).
- All rodent in vivo tumor models (23 independent studies with 31 cell lines and 1 primary tumor graft from a broad range of tumor types, including head and neck tumor cell lines) have demonstrated that ESAs alone do not enhance tumor growth or survival (Kelleher et al, 1996; Golab et al, 1998; Thews et al, 1998; Silver and Piver, 1999; Mittleman et al, 2001; Stuben et al, 2001; Thews et al, 2001; Golab et al, 2002; Blackwell et al, 2003; Kirkpatrick et al, 2006; Mittleman et al, 2003; Stuben et al, 2003; Sigounas et al, 2004; Van Halteren et al, 2004; Pinel et al, 2004; Ning et al., 2005; Shannon et al, 2005; Hardee et al, 2005; Hardee et al, 2006; LaMontagne et al, 2006; Kjellen et al, 2006; Bianchi et al, 2007; Tovari et al, 2005). Indeed in some studies ESAs have been shown to increase sensitivity of tumor cells to radiation or chemotherapy (tumor studies performed with chemotherapeutic agents, including cisplatin, cyclophosphamide, mitomycin C, gemcitabine, paclitaxel, and 5-FU) (Thews et al, 1998; Silver and Piver, 1999; Stuben et al, 2001; Thews et al, 2001; Kirkpatrick et al, 2006; Stuben et al, 2003; Sigounas et al, 2004; Pinel et al, 2004; Ning et al, 2005; Shannon et al, 2005; Tovari et al, 2005).

Taken together, these observations demonstrate that there is no compelling scientific evidence that ESAs promote tumor growth or survival. Importantly, Amgen is not alone in its assessment of the evidence regarding the putative role of EPO-R in tumor growth. As outlined in Table 1, the U.S. Food and Drug Administration's (FDA's) Oncologic Drug Advisory Committee (ODAC) Chair as well as the FDA shared concerns in this regard.

Table 1: Views of Clinical Oncology Experts on the EPO-R Hypothesis

Dr. S. Gail Eckhardt, Chair, FDA's ODAC 2007 (Eckhardt, 2007)

With respect to CMS basing its proposed policy on the EPO receptor hypothesis, "there is a huge amount of conflicting science on that issue, so I don't think that anybody can say definitively one way or the other, certainly not at ODAC."

FDA (FDA, 2007)

".. a direct relationship between the presence of erythropoietin receptors on tumor and tumor proliferation in response to exogenous erythropoietin has not been established. In vitro and in vivo data do not provide convincing evidence that erythropoietin promotes tumor growth and proliferation."

Stefan Constantinescu, MD, PhD; Ludwig Institute for Cancer Research and Institut de Duve, Brussels, Belgium (Constantinescu, 2007)

"In your document, data claiming a role for EpoR in tumor progression, angiogenesis and decreased survival are presented as established, accepted and valid, while they are preliminary, poorly controlled, insufficiently demonstrated and quoted due to the notoriety of the subject, and not because of their intrinsic quality. For many of those studies, others with opposing conclusions have been published, yet that data appears to have been overlooked."

Clive R Taylor, MD D.Phil., Department of Pathology and Laboratory Medicine, Keck School of Medicine, University of Southern California (Taylor, 2007)

"In summary, CAG #000383N – The Use of Erythropoiesis Stimulating Agents in Cancer and related Neoplastic Conditions, is a complex document, extensively researched, with an extensive bibliography, but it is incomplete in important areas, giving great credibility to preliminary and unproved work, and importantly not citing work that is contradictory to the preconceived position that the use of ESAs should be restricted in cancer sufferers."

If the clinical and scientific experts at the FDA and on the FDA's ODAC and at leading university laboratories do not find the data on EPO-R to be compelling in proving a link to tumor progression, it stands to reason that CMS should not restrict ESA coverage based on a hypothesis for which there is so little experimental support. After a thorough review of the evidence, we expect that CMS will revise this aspect of its proposed coverage policy in the final national coverage determination (NCD).

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