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Mr. Chairman, Representative Camp, and Members of the Committee:

Amgen is pleased to submit this written testimony for the record with regard to the use of Erythropoiesis-Stimulating Agents (ESAs) in Medicare beneficiaries with End-Stage Renal Disease (ESRD).

Amgen has pioneered the development of innovative medicines – ESAs – that safely and effectively treat anemia when used according to the U.S. Food and Drug Administration (FDA)-approved prescribing information. EPOGEN<sup>®</sup> (Epoetin alfa) is an ESA developed by Amgen scientists using recombinant DNA technology which has the same biological effects as naturally occurring erythropoietin. Nearly every patient with ESRD does not produce adequate amounts of erythropoietin, and consequently suffers from anemia (lack of red blood cells). EPOGEN<sup>®</sup> has been shown to increase hemoglobin levels (amount of red blood cells) and reduce the need for red blood cell transfusions; indeed the development of EPOGEN<sup>®</sup> as a therapeutic has been hailed as one of the major breakthroughs in treatment for dialysis patients.

Over recent months, new clinical trials published in November 2006 have raised important questions regarding the safe and appropriate use of ESAs in patients with kidney disease. These questions primarily arose from two studies conducted in non-dialysis patients with kidney disease,<sup>1</sup> and were also influenced by an earlier study, the Normal Hematocrit Cardiac Trial (NHCT) published in 1998, that was conducted in hemodialysis patients with pre-existing chronic heart failure or ischemic heart disease.<sup>2</sup>

***It is important to note that all three of these studies evaluated ESAs when used to target hemoglobin levels that are higher than those recommended in the FDA-approved product labels.***

Additionally, several recent oncology studies highlighted important potential safety risks of ESAs when used in off-label and experimental conditions – related to the potential for tumor progression and decreased survival. These issues are not directly relevant to dialysis patients who receive ESAs as physiologic replacement therapy, a very different situation that in cancer patients receiving cytotoxic chemotherapy.

On March 9, 2007, the FDA and Amgen announced that a black box safety warning was being added to all ESA labels, including new guidance for dosing and administration. Amgen immediately sent letters to all prescribing physicians and directed our professional staff to communicate these changes in full to prescribers. Amgen also sent letters to all physician prescribers in November 2006 communicating the results of two recent studies in non-dialysis patients with kidney disease.

These important safety issues will be discussed at a joint meeting of the FDA Cardiovascular and Renal Drug Advisory Committee and the Drug Safety Advisory Committee in September.

Amgen is committed to ensuring that our ESA medications are used in the most safe and effective manner. Amgen takes the recent questions that have arisen based on the results of the clinical trials conducted in patients with kidney disease not on dialysis targeting hemoglobin levels above 13 g/dL very seriously, and has undertaken a thorough review of all available clinical evidence. We appreciate this opportunity to comment on these important questions about the safe and appropriate utilization of ESAs in ESRD in this written testimony.

<sup>1</sup> Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med.* 2006;355:2085-98; Drüeke TB, Locatelli F, Clyne N, et al, for the CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med.* 2006;355:2071-84.

<sup>2</sup> Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med.* 1998;339(9):584-90.

## **THE BENEFITS OF EPOGEN® AND ANEMIA THERAPY IN ESRD**

***EPOGEN® has revolutionized the treatment of anemia in dialysis patients, while virtually eliminating the need for red blood transfusions that compromise the potential for subsequent successful kidney transplantation.***

Anemia affects approximately 9 out of every 10 dialysis patients, and is a consequence of reduced production of the hormone erythropoietin by the kidney. ESRD patients with anemia can suffer from fatigue and weakness. Dialysis patients with anemia are at significantly higher risk for cardiovascular events, such as heart attack or stroke, and are more likely to die than dialysis patients without anemia. Anemia, defined as a hemoglobin concentration below 11 g/dL, is associated with increased risk of hospitalization and death. As a result of this increased risk for hospitalization, Medicare beneficiaries with hemoglobin concentrations less than 11 g/dL incur higher costs and healthcare utilization: Collins et al demonstrated that Medicare member-per-month expenditures for patients with hematocrit values 30% to < 33% (hemoglobin 10 to < 11 g/dL) were 10.6% higher than for patients with hematocrit values 33% to < 36% (hemoglobin 11 to < 12 g/dL).<sup>3</sup>

Before the availability of EPOGEN® more than a decade and a half ago, physicians had few options for treating anemia in dialysis patients, and had to rely on blood transfusions. Unfortunately, blood transfusions put patients at risk for complications such as blood-borne infections, iron overload, and antibody responses that limit the chances for a successful kidney transplant.

EPOGEN®, a genetically engineered form of erythropoietin, has the same biological effect as naturally occurring erythropoietin. EPOGEN® dramatically reduces the need for red blood cell transfusions. In the EPOGEN® registrational clinical trials that targeted hematocrit levels between 32% and 38% (hemoglobin 10.7 to 12.7 g/dL), the percentage of patients requiring red blood cell transfusions was reduced from 55% at study inception to 0%-4% following 13-24 weeks of therapy.<sup>4</sup> When used as directed by the FDA-approved package insert, EPOGEN® has been shown to be safe and effective in multiple clinical trials, and has over a decade and half of safety monitoring in real-world use in almost 1.4 million dialysis patients for a total exposure of approximately 3.8 million patient-years.

## **PATIENT SAFETY AND QUALITY OF CARE ISSUES RAISED BY THE COMMITTEE**

***The nephrology community consensus is that a hemoglobin target range of 11 to 12 g/dL minimizes risk and maximizes benefit in ESRD patients, but due to the severity of additional disease burden and inherent natural hemoglobin variability, dialysis patients are difficult to consistently maintain within this relatively narrow hemoglobin range.***

Recently, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI™) Anemia Working Group reviewed all of the published clinical trial data to date. This analysis included the two recent trials and the one older trial that have raised these safety issues. They examined clinical outcomes associated with higher or lower hemoglobin targets including the NHCT in hemodialysis patients with chronic heart failure or ischemic heart disease, the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study, and the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study. Based on this review, the NKF-KDOQI™ Anemia Work Group recommended that physicians *target* a hemoglobin in the range of 11 to 12 g/dL, and also stipulated that the *target* not be above 13 g/dL.<sup>5</sup>

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<sup>3</sup> Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol.* 2001;12(11):2465-73.

<sup>4</sup> Amgen data on file.

<sup>5</sup> National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI™). KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of haemoglobin. (Draft under review).

It is important to recognize that dialysis patients are seriously ill. Seventy percent of patients are on dialysis as a result of diabetes and hypertension.<sup>6</sup> These two conditions are also risk factors for cardiovascular disease. Cardiovascular complications are endemic in dialysis patients, and account for the high rate of morbidity and mortality in this fragile population.<sup>7</sup> In addition, inter-current events such as hospitalization and infection often lead to frequent episodes of inflammation, a condition which can dramatically decrease an individual patient's responsiveness to ESAs.

Because of the general poor health status of a typical dialysis patient and the natural variability in patient hemoglobin levels, it is difficult to consistently maintain hemoglobin within a narrow band such as between 11 and 12 g/dL.<sup>8</sup> Consequently, physicians write anemia management protocols to *target* a specific hemoglobin range with the intent of maximizing the number of patients with *achieved* hemoglobin concentrations within this targeted range. However, due to hemoglobin variability, patients targeted to a specific hemoglobin range will at various times have *achieved* hemoglobin concentrations that are above and below the target at various times.

***Worse patient outcomes such as cardiovascular events or death have been consistently shown to be associated with hemoglobin levels below 11 g/dL compared with temporary excursions above 12 g/dL.***

It is well documented in both domestic and international studies that hemoglobin levels of less than 11 g/dL in dialysis patients are associated with increased hospitalization, healthcare expenditure, and mortality.<sup>9</sup>

In a recent study using United States Renal Data System (USRDS) data, Gilbertson et al demonstrated that patients with hemoglobin concentrations below 11 g/dL have the greatest risk for adverse clinical outcomes, and even transiently low hemoglobin concentrations are associated with worse outcomes than transiently high or persistently high hemoglobin concentrations above 12.5 g/dL.<sup>10</sup> Thus, these temporary high excursions must not be confused with the risks observed with targeting patient hemoglobin levels greater than 13 g/dL as was done in both the NHCT study in dialysis patients and the CREATE and CHOIR studies in nondialysis patients with kidney disease.

As a result of the numerous analyses demonstrating that achievement of hemoglobin levels below 11 g/dL is associated with adverse clinical outcomes, physicians strive to achieve maximum benefit by decreasing the percentage of patients with hemoglobin levels less than 11 g/dL at any time. Furthermore, CMS has independently established the percentage of patients with hemoglobin levels above 11 g/dL as a Clinical Performance Measure (CPM) for all dialysis clinics, and publishes this data on its website. Finally, the community and CMS recognize that when striving to achieve hemoglobin levels above 11 g/dL, hemoglobin concentrations fluctuate and often exceed the upper bound of the target range, temporarily.

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<sup>6</sup> USRDS Annual Data Report 2006.

<sup>7</sup> Sarnak MJ. Cardiovascular complications in chronic kidney disease. *Am J Kidney Dis.* 41(S5):S11-S17.

<sup>8</sup> Fishbane S and Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int.* 2005;68(3):1337-43.

<sup>9</sup> Wolfe RA, Hulbert-Shearon TE, Ashby VB, et al. Improvements in dialysis patient mortality are associated with improvements in urea reduction ratio and hematocrit, 1999 to 2002. *Am J Kidney Dis.* 2005 Jan;45(1):127-35; Locatelli F, Pisoni RL, Combe C, et al. Anemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS) *Nephrol Dial Transplant.* 2004 Jan;19(1):121-32; Volkova N and Arab L. Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. *Am J Kidney Dis.* 2006 Jan;47(1):24-36; Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol.* 2001;12(11):2465-73.

<sup>10</sup> Gilbertson D, Ebben J, Bradbury B, et al. The effect of hemoglobin variability & trends on mortality. American Society of Nephrology 39th Annual Scientific Meeting. San Diego, CA. November 14-19, 2006. Poster SA PO032.

***The majority of patients are not being maintained at hemoglobin levels above 12 g/dL.***

As discussed above, dialysis patients exhibit extensive variability in hemoglobin levels. ESAs are titratable drugs and ESA doses are adjusted in response to changes in patient hemoglobin concentrations over time in dynamic fashion. Targeting a hemoglobin in a dialysis patient is not like setting the cruise control in your car; it involves constant monitoring and ESA dose adjustments when hemoglobin values fall out of range. A number of studies in dialysis patients have provided a cross-sectional, or “snapshot”, view of hemoglobin concentrations for the entire dialysis population showing that at a *single* point in time, 50% of patients may have hemoglobin levels above 12 g/dL. However, because the majority of these hemoglobin concentrations above 12 g/dL are only transient, this snapshot view of the data does not accurately describe the natural fluctuations in patient hemoglobin levels over time, nor does it capture the consistent pattern of physician-directed ESA dose adjustment in response to out of target hemoglobin levels. The majority of physicians seek to achieve hemoglobin levels of greater than 11 g/dL and less than or equal to 12 g/dL.

Due to hemoglobin variability, 90% of patients have hemoglobin levels that move from within the recommended targeted hemoglobin range (11 to 12 g/dL) to above or below the targeted range over time when the data are looked at longitudinally instead of cross-sectionally. This is the difference between a “snapshot” (cross-sectional point in time) versus a “movie” (longitudinal view over time).<sup>11</sup> This critically differentiating concept was illustrated by Ebben et al in an analysis examining 152,846 patients over a 6 month period in 2003. The study found that only 2.0% of patients had hemoglobin levels that were persistently maintained at greater than 12.5 g/dL for a six month period, but 68.4% of patients had hemoglobin levels that were above 12.5 g/dL at least once during the same timeframe.<sup>12</sup> Similarly, Amgen has analyzed data and found that 83% of hemoglobin excursions above 12 g/dL return back below 12g/dL within 3 months.<sup>13</sup>

When hemoglobin levels exceed the upper bound, physicians adjust ESA doses downward, with the objective of returning hemoglobin levels to within target.

***An important finding is that the tendency to decrease ESA doses in response to hemoglobin levels being above 12 g/dL has increased as a result of recent ESA label changes and the CMS Erythropoietin Monitoring Policy (EMP).***

As of April 2007, 81% of hemoglobin excursions above 13 g/dL are followed by a dose reduction within 30 days compared to 72% in November 2005 when the EMP was announced. Data also demonstrate more ESA dose reductions occur following hemoglobin excursions between 12 g/dL and 13 g/dL since the ESA label change was communicated in March 2007. In April 2007, 49% of hemoglobin excursions between 12 g/dL and 13 g/dL are followed by an ESA dose reduction within 30 days, as compared with 37% in January of 2007. In addition, in some instances physicians implement a dose reduction after 30 days. There is a corresponding increase in the number of patients with hemoglobin levels in the 11 to 12 g/dL range, and the percentage of patients with hemoglobin levels above 13 g/dL has declined from 26% in January of 2007 to 23.6% in April of 2007.<sup>14</sup>

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<sup>11</sup> Ebben JP, Gilbertson DT, Foley RN, et al. Hemoglobin level variability: Associations with comorbidity, intercurrent events, and hospitalizations. *Clin J Am Soc Nephrol.* 2006;1:1205-10; Rubin RJ and Mendelson DN. Translating guidelines into policy. *Clin J Am Soc Nephrol.* 2007;2:209-10.

<sup>12</sup> Ebben JP, Gilbertson DT, Foley RN, et al. Hemoglobin level variability: Associations with comorbidity, intercurrent events, and hospitalizations. *Clin J Am Soc Nephrol.* 2006;1:1205-10;

<sup>13</sup> Amgen data on file

<sup>14</sup> Amgen data on file.

***Surveillance data from U.S. dialysis patients does not suggest evidence of increased mortality when ESAs are a routine component of care for dialysis patients.***

Surveillance of nearly 100% of the U.S. ESRD population via the USRDS shows that mortality rates have declined since the introduction of EPOGEN® (approximately 250 per 1,000 patient years at risk in 1989 versus 220 in 2004), coincident with the rise in population hemoglobin levels. While not proof of causality, these data do not suggest evidence of increased mortality when ESAs are a routine component of care for this very fragile dialysis patient population.<sup>15</sup>

These associations from the entire population level data appear to be at odds with correlations of individual patient data. One publication has suggested that patients receiving higher ESA doses are more likely to die, and has suggested that the high ESA doses cause these adverse events.<sup>16</sup> Similar correlations can be found between doctor visits and hospitalizations and death: the more one visits a doctor or is hospitalized, the greater the likelihood of death. It does not follow, however, that doctors and hospitals *cause* death. On the contrary, it is common sense that those individuals who require physician and in-patient care are more likely to die than those who do not require medical attention.

This paradox is called “confounding-by-indication”, and it occurs when there is an underlying factor (i.e., being ill) that is associated with two parallel outcomes (hospitalization and mortality). Those parallel outcomes will then also be correlated: both hospitalization and mortality rates increase with more seriously ill patients. A similar effect can be seen in the association between ESA dose and mortality. Dialysis patients who are relatively more ill have lower hemoglobin levels and may be relatively less responsive to ESAs, and thus physicians prescribe higher ESA doses in the attempt to achieve target hemoglobin levels. However, these relatively more ill dialysis patients are simultaneously more likely to die in addition to receiving higher ESA doses. This does not provide conclusive evidence that higher ESA doses *cause* increased mortality.

Fortunately, specific analytical methods have been developed to address the epidemiological problem of confounding-by-indication. They adjust for the degree of underlying illness in the population. When these appropriate techniques are applied to dialysis patients, they do not reveal an association between higher ESA doses and increased mortality. In fact, these adjusted analyses demonstrate that the achieved hemoglobin is a stronger predictor of better or worse outcome than is the ESA dose administered.

While there does not appear to be a causal relationship between ESA dose and mortality, Amgen recognizes that there remain unanswered questions regarding hemoglobin and ESA dose, especially in patients who require high doses of ESAs to achieve modest increases in hemoglobin (i.e., hyporesponsive patients). Amgen is evaluating ESA therapy in hyporesponsive patients based on all available data and is updating the FDA in an ongoing manner regarding the insights and findings. We are also informing CMS and the renal community on our findings.

***PAYMENT POLICY ISSUES RAISED BY THE COMMITTEE***

***ESA doses have increased in the U.S. in concert with substantial improvements in the quality of care, growth in the ESRD population, increased comorbidity burden, and increased racial disparities in ESRD – not due to inappropriate physician utilization or financial incentives.***

Medicare spending, as well as doses of EPOGEN® administered to U.S. dialysis patients, has increased since the introduction of this life-changing therapy due to four primary factors:

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<sup>15</sup> USRDS Annual Data Report 2006.

<sup>16</sup> Zhang Y, Thamer M, Stefanik K, et al. Epoetin requirements predict mortality in hemodialysis patients. *Am J Kidney Dis.* 2004;44:866-76.

- *Improvement in hemoglobin outcomes*—According to the USRDS 2006 Annual Data Report and the CMS 2005 Annual Report for the ESRD Clinical Performance Measures Project, the percentage of patients with hemoglobin concentrations below 11 g/dL has decreased from 84% in 1991 to 17% in 2004.<sup>17</sup> This is a remarkable achievement by the nephrology community and a benefit to patients.
- *Comorbidity burden*—The percentage of ESRD patients with diabetes has increased over time from 59% to 66% in whites and from 60.6% to 66.3% in blacks respectively from 1995 to 2004. It has been observed that diabetic patients and patients with other comorbidities often require higher ESA doses.<sup>18</sup>
- *Increased racial disparities*—Racial minorities are also disproportionately represented in the ESRD population and this trend has increased over time: approximately one-third are African-American, and 1 in 7 are Hispanic. African-Americans in particular receive higher ESA doses to achieve similar hemoglobin levels as other patient subgroups.<sup>19</sup>
- *Growth in the number of patients on dialysis*—USRDS reports that prevalent dialysis patients have more than doubled since 1988. This growth in dialysis patients means that more patients require treatment which increases Medicare spending.<sup>20</sup>

A recent article in the New York Times indicated that ESA doses in the U.S. are twice that observed in Europe.<sup>21</sup> However, the article did not describe the achieved hemoglobin levels in the U.S. compared with EU countries, or other differences in the U.S. and EU patient populations that impact ESA dose requirements.

- The U.S. had the second highest hemoglobin level, a marker of quality care, of all the countries studied (the best hemoglobin outcome was observed in Sweden, which had the second highest unadjusted mean ESA dose).<sup>22</sup>
- The differences in ESA dose across world regions can be explained in part by differences in patient comorbidities, race, and dialysis vascular access type.<sup>23</sup> This has been shown in the Dialysis Outcomes and Practice Patterns Study (DOPPS), the largest global registry of dialysis patients.

The most recent data suggests that ESA doses are stabilizing. The Medicare Payment Advisory Commission (MedPAC) indicated in its March 2007 Report to Congress that there has been a 0.6% decline in the EPOGEN<sup>®</sup> dose from 2004 to 2005.<sup>24</sup>

***Current Medicare payment policy for ESRD drugs, average sales price (ASP) + 6%, has reduced Medicare expenditures for ESRD drugs in general, and for ESAs specifically, thereby minimizing incentives for ESA overutilization.***

As already discussed above, the evidence demonstrates that most ESA dosing decisions are appropriate; i.e., ESA doses are adjusted up or down in response to out-of-target hemoglobin levels, and there is no compelling evidence of

<sup>17</sup> USRDS 2006 Annual Data Report, CMS' 2005 Annual Report ESRD Clinical Performance Measures Project

<sup>18</sup> USRDS 2006 Annual Data Report; Bárány P, Divino Filho JC, Bergström J. High C-reactive protein is a strong predictor of resistance to erythropoietin in hemodialysis patients. *Am J Kidney Dis.* 1997;29(4):565-8; Del Vecchio L, Pozzoni P, Andrulli S, et al. Inflammation and resistance to treatment with recombinant human erythropoietin. *J Ren Nutr.* 2005;15(1):137-41; Hsu SP, Peng YS, Pai MF, et al. Influence of relative hypoparathyroidism on the responsiveness to recombinant human erythropoietin in hemodialysis patients. *Blood Purif.* 2003;21(3):220-4; Ifudu O. Patient characteristics determining rHuEPO dose requirements. *Nephrol Dial Transplant.* 2002;17(Suppl5):38-41.

<sup>19</sup> USRDS 2006 Annual Data Report

<sup>20</sup> USRDS 2006 Annual Data Report

<sup>21</sup> Berenson and Pollack The New York Times, May 9, 2007

<sup>22</sup> Pisoni RL, Bragg-Gresham JL, Young EW, et al. Anemia management and outcomes from 12 countries in the dialysis outcomes and practice patterns study (DOPPS). *Am J Kidney Dis.* 2004;44(1):94-111.

<sup>23</sup> Goodkin DA, Bragg-Gresham JL, Koenig KG, et al. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 14:3270-3277, 2003; Pisoni RL, Young EW, Dykstra DM, et al. Vascular access use in Europe and the United States: Results from the DOPPS. *Kidney Int* 61:305-316, 2002.

<sup>24</sup> Medicare Payment Advisory Commission. Report to the Congress: Medicare Payment Policy. March 2007

inappropriate utilization. However, the announcement for this hearing suggested the existing Medicare system may incentivize overutilization of ESAs, at higher costs to taxpayers and risk to patients. The data suggest otherwise.

In fact, Medicare spending on ESRD drugs has been reduced under the ASP+6% system. According to MedPAC in its March 2007 report to Congress, the use of the ASP+6% methodology lowered Medicare payment for ESRD drugs by about 10% from 2004 to 2005 (a \$300 million reduction) and shifted drug profits to the dialysis add-on payment.<sup>25</sup>

The Medicare per unit payment limit for EPOGEN<sup>®</sup> also has decreased under the ASP+6% system, declining almost 7% since ASP-based reimbursement was instituted (Q4 2005 versus Q3 2007). Furthermore, while MedPAC did not provide a dollar amount for total Medicare EPOGEN<sup>®</sup> spending in its 2007 March report to Congress, figures included in the report show a slight decline in total EPOGEN<sup>®</sup> spending between 2004 and 2005.

Changes to ESRD drug reimbursement from the ASP+6% methodology may result in serious unintended consequences to specific dialysis populations, in particular those patients that are treated by smaller, independent dialysis facilities, including in rural areas and centers located in underserved urban areas. Small dialysis providers may just be breaking even on ASP+6% reimbursement. ASP is a weighted average of all prices and the Department of Health and Human Services Office of the Inspector General has found that smaller providers have higher drug acquisition prices than larger providers.<sup>26</sup> If the payment rate were changed or lowered, smaller dialysis facilities may lose money in an effort to provide needed drugs to their patients, potentially forcing these facilities to close and inhibiting sustained access to quality care for dialysis patients nationwide.

***New analyses of ESA utilization data since the FDA updated the ESA labels in March 2007 reinforce the recommendation that a change in the EMP is not necessary at this time.***

CMS developed the EMP after several years of extensive deliberation and consultation with the nephrology community. CMS and the nephrology community have long recognized the need for CMS ESA payment policies in ESRD to account for the temporary fluctuations of hemoglobin levels that commonly occur. When physicians target hemoglobin levels between 10 g/dL and 12 g/dL (consistent with the prior FDA-approved label hemoglobin target), the majority of those patients – even those on a stable dose of EPOGEN<sup>®</sup> – can experience temporary elevations above 12 g/dL, as discussed earlier.

Prior to the implementation of the EMP, analyses demonstrated that ESA dosing decisions were generally consistent with the FDA-approved product labels. Although patients may have temporary excursions above 12 g/dL, 83% of hemoglobin concentrations above 12 g/dL return below 12 g/dL within three months, and thus it does not appear that physicians are maintaining patient hemoglobin levels persistently above 12 g/dL.<sup>27</sup>

Early results post-EMP implementation demonstrate stability of population hemoglobin levels and ESA doses.<sup>28</sup> Amgen analysis of data collected since the EMP implementation suggests that 81% of physicians are reducing ESA doses within 30 days when hemoglobin exceeds 13 g/dL, compared to 72% at the time the EMP was announced in November 2005.<sup>29</sup>

Additionally, newly analyzed data collected following the recent ESA label changes show the percentage of patients with hemoglobin concentrations above 13 g/dL has been reduced with a corresponding increase in the number of patients in the 11 to 12 g/dL range, and there is an increased frequency of ESA dose decreases made in response to

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<sup>25</sup> Medicare Payment Advisory Commission. Report to the Congress: Medicare Payment Policy. March 2007

<sup>26</sup> Department of Health and Human Services Office of the Inspector General. Medicare Reimbursement for Existing End stage Renal disease Drugs. May 2004. OEI 03-04-00120.

<sup>27</sup> Amgen data on file.

<sup>28</sup> Ofsthun NJ and Lazarus JM. Impact of the change in CMS billing rules for erythropoietin on haemoglobin outcomes in dialysis patients. *Blood Purif.* 2007;25:31-5; Amgen data on file.

<sup>29</sup> Amgen data on file.

achieved hemoglobin between 12 and 13 g/dL, as well as above 13 g/dL. As of April 2007, 49% of hemoglobin excursions between 12 g/dL and 13 g/dL are followed by an ESA dose reduction within 30 days, as compared with 37% in January of 2007.<sup>30</sup> In addition, in some instances physicians implement a dose reduction after 30 days. We anticipate that additional changes to physician ESA prescribing trends will continue.

***Payment changes for ESAs in ESRD based on an insufficient analysis of scientific data could lead to negative outcomes for patients and for health care in the U.S.***

Amgen believes that any change to the ESRD payment system should have a strong policy or clinical rationale, and any new system should maintain patient quality of care, ensure patient access, and be financially viable for dialysis providers, patients, and taxpayers. As this document describes, there does not appear to be a compelling policy or clinical rationale to make fundamental changes to the ESRD payment system based on the best available scientific evidence and utilization data. Congress should carefully consider the potential for negative patient outcomes as an unintended consequence of payment changes that are not carefully designed, considered, and implemented.

Accordingly, Amgen does not believe that Congress should consider implementing a single bundled payment for drugs and dialysis services in dialysis until the Medicare Prescription Drug, Modernization, and Improvement Act (MMA) mandated CMS demonstration project to test a bundled payment in ESRD is completed. As bundled payment systems create powerful financial incentives to save money by underutilizing and withholding needed medical services, bundling methodologies must be balanced by a robust and clinically valid risk-adjustment system, as well as an agreed-upon set of quality safeguards, lest they result in the under-treatment of vulnerable dialysis patients. In particular, there may be serious unintended consequences to specific dialysis populations, such as those residing in rural areas and those receiving dialysis care in centers located in underserved urban areas from independent dialysis centers. Ultimately, if there is under-treatment of dialysis patients, not only would dialysis patients be harmed, it could cost taxpayers more money in hospitalizations and other patient care expenses. Congress recognized these complex issues, and mandated the conduct of a demonstration project before implementing a bundled dialysis and drug payment rate.

ESRD patients represent a seriously ill and vulnerable patient group, at high risk of death, with minorities disproportionately represented. Even among ESRD patients, there are some who are more gravely ill and require significantly greater health care intervention. Unless Medicare appropriately reimburses for these patients, even one or two such patients in a single dialysis center can literally “tip the scales” and cause a provider to lose money and even risk closure. Many believe that the risk is highest for the small dialysis organizations that serve poor patients in rural areas.

Other changes to ESA reimbursement policy could also have serious consequences for patients and providers. Changes to ASP+6% reimbursement, a system that has reduced spending and saved taxpayer dollars, could in particular harm smaller dialysis providers and the patients they service. Changes that mandate specific physician treatment decisions, such as mandating a particular ESA route of administration, also should be avoided.

Any of these changes could lead to unintended consequences including:

- Poorer quality of care, as dialysis providers may need to make compromises to offset lower overall reimbursement.
- Higher overall Medicare costs as a result of poor quality dialysis care.
- Threats to access to quality care for patients treated in small dialysis facilities in both rural and underserved urban areas. Small clinics may begin to avoid more ill/costlier patients in order to control costs, or even close as a result of financial burden.

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<sup>30</sup> Amgen data on file.

Finally, given the evolving data on physician prescribing of ESAs since the announcement of the revised FDA product labels and implementation of the EMP, it may be inappropriate for Congress to implement new legislation or direct CMS to alter the existing reimbursement paradigm for ESAs prior to allowing the Agencies and community to review and respond to this most recent and highly relevant information.

## **CONCLUSION**

In conclusion, Amgen thanks the Committee for the opportunity to submit written testimony. We are proud of EPOGEN<sup>®</sup>'s long history of safely and effectively treating anemia in ESRD patients. We stand alongside the physicians, nurses and other healthcare providers in supporting the best possible care for highly vulnerable kidney disease patients. Amgen remains concerned that legislation based on an insufficient analysis of relevant clinical data could result in unintended negative consequences for patients and for U.S. health care.