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STATEMENT OF

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INTRODUCTION

Mr. Chairman and Members of the Committee, I am John K. Jenkins, M.D., Director of the Office of New Drugs within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to participate in this hearing regarding erythropoiesis-stimulating agents (ESA).

In my testimony, I will provide background information on the drug approval process in general, and will discuss FDA's regulatory history related to ESA products.

DRUG APPROVAL PROCESS

Before any new drug is approved for marketing in the United States, FDA determines whether the data submitted by the product's sponsor (usually the manufacturer) in the new drug application (NDA) or biologics license application (BLA) show the product to be safe and effective for its intended use. Prior to the submission of an NDA or BLA, a sponsor generally conducts a series of clinical trials to assess the effects of the experimental new product in humans. To conduct these clinical trials in the U.S., the sponsor submits an investigational new drug (IND) application to FDA. If FDA finds the manufacturing and supportive laboratory and animal data sufficient to support use of the experimental product in humans, clinical trials in humans can begin.

Generally, there are three phases of studies in the investigation of a new drug or biologic product. Phase I trials are conducted in a small number of people to gather early safety information that will support conducting studies in larger numbers of people and to determine how the drug works in humans (e.g. metabolism, absorption, and excretion). If those trials are successful, Phase II trials are designed to study the effects for a particular use of the new drug, including how people respond to various dosages or dose regimens. In Phase II trials, patients are monitored closely for any side effects or particular risks that might be associated with the product under study. If Phase II trials are successful, Phase III trials are designed to build on the information learned in the earlier trials in order to establish the safety and effectiveness of the new drug. If the new drug successfully completes all phases of the investigation, the sponsor assesses the data and decides whether to submit a marketing application (NDA or BLA) for the Agency's review. Following submission of an NDA or BLA, FDA must decide whether all of the information (clinical trial results and animal and laboratory data, and information on the manufacture of the product) submitted by the new drug's sponsor adequately demonstrates that the product is safe and effective under the conditions of use in the drug's proposed labeling.

It is important to realize, however, that no drug is absolutely safe. There is always some risk of adverse reactions with drugs. FDA's approval decisions, therefore, always involve an assessment of the benefits and the risks for a new drug. These approval decisions also apply when a previously approved drug is under consideration for a new use (i.e. a new indication). When the benefits of a new drug are thought to outweigh the risks, and if the labeling instructions allow for safe and effective use, FDA considers the new drug safe for approval and marketing.

DRUG SAFETY: A RISK-TO-BENEFIT BALANCE

FDA has a strong record on issues of safety and remains the world's gold standard for drug regulation. In reflecting on the concept of drug safety, it is important to remember not only that no drug is absolutely safe, but also to recognize that sometimes information about the safety of a drug emerges only after the drug is on the market. Because all possible side effects of a drug cannot be anticipated on the basis of pre-approval studies – which usually involve only several hundred to several thousand patients -- FDA maintains a system of post-marketing surveillance and risk assessment programs to identify adverse reactions and safety risks that did not appear in the clinical trials conducted to gain approval to market the drug. The Agency uses this information to update drug labeling, and, on rare occasions, to re-evaluate the decision to approve the drug.

FDA's role as a public health agency is to protect and promote the nation's health by assuring that patients and health care providers have access to safe and effective drugs as well as accurate benefit and risk information to make informed choices. Weighing the impact of the potential safety risks for drugs against their known benefits, for individual patients and the public health as a whole, is a multifaceted and complex process, involving scientific as well as public policy issues. As described below, FDA has approached the issues associated with ESA products mindful of our important role as a public health agency, and the need to make the best regulatory decisions we can for patients and health care providers.

ERYTHROPOIESIS-STIMULATING AGENTS (ESAs)

Erythropoiesis-stimulating agents are man-made versions of a natural protein known as erythropoietin. Erythropoietin is made by the kidney and stimulates the primitive cells in the bone marrow to produce red blood cells, the main oxygen-carrying cells in the blood. An increase in the number of red blood cells is commonly indicated by an increase in the laboratory measures known as the blood hemoglobin level and the blood hematocrit. An abnormally low hemoglobin or hematocrit value is one of the hallmarks of anemia.

Multiple conditions may cause anemia, including the loss of erythropoietin due to the destruction of kidney function by chronic kidney disease. Other conditions that may cause anemia are generally unrelated to a deficiency of erythropoietin and are exemplified by anemias due to iron deficiency, certain vitamin deficiencies, hemorrhage, and various intrinsic bone marrow disorders. Generally, regardless of the cause of anemia, blood transfusions may be necessary to relieve patient symptoms and maintain life when the anemic condition becomes severe. The main goal of treatment with ESAs is to increase the number of red blood cells in patients with the specific types of anemia that are responsive to the ESAs so that blood transfusions are not needed.

Procrit/Epogen (Epoetin alfa)

FDA approved Procrit/Epogen in 1989 for the treatment of anemia associated with chronic renal failure (CRF), (including end stage renal disease) patients and patients not on dialysis) to elevate or maintain the red blood cell level and to reduce the need for transfusions in these patients.

Epoetin alfa is manufactured by Amgen and marketed under the two proprietary names of Epogen and Procrit. Except for the difference in the marketing names for Epoetin alfa, the Epogen and Procrit labeling are identical.

The initial approval of Procrit/Epogen for use in treating anemia due to chronic renal failure was followed by approval for additional indications for use in patients with certain cancers with anemia due to concomitant chemotherapy, in patients with HIV-infection with anemia due to anti-viral drugs, as well as to decrease the need for transfusion in patients scheduled for certain types of surgery.

Epogen is distributed by Amgen for use in dialysis patients. Procrit is distributed by Ortho Biotech (a subsidiary of Johnson & Johnson) for use in anemic chronic renal failure patients who are not on dialysis, and for the three non-renal indications described above.

Aranesp (Darbepoetin alfa)

FDA approved Darbepoetin alfa (Aranesp) in 2001 for the treatment of anemia associated with chronic renal failure, including patients receiving dialysis as well as patients not on dialysis. The indication for Aranesp use was expanded in 2002 to include use treatment of anemia caused by chemotherapy in patients with some types of cancer. Aranesp is manufactured and marketed by Amgen.

FDA POST-MARKETING ACTIONS

Evaluating the benefits and risks of all drug products is a dynamic process—and FDA's ongoing evaluation of ESAs is no exception. FDA has received and is continuing to receive data from several different clinical trials studying the risks and benefits of ESAs, primarily in clinical trials of unique dosing regimens or clinical situations not described in the labeling (off-label unapproved uses). The product labeling for all U.S. marketed ESAs has been updated several times since the original approvals to incorporate new safety information. The most recent labeling is based upon the submission of extensive new safety information late in 2006 and early 2007. These data prompted a major revision of the ESA labels to include, for the first time, a boxed warning. I will discuss initially the major labeling safety updates and actions that preceded the activities of late 2006 and early 2007.

In 1996, FDA approved changes to the Procrit/Epogen labeling adding a new subsection in warnings regarding higher mortality with treatment regimens intended to maintain a higher hematocrit level in patients with anemia due to chronic renal failure who were undergoing dialysis. The Normal Hematocrit Study provided the first evidence of important cardiovascular safety risks, including a risk for death, when ESAs were administered in dosages that resulted in hematocrit levels that were closer to the normal range, and higher than the target levels stated in the product labeling. With respect to another safety concern, in May 2003 and in October 2005, FDA approved revisions to the Warnings and Adverse Reaction sections of the labeling to include information regarding pure red cell aplasia, a risk related to rare immunological reactions among all patients receiving ESAs.

1. Actions Related to Labeling for Anemia Among Cancer Patients

In late 2003 and early 2004, FDA received clinical trial reports of risks for tumor promotion and increased mortality among cancer patients who were receiving ESAs in the treatment of chemotherapy-induced anemia. These risks were discussed at a May 2004 Oncologic Drugs Advisory Committee and subsequently, in 2004, ESA labels were revised to describe these trials and the risks for tumor promotion and death. These activities were accompanied by requests for additional clinical trials to more thoroughly evaluate the risks for ESA use among cancer patients.

2. Most Recent FDA Actions

More recently, FDA issued a series of public health advisories (November 2006, February 2007, and March 2007) describing further emerging safety information that applies to all patients as well as specific risks in cancer patients. In November 2006, FDA alerted health care professionals that a newly published clinical study ("Correction of Hemoglobin and Outcomes in Renal Insufficiency" [CHOIR] study, *New England Journal of Medicine*, November 16, 2006, discussed in more detail below) showed that patients treated with ESAs and dosed to a target hemoglobin concentration of 13.5 g/dL are at a significantly increased risk for serious and life-threatening cardiovascular complications, as compared to use of the ESA to target a hemoglobin concentration of 11.3 g/dL. FDA public health advisories emphasized that the study's findings underscored the importance of following the currently approved prescribing information for ESAs including the dosing recommendation that the target hemoglobin NOT exceed 12 g/dL.

In February 2007, FDA notified health care professionals of the results from a large clinical trial evaluating the use of an ESA to treat anemia in cancer patients not receiving chemotherapy. In this trial, patients received either Aranesp according to the approved dosing regimen or a placebo. Patients treated with Aranesp had a higher death rate and no reduction in the need for transfusions compared to those treated with placebo. FDA warned that the findings in the Aranesp trial also may apply to other ESAs, and furthermore, that the finding show that treating anemic cancer patients NOT currently on chemotherapy with an ESA may offer no benefit and may cause serious harm.

The most recent public health advisory in March 2007 outlined new safety information based upon the CHOIR trial and several newly reported trials conducted among cancer patients that prompted extensive revision of the ESA product labels. Concomitant with this March advisory, FDA posted an "Information for Health Care Professionals" sheet to further inform prescribers and other health care professionals about these important new safety findings. See: *http://www.fda.gov/cder/drug/infopage/RHE/default.htm*.

The revised product labeling from March 2007 included updated warnings, a new boxed warning, and modifications to the dosing instructions. The boxed warning, the strongest warning for an FDA approved product, advises physicians to use the lowest ESA dose that will gradually increase the hemoglobin level to a concentration sufficient to avoid the need for blood transfusions. Also, the boxed warning highlights the major safety risks for ESAs and important dosing information.

The March 2007 ESA label revisions were based upon recently completed trials that described an increased risk of death, blood clots, strokes, and heart attacks in patients with chronic kidney failure when ESAs were given at doses that resulted in higher than recommended hemoglobin levels. The label revisions also addressed recently reported trial findings for cancer patients, both when ESAs were given at doses intended to result in higher than recommended hemoglobin levels, and when ESAs were given to cancer patients whose anemia was not chemotherapy-related. The revised labeling also summarized the information from the trial that showed an increased risk for blood clots in patients following orthopedic surgery when ESAs were administered without the blood clot prevention measures described in the product label.

Because all ESAs have the same mechanism of action, FDA believes these new concerns apply to all ESAs and is re-evaluating how to safely use this product class. The new label changes are specifically summarized below:

- A new boxed warning states that prescribers should use the lowest dose of Aranesp/Epogen/Procrit that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion.

- The boxed warning also notes that Aranesp /Epogen/Procrit increased the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL.

- For cancer patients, the boxed warning notes that use of ESAs
    - shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy;
    - shortened overall survival and increased deaths attributed to disease progression in patients with metastatic breast cancer receiving chemotherapy; and
    - increased the risk of death in patients with active malignant disease not under treatment with chemotherapy or radiation therapy. ESAs are not indicated for this patient population.

- The boxed warning also notes that patients treated before surgery with ESAs to reduce allogeneic red blood cell transfusions had a higher incidence of deep venous thrombosis. Only Procrit/Epogen is approved for this indication.

Additional Warnings section information describes these increased risks for mortality, cardiovascular events, and tumor progression:

- *Increased Mortality and Cardiovascular Events* – the warnings now describe the results of new studies showing an increased incidence of cardiovascular and thrombotic events in patients with chronic renal failure, cancer patients on chemotherapy, and surgical candidates.

- *Potential for Tumor Growth Progression* – A new subsection in Warnings describes the new data and emphasizes the evidence for increased rate of tumor progression.

In addition, FDA has issued letters describing the new data to all active IND holders investigating new uses of ESAs. These letters described the new trial data and revised ESA labeling, advised discussion of this information with patients, investigators, and investigational review boards, and recommended re-consideration of the safety of studies in light of these new data.

FDA ADVISORY COMMITTEE INPUT

FDA often seeks advice from its advisory committees regarding emerging safety issues. Advisory committees provide independent, expert advice on scientific, technical, and policy matters related to the development and evaluation of products regulated by FDA. The advisory committee system enhances FDA's ability to protect and promote the public health and maintain the public trust by enabling the Agency to obtain the benefit of independent, professional expertise. Although advisory committees provide recommendations to the Agency, final decisions are made by FDA.

As previously noted, FDA convened a meeting of the Oncologic Drugs Advisory Committee (ODAC or the Committee), on May 4, 2004, so that FDA could present and seek advice regarding safety signals (evidence of adverse effects on survival and shorter time-to-tumor progression) observed in two studies. In addition to presenting data from these two studies (the ENHANCE and BEST studies discussed below), FDA presented the results of a study conducted under an agreed-upon post-marketing commitment to assess the tumor-stimulating potential of Procrit/Epogen. The Committee agreed that the results of these studies raised concerns that should be investigated through additional studies.

FDA convened ODAC again on May 10, 2007, to discuss the recently reported information on risks of ESAs, specifically, Aranesp, Epogen, and Procrit, for use in the treatment of anemia due to cancer chemotherapy. The results of the trials in patients with cancer were presented. The results of trials that have completed accrual but have not been analyzed were identified, and it was noted that these trials may provide additional information on tumor progression, mortality, and thromboses when ESAs are used at doses higher than recommended in patients with cancer.

ODAC recommended that the results of these trials be submitted for FDA review as soon as the data are available, that additional trials be conducted by the sponsors to evaluate the safety of the recommended doses, and that further marketing authorization be contingent upon additional changes in product labeling and additional trials. ODAC also recommended revisions to product labeling to provide more direction on safe use among cancer patients, as follows:

- That product labeling should specifically state that ESAs are not indicated for use in specific tumor types (breast cancer, head and neck cancer, and non-small cell lung cancer) studied in trials that showed adverse safety signals. The Committee did not specify which tumor types should be added.

- That product labeling should define a hemoglobin level in asymptomatic patients at which ESA should be initiated.

- That the hemoglobin level at which dosing should be suspended should remain, as described in the March 2007 revised labeling, at 12 g/dL.

- That product labeling should recommend discontinuation of ESAs following the completion of a chemotherapy regimen and re-evaluation of the degree of anemia with subsequent chemotherapy regimen(s).

FDA is working with the companies to address ODAC's recommendations. Also, FDA is planning discussion of ESA safety issues associated with the chronic renal failure indications at a Cardio-Renal Drugs Advisory Committee meeting later this summer.

DATA SUMMARY

I will now briefly review the clinical trials that have provided important new safety information since the original approval of ESAs. These trials may be grouped into three categories based upon the treated patient population: 1. Patients with chronic renal failure; 2. Patients with cancer; and 3. Patients undergoing surgical procedures.

1. Trials in patients with chronic renal failure

a. <u>Normal Hematocrit Study Evaluating Patients with CRF</u>

The first trial to raise serious concerns about the risks of ESAs was a report from a trial entitled, the Normal Hematocrit Study. FDA was informed of the results of the Normal Hematocrit Study in 1996 and incorporated the important safety information into the product labeling shortly following the review of the information. The Normal Hematocrit Study was designed to evaluate whether certain patients with chronic renal failure undergoing dialysis had fewer

cardiovascular complications if the ESA was administered to attain a higher hematocrit level as compared to a lower hematocrit level. However, the trial was terminated early because of the unexpected finding of more deaths and non-fatal myocardial infarctions in the patients randomized to the higher hematocrit target level. The 1996 labeling revision based upon this study recommended that the ESAs not be used to achieve hematocrit in excess of 36 percent, a value that corresponds to a hemoglobin level of 12 g/dL. This label revision was also accompanied by the sponsor's commitment to conduct a study that further examined the risk for thrombotic events (blood clots) among patients receiving ESAs. An increased thrombotic risk in association with ESA use was thought to be one of the potential causes for the safety risks detected in the Normal Hematocrit Study.

b. <u>Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study and Cardiovascular Risk Reduction by Early Treatment with Epoetin Beta (CREATE) study</u>

Two clinical trials and an editorial published in the *New England Journal of Medicine* in November 2006, addressed safety concerns about the use of ESAs in the treatment of anemia of chronic renal failure (CRF). The 1,400 subject Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study demonstrated increases in serious and potentially life-threatening cardiovascular events when Epoetin alfa (Procrit) was administered to reach higher target hemoglobin levels than lower target hemoglobin levels. The 600-subject Cardiovascular Risk Reduction by Early Treatment with Epoetin Beta (CREATE) study trended toward more cardiovascular events in a pattern similar to the CHOIR study, thus strengthening the findings of the CHOIR study. The CREATE study examined the use of Epoetin beta, a product not approved in the USA.

The CHOIR study was an open label study in which patients with anemia due to chronic kidney disease subjects were randomized to be dosed with Procrit to either a higher target hemoglobin (13.5 g/dL) or a lower target hemoglobin (11.3 g/dL). The primary endpoint was a time to event analysis for a composite cardiovascular endpoint (all cause mortality, congestive heart failure (CHF) hospitalization, non-fatal myocardial infarction [MI], or non-fatal stroke).

Procrit was administered as 10,000 U SC weekly and titration allowed to a maximum dose of 20,000 U weekly. Overall, 715 subjects were randomized to the high hemoglobin target and 717 randomized to the low hemoglobin target. At the end of the study, the average hemoglobin was 12.6 g/dL for the high target group and 11.3 g/dL for the low target group. The primary endpoint showed statistically significantly worse cardiovascular outcomes in the higher target hemoglobin group ($p = 0.03$ by log rank test) with a hazard ratio of 1.3 (95 percent CI 1.03, 1.74). The rates for the individual components of the composite primary endpoint were (high target hemoglobin vs. low target hemoglobin):

Death: 7.3% vs 5.0% ($p = 0.07$)

CHF hosp: 9.0% vs 6.6% ($p = 0.07$)

Non-fatal MI: 2.5% vs 2.8%

Non-fatal stroke: 1.7% vs 1.7%

The findings from the CREATE trial were generally less notable with respect to safety risks than the CHOIR trial, a finding that may relate to the smaller patient population enrolled in the CREATE study and other design features. In the CREATE trial, anemic patients not undergoing dialysis were treated with Epoetin beta to attain a hemoglobin level of 13 to 15 g/dL

or a level of 10.5 to 11.5 g/dL. The primary endpoint was similar to that for the CHOIR trial but included a few additional cardiovascular complications. Specifically, the endpoint consisted of any occurrence of sudden death, MI, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization, complications of peripheral vascular disease, or cardiac arrhythmia requiring hospitalization. Overall, the primary endpoint events occurred in 19 percent of the patients in the high hemoglobin target group and 16 percent of the patients in the low target group, a result that was not statistically significantly different (p=0.20).

The published CHOIR and supportive CREATE study findings underscore the importance of the warnings previously described in the labeling for Procrit, Epogen, and Aranesp regarding cardiovascular risks that include thrombotic events and increased mortality in hemodialysis patients who participated in the Normal Hematocrit Study. Importantly, the new data from the CHOIR study, combined with the findings previously reported from the Normal Hematocrit Study, showed that patients with anemia due to chronic renal failure (whether or not receiving dialysis) were at increased risk for serious cardiovascular complications when ESAs were administered to attain hemoglobin levels in excess of the 12 g/dL level recommended in the ESA product labels.

2. ESA Trials in Cancer Patients

Between 2001 and 2003, FDA became aware of the results of new trials that raised safety concerns for the use of ESAs in patients with cancer. Specifically, during this period, FDA received reports from three trials of ESAs in patients with cancer receiving chemotherapy. While one trial (N93-004) did not suggest harmful effects of the use of ESAs, the other two trials

(BEST and ENHANCE) demonstrated higher mortality and more rapid tumor progression when the ESAs were given in an unapproved manner, i.e., to maintain hemoglobin levels of greater than 12 g/dL. These findings were discussed at a May 2004 meeting of the ODAC and the new safety data were added to product labeling for ESA products shortly following that meeting. ODAC recommended that additional data be gathered to further evaluate these new safety concerns in patients with cancer receiving ESAs.

In late 2006 and early 2007, FDA was informed of several new trials in cancer patients that raised additional safety concerns. We have described these trials below.

a. <u>Danish Head and Neck Cancer Study</u>

In December 2006, the manufacturer of ESAs informed FDA of the interim results of the Danish Head and Neck Cancer Study Group trial (DAHANCA 10). This open-label, randomized trial compared radiation therapy alone to radiation therapy plus Aranesp in the treatment of advanced head and neck cancer. The trial assessed whether treating anemia to achieve and maintain a hemoglobin concentration of 14.0-15.5 g/dL during radiotherapy would improve local-regional disease control. The DAHANCA 10 data monitoring committee found that 3-year local-regional control in patients treated with Aranesp was worse than for those not receiving Aranesp ($p=0.01$). Overall survival time also favored those not treated with Aranesp, though this finding was not statistically significant ($p=0.08$). The data monitoring committee recommended the ESA treatment be stopped in the experimental arm on December 1, 2006. The DAHANCA 10 trial was similar in design and in outcomes to the ENHANCE trial noted above.

b. <u>Study in cancer patients NOT receiving chemotherapy</u>

FDA was notified in January 2007 of the results of a 989 patient, multi-center, double-blind, randomized, placebo-controlled trial of Aranesp (Darbepoetin alfa) in cancer patients with anemia who were not receiving chemotherapy. The target hemoglobin in the Aranesp treatment group was 12 g/dL. FDA's analysis of the primary study data demonstrated that Aranesp did not significantly reduce the need for red blood cell transfusions and showed an increase in mortality in patients receiving Aranesp compared to those receiving placebo (hazard ratio 1.30; 95 percent confidence interval: 1.07, 1.57).

c. <u>Study in non-small cell lung cancer patients</u>

FDA was notified in February 2007 of the final results of a double-blind, placebo controlled study that was designed to evaluate whether Epoetin alpha improved the quality of life for patients with non-small cell lung cancer who were not receiving chemotherapy. The Epoetin alfa dose was titrated to maintain a hemoglobin level of 12 to 14 g/dL. Though planned to enroll 300 patients, the study was closed to accrual in December 2003, after enrolling only 70 patients because its data monitoring committee found higher mortality in those treated with Epoetin alfa. It should be noted that although the study size was small, prognostic factors and extent of previous cancer treatments were reported to be well balanced between the study arms. Median time to death in those treated with Epoetin alfa was 68 days and significantly shorter than the median time to death of 131 days in those treated with placebo ($p = 0.04$), with the majority of deaths reported as due to disease progression. Also, treatment with Epoetin alfa did not significantly reduce the need for red blood cell transfusion or improve quality of life.

3. Trial in patients undergoing surgery

In 1996, the indication for use of Procrit/Epogen was broadened to include its use to reduce transfusion in patients with hemoglobin values between 10 and 13 g/dL scheduled to undergo non-vascular, non-cardiac surgery. In these patients, the ESA reduces the need for blood transfusions. The approval of this peri-surgical indication was accompanied by a commitment to complete a post-marketing study that explored the risk for thrombotic events among patients who were not receiving preventive therapy with anti-thrombotic drugs. As previously noted, the Normal Hematocrit Study had suggested that ESAs may increase the risk for thrombotic events in certain patients. The results of this post-marketing study were supplied in 2007. Specifically, FDA was notified in February 2007 of the preliminary results of a 681-patient, multi-center, randomized, open-label, non-inferiority trial of Procrit compared to the standard of care in adult patients undergoing elective spinal surgery. In this trial, the frequency of deep venous thrombosis in patients treated with Procrit was 4.7 percent (16 patients), a rate more than twice that of patients who received usual blood conservation care (2.1 percent, seven patients). Hence, this trial suggested that, in the peri-surgical setting, ESA use increases the risk for thrombotic events.

CONCLUSION

FDA's mission is to promote and protect the public health. A major component of that mission is to ensure that the American public has access to safe and effective medical products. At this time, FDA continues to believe that ESAs are safe and effective when used according to the recently revised product labeling, at the recommended dose and approved indication. The

revised labeling reflects the current knowledge regarding risks and benefits that patients and their physicians should consider. FDA continues to assess data as it becomes available.

Thank you for the opportunity to testify before the Committee today. I will be happy to respond to questions.