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SUMMARY

An FDA advisory panel refused to put a target ceiling of ~11 g/dL on hemoglobin levels for ESAs in patients with chronic renal failure (CRF) either on dialysis or pre-dialysis, but many members were not opposed to a target range of 10 to 11.3 or 11.5 g/dL. ♦ The FDA will likely identify a target range and perhaps put a ceiling on hemoglobin levels in the ESA labels in the next few weeks. ♦ New labeling will also address issues with cycling and hypo-responders to ESA therapy.

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FDA Advisory Panel Unclear on Limits on EPO Use in Kidney Patients

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Bad news for Amgen: The FDA is likely to put new limits on the use of erythropoiesis-stimulating agents (ESAs) in patients with chronic kidney disease (on dialysis and pre-dialysis) – and that means the Centers for Medicare and Medicaid (CMS) will probably limit reimbursement in line with the new FDA guidance. It appears the FDA is preparing both a target range, and perhaps a ceiling, on ESA use in renal patients, and the agency plans to announce the new label changes in the next few weeks.

The FDA's Cardiovascular and Renal Drugs Advisory Committee (CRDAC), in a joint meeting with the FDA's Drug Safety and Risk Management Advisory Committee (DSaRM) on Tuesday, September 11, 2007, refused to recommend a hemoglobin (Hb) target ceiling of ~11 g/dL for erythropoiesis-stimulating agent (ESA) use in patients with chronic renal failure (CRF) either on dialysis or pre-dialysis. However, the FDA may still be preparing a target range and perhaps a ceiling on ESA use in renal patients, and the agency plans to announce the new label changes in the next few weeks. The FDA presentation to the panel favored a ceiling of 11 g/dL on the label and a target range of 10 to 11.3 g/dL. The panel did not appear to convince the FDA that its approach was wrong.

There is no question that the ESA labels will be changed. The bottom line is that the FDA wants stricter labeling, and it is going to do just that. An FDA official said, "At the end of the day, we…want product labels to provide more useful directions." Leaving the label alone would not achieve that goal.

ESAs – epoetin alfa (manufactured by Amgen and marketed by Amgen as Epogen and by Johnson & Johnson as Procrit/Eprex) and darbepoetin alfa (Amgen's Aranesp) – are approved to treat anemia in patients with chronic kidney failure and in cancer patients whose anemia is caused by chemotherapy. Epogen and Procrit are also approved for patients scheduled for major surgery to reduce potential blood transfusions and for the treatment of anemia for certain HIV patients. These drugs were widely used off-label to treat patients with anemia of cancer not on chemotherapy and patients with chronic kidney disease not on dialysis until the CHOIR and CREATE trials raised questions last fall about their safety in the oncology setting and CMS restricted coverage in cancer patients.

In March 2007, the FDA ordered a "black box" warning on ESA labels, asking doctors to use the lowest dose possible to avoid the risk of heart attack and stroke. In May 2007, the FDA's Oncologic Drugs Advisory Committee (ODAC), citing concerns about safety, voted 15-2 that the FDA should impose additional

restrictions on the use of ESAs in cancer, and the panel unanimously agreed that additional safety trials are needed. Then, in July 2007 CMS limited coverage of ESAs. The FDA scheduled this meeting in order to get recommendations on label changes on ESAs used to treat CRF patients.

Ceiling

The panel voted 14-5 ***against*** new labeling language recommending a hemoglobin ceiling of ~11 g/dL for ESA use. However, it is very possible that the FDA will set a ceiling, probably at a hemoglobin under 12.

The FDA staff argued that clinical studies suggest that safety problems can occur above 12 g/dL, including higher mortality rates and serious cardiovascular problems, and FDA officials severely questioned the clinical benefits of epoetin alfa in patient performance, anemia symptoms, and quality of life. FDA reviewers said that randomized clinical trial data, not observational studies, should be relied on to come up with an ideal hemoglobin target, and that the best randomized clinical trial data available point to an ideal hemoglobin target of 10 g/dL for dialysis patients and 11.3 g/dL for pre-dialysis patients.

The panel rejected the FDA staff's proposal to establish a ceiling "not to exceed ~11 g/dL," but largely because panel members did not like the "not to exceed" language. This may have led some panel watchers to conclude, ***incorrectly***, that the idea of a ceiling is dead. After the meeting, Dr. Rafael Dwaine Rieves, acting director of the FDA's Division of Medical Imaging and Hematology products in the Center for Drug Evaluation and Research (CDER), said, "It was impressive that many of the committee members – not the majority, but many – did not feel comfortable with a single number (ceiling). Clinicians in general don't like the single number. They like a range, and the take home message of towards a range is an important one, and we will take that to heart…(But) I asked for a consensus, and there was no consensus."

One interpretation of his "take it to heart" comment could be: "Thanks, but no thanks. We'll do what we think is best, based on what facts and randomized clinical trial (RCT) data that we have."

Target dosing range

The panel did not give the FDA persuasive guidance on this. Given the panel's inability to come up with a specific target range, the FDA is almost certain to set its own target hemoglobin range, probably 10-11.5 g/dL, but perhaps 10-11.3 g/dL. The FDA probably will concentrate on the randomized clinical trial data, which point to a hemoglobin target of 11.3 g/dL.

The FDA presentation favored a target range of 10-11.3 g/dL, saying that the "ideal" hemoglobin target is 10 g/dL for hemodialysis (HD) patients and 11.3 g/dL for pre-dialysis patients. FDA staff argued that any evidence to support a hemoglobin target as high as 12 g/dL is "observational" in nature and "of limited utility." A reviewer noted that a majority of patients in the U.S. have a hemoglobin level >12 g/dL but said this is not necessarily inevitable and may be modifiable. The FDA's Dr. Rieves said, "We are not aware of a randomized clinical trial that demonstrates, in a convincing way, that a higher hemo-globin target is associated with less cardiovascular morbidity and mortality than a lower target."

The FDA staff suggested prospective, randomized, controlled, cardiovascular outcome studies to determine optimum hemoglobin targets and help in development of new dosing paradigms for hyporesponders, and the panel generally agreed with that.

Amgen wants the FDA to recommend a target range of 10-12 g/dL, with no ceiling. A hemoglobin target range of 10-12 g/dL was included in ESA product labeling from 1992 to 2007. However, the target range was removed in March 2007, when black box warnings were added to all ESA labels.

When discussing the FDA's first question concerning a ceiling of ~11 g/dL for patients on dialysis, the 19 panel members voted this way: four wanted to recommend a 10-12 g/dL range, one wanted a ceiling of 12 g/dL, six did not have any concrete ideas, one wanted a ceiling of 11 g/dL, and seven wanted a target range of 11-11.3 or 11.5 g/dL. In interpreting an advisory committee vote, the FDA generally puts a great deal of emphasis on the individual comments accompanying that vote than to the final tally for or against.

Cycling and hyporesponsive patients

The problems of cycling and hyporesponsive patients contribute to the muddle and should be addressed by conducting more studies, the FDA believes – and the panel generally agreed. An FDA official said, "A target of 12 g/dL may pose excessive risk to a patient with advanced renal disease and a low hematocrit who is poorly responsive to ESAs…The critical, unanswered question is whether poorly responsive patients might incur less cardiovascular risk if attempts were not made to raise their hemoglobin to this 'ideal' concentration, and/or if there were a recommendation for a maximum dose."

FDA Perspective

The FDA staff said that clinical studies have not established a target hemoglobin range except to suggest safety problems can occur above 12 g/dL. However, they also noted that observational studies suggest that patients who reach a target hemoglobin level of 11 g/dL have a greater chance of survival and better quality of life. FDA reviewers told the panel that studies showed higher mortality rates and serious cardiovascular problems when ESAs are given to kidney failure

patients in order to achieve higher hemoglobin levels. The staff also said that data do not establish the benefits of ESAs on patient performance, symptoms, or quality of life.

The reviewers suggested:

- Prospective, randomized, controlled cardiovascular outcome studies to determine optimum hemoglobin targets.
- Consideration of *a priori* disparate targets based on risk factors.
- Development of new dosing paradigms.

Dr. Rieves told the panel that its goal would be to try to optimize dosing for ESAs, adding, "By the end of the day we …want product labels to provide more useful directions." He said that the meeting was a continuation of the FDA and Amgen's "ongoing review of ESA safety," prompted in part by the two major clinical studies – Normal Hematocrit (NH) (patients undergoing hemodialysis and with evidence of heart disease) and CHOIR (patients not on dialysis and with no heart disease). Both studies showed increased risk for patients in the higher hemoglobin groups. He said, "The question is whether the risk is related to the ESA dose itself, the hemoglobin response to the dose, or other factors."

The two major topics of discussion for the day, he said, were:

1. Hemoglobin goals when using ESAs.
2. Identification and management of ESA hyporesponders.

Dr. Ellis Unger, acting deputy director for science in the FDA's Office of Surveillance and Epidemiology, CDER, reviewed the NH study, which he said showed a "startlingly high" mortality rate of 7% in patients with the higher hemoglobin target. He added, "We don't know who we hurt in this patient population."

As for the CHOIR trial, which was terminated early because of an unfavorable outcome, Dr. Unger said, "In retrospect this looked like a brilliant idea…These patients were not on dialysis yet…Patients assigned to the higher hemoglobin group tended to achieve the higher hemoglobin…There was a cap at 20,000 units for any given dose. It trended unfavorably for the high hemoglobin group. These were pre-dialysis patients, and mortality was better compared to the NH study. But, again, if you look at mean hemoglobin and look at mortality, you see a negative association between mean hemoglobin and mortality. If we look at the data from these two studies, if we ignore the randomization and say what's the right hemoglobin target, most people would say higher is better if we didn't know anything about the randomization."

Dr. Unger summarized:

- From the best randomized clinical trial data available, "ideal" hemoglobin target is 10 g/dL for dialysis patients and 11.3 g/dL for pre-dialysis patients.
- Data to support a hemoglobin target as high as 12 g/dL are observational in nature and of limited utility.
- Association is not equal to causality – achieved hemoglobin is not equal to target hemoglobin.
- It is unknown if ESA hyporesponsive and/or high risk patients should be treated differently.
- There are little data showing that current labeling addresses how best to reduce Hb overshoot and cycling.

At the FDA's request, Dr. Ajay Singh, clinical chief of the renal division at Brigham and Women's Hospital, gave an update on hemoglobin target studies, using observational and randomized clinical trial data. He said:

- Observational studies show that higher hemoglobin values are associated with a modest survival advantage, but this is a confounded relationship.
- The NH and CHOIR trials show statistically significant worse outcomes for hard endpoints.
- An epoetin dose effect cannot be ruled out.
- A post-hoc analysis of CHOIR supports both a hemoglobin level and a dose effect in patients who don't achieve target (among likely hyporesponders).

Potential explanations for hemoglobin levels >12 g/dL in dialysis patients included:

- Curve-shifting.
- Dialysis chain-specific factors (protocol-specific, profit-status).
- Anemia algorithm.
- Physiologic factors (hemoglobin cycling, patient-specific factors).

A majority of patients in the U.S. have Hb >12 g/dL (beyond the FDA label), and Dr. Singh wondered if this is inevitable or modifiable. He said that there was a statistically significant higher rate of death in the higher hemoglobin arm of the NH study compared to the lower hemoglobin arm. The CHOIR study also showed a higher risk and higher rate of adverse events in patients with increased hemoglobin compared to lower hemoglobin rates:

- 24% increased risk with targeting Hb ≤13.5 g/dL (p=0.03).
- Strong trends for increased death (48%, p=0.07).
- Trend for time to recommended replacement time (RRT) (19%, p=0.15).
- 23% higher rate of cardiovascular (CV) events (p=0.03) and an 18% increase in all hospitalization (p=0.03).
- No incremental quality of life benefit with higher hemoglobin.
- A 15% increase in serious adverse events in the higher hemoglobin group (p=0.02).

Hyporesponders

Dr. Unger wondered if it is possible to prospectively identify hyporesponders who are at higher risk of cardiovascular events, and, if they can be identified, how should they be treated? He explained the FDA's exploratory analysis on prospective evaluation of ESA-responsiveness, using the NH study, "We can calculate epoetin alfa-responsiveness for patients who received constant weekly epoetin alfa dosing for 2-6 weeks following study entry." In the study, 618 patients were randomized to a "normal" hemoglobin target. EPO-responsiveness could be calculated for 414:

- 117 patients experienced a decrease in hemoglobin, despite a 50% increase in epoetin alfa dose.
- 297 patients experienced no change or an increase in hemoglobin.

Dr. Unger said, "We looked at survival and overall responsiveness…Initial epoetin alfa-responsiveness does not predict overall hemoglobin response in the Normal Hematocrit Cardiac Trial (NHCT) study. The question is: Could we prospectively identify hyporesponders at a higher rate of CV events? The answer was that initial hemoglobin response did not predict subsequent mortality rates, and ESA-responsiveness may need to be assessed on an ongoing basis."

For hyporesponsive patients, Dr. Unger said that current labeling suggests a search for causative factors but doesn't explicitly state a maximum ESA dose. He asked: "Is risk related to hemoglobin response? If yes, then it doesn't make sense that a patient's risk is constant throughout time. It makes more sense that it relates to the rate of hemoglobin and the rise of the rate of hemoglobin…The higher hemoglobin tends to be associated with fewer adverse events, but the rates of change seem to be strongly associated with events…So, it seems best to be in the middle in terms of your hemoglobin and not cycle…The ESA labeling warns against excessive rate or rise (>1 g/dL per 2 weeks), but…which came first the chicken or the egg?" He suggested one or more prospective, randomized, controlled CV outcome studies as well as new dosing paradigms and special dosing strategies for hyporesponsive patients and patients at higher risk of CV events.

Dr. Rieves told the panel that one of its missions was to help improve ESA labels for hyporesponders, "Current labels don't explicitly address how to treat these patients…Prospective identification of hyporesponders may be difficult, for example, erythropoietic response to an ESA challenge. Identification of hyporesponders is feasible in practice…For hyporesponsive patients, the labeling suggests a search for causative factors but does not explicitly state a maximum ESA dose or what constitutes an adequate attempt to raise hemo-globin."

EPO study

Dennis Cotter, president of Medical Technology and Practice Patterns Institute (MTPPI), in an overview of a decade-long study of EPO in Medicare and non-Medicare users, said that survival findings in observational studies of EPO may have been confounded by the EPO treatment itself. He said that a normal hematocrit target might not be achievable for the dialysis population and argued that FDA-recommended starting doses are appropriate for that population.

Cotter also said, "EPO dose higher than 12,000 U/week would result in progressively higher mortality risks and the risk of increased mortality is greatest among hyporesponsive patients who receive the largest EPO dose."

Patient Reported Outcome (PRO) claims

Dr. Ann Marie Trentacosti, medical officer with the FDA's Office of New Drugs, CDER, gave the staff overview of PRO claims, concluding, "The PRO claims are not adequately supported by the instruments used or by the clinical studies reviewed to date…The clinical benefit of epoetin alfa in improvement of patient performance, anemia symptoms, or health-related quality of life (HRQoL) has not been adequately established."

PRO claim issues include clinical study design and instruments. Dr. Trentacosti said that the clinical studies were not adequately designed to measure HRQoL/anemia symptoms and that the instruments used in the clinical trials were not adequate measures of anemia or HRQoL for the target population indication.

Industry Perspective

Amgen officials and experts told the panel that ESAs show clear benefits in CRF patients, including decreasing the need for blood transfusions. Officials told the panel that the company wants a target hemoglobin of 10-12 g/dL. They said that Amgen is conducting randomized controlled trials and working on risk management guidelines. The company proposed a randomized clinical trial to evaluate ESA-appropriate management and clinical studies on hemoglobin cycling, and emphasized that the risk management/assessment plan includes the ongoing TREAT study, a randomized, double-blind trial of Aranesp vs. placebo in anemic diabetic patients, with a primary endpoint of all-cause mortality or CV mortality.

An Amgen official said that the TREAT study results so far show that "the event rate is right on track." TREAT's target hemoglobin level is 13.0 g/dL.

Speaking on behalf of Amgen, Dr. Marc Pfeffer, a Harvard Medical School and Brigham and Women's Hospital cardiologist and chair of the TREAT executive committee, said, "There's enough of a question in the CV area that treating patients with anemia is a high level question. If the canary in the coal mine is precipitating heart failure, then patients with heart failure should do worse…The event rate is right on track…If the emperor has no clothes, we will know that. If, on the other hand, we are altering disease progression and outcomes, we will know that."

Dr. Paul Eisenberg, head of global regulatory affairs and safety for Amgen, said, "(ESAs provide) clear clinical benefits in CRF patients, (such as) avoidance of transfusions and improvement of anemia symptoms, physical function, and exercise capacity…We believe there is risk when targeting Hb >13 g/dL. However, there is no question that despite the complication by factors such as underlying health status, that achieving Hb >11 g/dL is associated with better outcomes… The target Hb range of 10-12 g/dL, which was the range we recommended for prior to the recent label change, is a prudent approach to risk management. What we're being asked to consider today is a ceiling. This is not consistent with the results of randomized clinical trials...I agree completely with the contention that randomized clinical trials are what we should base our evidence on. On the other hand…we also do observational studies."

A dialysis program director at UCLA, speaking for Amgen, told panel members that voting for lower target hemoglobin levels than what the company recommended would result in "higher mortality, more hospitalization, poor quality of life, more blood transfusions, and higher costs to the healthcare system." He said that his patients have reported dramatic improvements in well-being and quality of life with higher hemoglobin levels, including improved brain function and energy, adding, "They felt so much better that they requested being taken off of transplant lists…I was convinced, as are my colleagues and patients, that there is a significant, clinically meaningful improvement in functional ability."

PUBLIC WITNESSES

Five of the eight people who spoke during the public witness period want current practice to remain as it is, with a target Hb range of 10 to 11-12 g/dL. Two made no specific recommendations, and one suggested more specific labeling.

- **Robert Wagner, a nurse and kidney patient representing the American Association of Kidney Patients,** said that ESAs "make a difference" and asked the panel to target Hb levels at 11-12 g/dL.

- **Dr. Jonathan Himmelfarb of the American Association of Nephrology** said that a kidney transplant is the preferred option for end-stage renal disease (ESRD) patients.

- **Robert Wolfe of the University of Michigan** and **Friedrich Port of Arbor Research** said that their research of CMS patient data showed that mortality is lower in dialysis facilities with more patients with Hb >11 g/dL, and mortality is lowest in the range of 11-12 g/dL.

- **Dr. Robert Provenzano, chief medical officer of DaVita,** a dialysis company, said that facilities using higher EPO doses have better anemia management and suggested changing ESA labels to say that EPO should be administered at the lowest dose needed to achieve a Hb 11 g/dL and to decrease the dose if Hb >12 g/dL or if the Hb rate or rise exceeds 1 g/dL per two weeks or 2 g/dL per four weeks. He urged the panel not to encourage withholding EPO as standard practice or making large dose decreases for Hb values above target. He said that current CMS regulations and clinical performance measures are safe, sufficient, and well-supported by the evidence.

- **Dr. Michael Lazarus, chief medical officer of Fresenius Medical Care,** another dialysis company, and a professor of medicine at Harvard Medical School, said, "We believe the FDA must develop separate and distinct indications and dosage recommendations for the different varieties of patients." He said that there is increased risk for death with lower Hb levels.

- **Dr. David Van Wyck – co-chair of the National Kidney Foundation's KDOQI working group, a professor at the University of Arizona College of Medicine, and a part-time DaVita employee –** said the working group recommended a hemoglobin target generally in the range of 11-12 g/dL. In dialysis and non-dialysis CKD patients receiving ESA, the hemoglobin target should not be >13 g/dL, he contended.

- **Dr. Alan Klinger, president of the Renal Physicians Association and also representing the American Society of Pediatric Nephrology,** said, "These studies have surely raised our concerns just as they have raised yours." He asked the panel to help create population-specific warnings, create policies that expect variations, keep quality of life as an indication for ESA use, and respect the rights of patients and doctors to consider risks and benefits. He told the panel:

  - *Consider warning labels that are very patient-specific.* The needs of adults and children differ, he emphasized. "Children are different and more vulnerable than adults. Blood transfusions can cause infections and induce antibodies. Those of us who practiced before ESAs were available remember the hardships of our patients."

  - *Avoid a ceiling.* "Warnings or prohibitions at the high end will surely increase the curve to the left. Clinicians should be warned that patients should not have Hb >11, that will shift to the lower end."

  - *Preserve improvement in the quality of life* as an indication for ESA use for anemia in kidney disease patients, particularly at the lower end of the hemoglobin curve. "Please listen to what our patients say about importance of ESAs."

  - *Each patient is unique*, with their own risk profiles, response to anemia, and own choices. "Some of our ESRD networks have already received complaints that their doctors have cut their hemoglobin doses. They say they feel much worse with lower hemoglobin, and they are willing to sign releases. Please help us to reverse this fear among nephrologists."

- **Lori Hartwell, a kidney transplant patient representing the non-profit Renal Support Network,** told the panel that patients will suffer if Hb target levels are lowered. She said that she relies on ESAs and doesn't feel well if her hemoglobin level is <12 g/dL.

PANEL DISCUSSION

Panel members were mostly concerned with the target ceiling question, target levels, and, to a lesser extent, hyporesponsiveness and quality of life. Some panel members spoke about a target range, and some suggested ranges for a ceiling target level, instead of a single number. Despite prodding from the FDA staff, the panel was reluctant to spend much time discussing hyporesponders or cycling.

Target Range

Dr. Jeffrey Kopp, a Maryland nephrologist, asked on what basis Amgen was proposing a target Hb range of 10-12 g/dL. Amgen's Dr. Eisenberg replied, "We think the target should be 10 to 12 and if someone exceeds the 12 range, the dose should be reduced. That's on the label, and we should get those patients back under 12."

James Neaton PhD, a biostatistician from the University of Minnesota School of Public Health, asked Amgen about its hemoglobin target levels in early trials and why the highest target was chosen in the control arm, "Of the three studies, nowhere is there any evidence of superiority of the higher target to the lower target, and yet you're now saying the target should be 10-12 g/dL…CREATE was 11.5, CHOIR was 11.3, and Normal Hematocrit was 10 g/dL. Where did the 10-12 come from?"

- *Amgen official:* "Normal Hematocrit was the only outcome study in that population, in terms of improvement of cardiovascular performance in dialysis patients. The idea that higher target levels are better – that turned out to be clearly wrong, but up to then there was a clear benefit in the 10-12 range, and that has been where practice has remained."
- *Dr. Neaton:* "I'm just trying to understand what you're doing in the interim before the (TREAT) trial is completed."
- *Amgen:* "You see a target below 10, and transfusions increase dramatically. The targeting between 10 and 12 reduces transfusions."
- *Dr. Neaton:* "But there is no randomized evidence of 12 vs. 10 or 11."

Dr. Michael Lincoff, an interventional cardiologist from the Cleveland Clinic, asked about transfusion rates and patients with Hb <11, "I'm not clear why an approach that is currently labeled – to use the lowest dose necessary to prevent transfusions – is unfeasible? What are the triggers for transfusion? It seems that <9 might be a more conservative approach."

- *Amgen:* "It's an issue of clinical practicality and patient symptoms. These patients are terribly ill, and if we don't have a target range of hemoglobin to shoot for which seems to be reasonably safe and minimizes the symptoms, then we're going to have to treat entirely based on symptoms, and the majority of patients already have symptoms. Then, we'd have to start transfusing them more frequently."
- *Dr. Lincoff*: "Is there a relationship between mortality and dose?"
- *Independent analyst for the FDA:* "There are significant differences, with the moderate doses showing a lower mortality rate compared to higher doses. The differences are quite significant."
- *Dr. Lawrence Hunsicker, a nephrologist from the University of Iowa Hospitals and Clinics:* "I'm…aware that the Hb measure at any one time is going to be predictive of the need for some sort of intervention down the line, because people vary. And if you're trying to stay above the level at which transfusions are needed, my question gets back to the data presented by Amgen showing the relationship between previous hemoglobin level and the need for transfusions. Would you be willing to get guidance for a level that was in the neighborhood of 10 or 11? We have no inclination about which hemoglobin level is associated with a good biological effect. So, when a hemoglobin level goes below 11 or 10, the incidence of transfusion is higher. Would it be sufficient for the FDA to suggest that these are levels at which transfusions are avoided?"
- *FDA official:* "The current label does not identify a target. The consideration is tied not only to safety, but considerations related to transfusion would be reasonable. We have no data on transfusion triggers, but that could be part of the considerations from this committee."
- *Dr. Hunsicker:* "You (FDA) said that the best current evidence suggests the optimal hemoglobin was in the range of 10-11. What is the nature of that evidence? Is it admissible or useful for FDA purposes?"
- *FDA:* "That's the information that we have from the randomized control trials. That's the randomized clinical trial data that we have."
- *Dr. Neaton asked Amgen officials:* "How did you come up with a lower target level of 9 in the TREAT trial?"
- *Amgen:* "Nine was a compromise of what is the best way to conduct this trial to address the question. The nephrology community wanted an even higher low value. We did know that 9 was a magical number – a hemoglobin at which people uniformly did not feel well, and we felt patients needed rescue from that."

- *Dr. Neaton:* "My read is that randomized trials are the gold standard, and I think if they're done well, that's the case. My sense of CHOIR and CREATE is that these trials were not done well…TREAT could be a definitive trial in a non-dialysis population."

Dr. Chester Good, an interventional cardiologist and drug safety expert from Veterans Medical Center in Pittsburgh, asked about CHOIR, which, while it had a target of 11.3, the average achieved hemoglobin was 11.4, "I'm wondering where these data come from."

- *Amgen:* "The distribution that we see through time and in the data sets is a standard deviation of 1.4 g/dL. So, you can estimate what the target would be if you shifted…It was not an on-label use – 10,000 units in all patients – but there was a dose cap. And understanding the dose distribution is more unclear."
- *FDA official:* "One difference between FDA's analysis and Amgen's analysis is that for doses >15,000 U/week, mortality greatly increases." She called Amgen's analysis "very misleading."
- *Timothy Lesar, a pharmacist from Albany Medical Center:* "What struck me is that some of the confusion (is that) people are going to see what was achieved, not what the target was. Another thing on the dosing: The higher hemoglobin improves responses. How did it get there? Any number has to be tied to what was the process at which you achieved your goal and achieving a goal may not be a good thing for a patient. There is strong evidence that rates of dose increases may be problematic, so how you achieve that goal may be problematic."
- *Dr. John Teerlink, a cardiologist from the University of California, San Francisco:* "Dancing around a range, I would encourage the FDA to try to find a middle way between a Draconian (range) and current data – and balancing that between claims and truly poor data. This is an interesting issue because typically when a sponsor comes to us with trials and says, 'This is what we did, and this is what happened,' we say that was good or bad, and we approve that drug for that dosing regimen. It seems as if the dose is actually the targeted hemoglobin at 11 or 11.3, and that our concerns are that that was established by the clinical data that we have. So, this range thing is bringing in safety concerns, and they need to be addressed by finding out more information on the cycling phenomena. If we pick a target of 11, how do we get it, and how do we prevent bad things from happening? I'm confused about the number 12, and I don't know where it came from. I think we should give clinicians a target dose, and then work on giving information on how to appropriately hit that target dose."
- *Dr. Neaton, the biostatistician:* "I look at the early trials, and I guess there are some concerns that remain to be addressed. I'm more concerned about the instruments used and the tests than the completeness of the data that was alluded to in the FDA summary. There seem to be remarkable differences. I think a range is in order. It has been used in the past. It's roughly 10-11 vs. 14-15, and so I'm comfortable with a range between 10 and 12, but if I had to choose a number I guess I'd choose 11. And I wouldn't confuse populations because the data presented today come up consistently that around 11 is pretty good."
- *Dr. Judith Kramer, an internist from Duke University:* "I think the FDA is saying to us: If we believe randomized clinical trials demonstrate a statistically significant improvement in outcome vs. observational data, we have clear-cut evidence that shows statistical superiority of a lower target. These trials tested a target hemoglobin. We're trying to come up with recommendations for the population, an overall recommendation. It seems that, granted, there are some issues with the trials, but they are by and large quite convincing and consistent across the trials, and, yes, that is a reasonable target hemoglobin. It is unconscionable when we don't know any more about specific adjustments, algorithms, and that is ultimately the responsibility of the sponsor to do, and they have not. I would directly take the results of the randomized trials to pick a target hemoglobin."
- *Dr. Henry Black, a nephrologist from NYU School of Medicine:* "I think having a single number…makes no sense whatsoever. It has to have a range, and I like the 10-12 range. We could abdicate our responsibility. We're asked to give guidance with a number that hasn't existed for 20 years, and we could say come back to us in two years with more data. I think we have to take some stand and include observational data…We have to have some range, and I tend to go with the 10-12 range, knowing that we don't have all the support that we really need to make that decision."
- *Dr. Alfred Cheung, a nephrologist from the University of Utah:* "I support a target, just like blood pressure…Even though I fully believe in randomized trials, I am also mindful that how you achieve the target in a trial can be very different from clinical practice. In terms of the range, there is some question whether it should be 12. I believe we should have the wider range, so I am comfortable with 12. Whether we should have a lower range or not, I'm afraid that people will look at the label, and it will be nebulous."

Ceiling

- *Dr. Hunsicker, nephrologist:* "I'm confused. Transfusion targets have changed over the years…I think the numbers are not 11 and 12. What's the upper, and what's the lower? What's 12? I don't know, and we don't have any data to decide whether the upper end of the target should be 11 or 12. On the bottom, I like the fact that when the hemoglobin level is less than 10, the risk for transfusion is higher. So, I feel comfortable with those two numbers, 10 and 12. The question is, what is the target? I think maybe it should be 11, plus or minus 1. The question is, how do

we avoid cycling? What was tested was the target. A target of 13 is not good, but achieving 13 is okay, as far as I can see. So, when I look at the issue of target, I would like the FDA and the sponsors to tell me what the hell they want me to do with the target."

- *Acting panel chair Dr. Richard Platt, an epidemiologist from Harvard Medical School:* "We have one number, we have another number, and I think we have no number. Everybody recognizes the therapeutic agent contains harms as well as benefits. Exactly this kind of information lack pervades so much of therapeutics. If there's a larger lesson from this, we should demand much better evidence much further on rather than let clinical practice evolve as we have seen here. Secondly, we are being asked whether there is enough information that, in a sense, adjudicates a disagreement on 12 vs. 11, but we wouldn't have this meeting if the sponsors and FDA agreed on an upper level…This is a very fine distinction. So, I would say there isn't enough 'evidence' to support a change in any number. I guess I would say that the public is better served by having a number than by having the existing guidelines, and there seems to be no evidence for anything higher than 11…A guideline might also be aimed at a group. Some groups might be the values of the population treated at a dialysis center or renal clinic…My final comment is: It seems the largest opportunity for improving the ratio of benefit to risk might result from attention on how to prevent the excursions above and below the target range. If we perceive there is a big gap in the ways these compounds are used, and there is a way to improve the welfare of individuals who use them, it might be good to figure out ways to keep in the target range."
- *Dr. Kopp, a nephrologist:* "I also favor a range. For normal hematocrit, the low point started out at 10.5-11 and was increased to 11.3. For CHOIR it was 11.3. Where that takes me is somewhere no one has suggested before – not focusing on an integer but trying 10.5-11.5. If we give a single number, physicians will try to treat to that number and avoid toxicity. I don't insist – this is not a firm statement – but I'd be inclined to go from 10.5-11.5."
- *Dr. Frederick Kaskel, a pediatric nephrologist from Albert Einstein College of Medicine:* "I would not be in favor of changing/lowering the number. I also recommend that because of limitations in the data, we need to develop algorithms and assess a critical period. Each patient is different. It's very difficult to get a value on this."
- *Malazia Scott, the patient representative:* "Keeping the range 11-12 gives an alternative to people who at 11 feel sick and need to stay in bed."
- *Sean Hennessey, a pharmacist from the University of Pennsylvania School of Medicine:* "My question is whether the current label should be changed. (What would have happened) if we were sitting here when EPO was just being looked at for approval…Mortality bottoms out between something like a dose of 10,000 to ~12,000 units per week. That looks to be a hematocrit of ~35-36, which is a hemoglobin of ~12 g/dL. We don't have randomized data telling us that 11 is better than 12, but we have data that tells us that mortality may be lowest at 12. I'm reluctant to reduce the number to 11 when a number out there may be there to protect against unintended consequences."
- *Dr. Andrew Narva, a nephrologist with the National Kidney Disease Education Program:* "We need a range. A range is what will be adopted by CMS, and that will determine what happens to our patients. I'm ambivalent about what that target should be. I feel that suggests we should endorse a more conservative role, but I'm worried that would result in patients ending up with a hemoglobin very low. Perhaps that could be reduced by better dosing algorithms. We don't need to be married to the kind of disparities in care that we've tolerated in the past, and I think we can do better. Regardless of what we recommend, we need to recognize that there are certain people who will benefit from higher targets, especially those who live at higher altitudes. There are several thousand people in the western part of the country who would not do as well on the lower target rates."

Quality of Life

Dr. Hunsicker asked for a discussion of quality of life, asking about the relevance of quality of life instruments and saying that the legitimacy of the current quality of life data should be addressed.

- *Chair:* "Unless someone is going to bring additional quality of life data to us, we're not in a position to have a full explication at a level that would make a difference to our decision making."
- *Dr. Hunsicker:* "We're going to be talking about targets, but there is nothing about how we should or should not be using existing quality of life data. I'm not proposing that we should use it. I just think it should be discussed explicitly. It will be very puzzling to the public and to practitioners to throw out this information about quality of life."
- *FDA official:* "One of the reasons we didn't include questions directly addressing quality of life is that we need to explore that a bit more thoroughly…We're not ready to discuss it. We would be hindered in terms of substantive discussion."
- *Dr. Findlay:* "I thought the labeling had already been changed with regard to quality of life."
- *FDA:* "That's part of our ongoing discussions with Amgen. That process is actually going on. But there are not any changes re quality of life. It's only in the epoetin alpha label. Amgen said that it is reviewing that with the FDA and has proposed changes to the PRO labeling."

- *Dr. Kramer:* "The quality of life analyses are inferior, and more data are needed…I was really struck that there wasn't as much of a distinction between qualifications for transfusions with no difference in quality of life between the two arms. We have to be careful not to use our emotions and our fears but to use the data."
- *Dr. Good:* "I'm trying to weigh the risks and benefits of ESAs. We've put a lot of thought into patients' quality of life, and I have a hard time working through the evidence reported on industry-sponsored trials that are open-label and on evidence gathered from research assistants who are probably very eager to gather this from patients. The CHOIR study found no difference in patient quality of life, and I was wondering why that is. Is there an attenuation of patient quality of life once hematocrit reaches a certain level? Maybe above 11 or 12?"
- *FDA guest analyst*: "The quality of life improved in both arms (of CHOIR) – lower and higher hemoglobin arms…I would suggest there is no quality of life benefit in raising hemoglobin from an 11.3 target to 13.5 g/dL. I can't speculate about lower levels. There are a number of studies…that suggest improvement for very low hemoglobin levels. But for CHOIR, there was no difference between the two groups."

Comments on other issues

- *Dr. Lewis Nelson, a medical toxicologist from the NYC Poison Control Center:* "I see two issues. The efficacy doesn't seem to be a big issue today…When we talk about safety, we have to start looking at the population that is not responding very well." He asked for comments on what the underlying action of ESAs is, noting that EPO is being used for other diseases. Amgen said that the bottom line is that the underlying action of ESAs is defined through EPO receptors, and the company hasn't been able to conclusively determine any other action.
- Dr. Kopp asked if there were any measures of inflammation or clotting values that could be possible markers for hyporesponsiveness, and Amgen said it hadn't looked at those factors.
- Dr. Kaskel asked about children, suggesting that future studies take a separate look at them. He also asked for new guidelines and data on children.
- *Dr. Nelson:* "Rather than giving once-a-week dosing in a fairly substantial dose, maybe splitting into two doses or low levels for longer periods of time."

FDA Questions to the Panel and Votes

The panel voted only on three of the six questions posed by the FDA.

Question 1. ***For patients on hemodialysis*, based on the available data, primarily derived from the NH study, should the ESA product labels be changed to state that the target hemoglobin should not exceed ~11 g/dL for patients on hemodialysis, the level associated with better survival in the NH study?** Any such Hb target necessarily assumes achieved excursions into the ~12 g/dL range. If no, provide a target hemoglobin and the basis for this suggestion. Describe the role that the NH study contributed to your recommendation.

NO, by a vote of 14 No to 5 Yes

Voting for the target ceiling were the consumer representative, interventionalist and drug safety expert, pharmacist, internist, and medical toxicologist.

Question 2. ***For patients not on dialysis*, based on the available data, primarily derived from the CHOIR study, should the ESA product labels be changed to state that the target hemoglobin should not exceed ~11 g/dL for patients on hemodialysis, the level associated with better survival in the NH study?** Any such Hb target necessarily assumes achieved excursions into the ~12 g/dL range. If no, provide a target hemoglobin and the basis for this suggestion. Describe the role that the CHOIR study contributed to your recommendation.

NO, by a vote of 14 No to 5 Yes

Again, voting for the target ceiling were the consumer representative, interventionalist and drug safety expert, pharmacist, internist, and medical toxicologist.

Question 3. Considering the NH and CHOIR designs and results and lack of randomized controlled clinical data to support the safety of specific Hb targets lower than 11 g/dL or >11 g/dL but <13 g/dL, discuss design considerations for subsequent studies that may provide additional dose optimization information. ***Specifically, should randomized clinical studies examine an array of Hb targets?*** If yes, what are the reasonable targets to study?

No formal discussion or vote taken.

The panel generally agreed that randomized clinical trials should examine an array of Hb targets.

Question 4. ***Are the ESA dosages used to achieve the hemoglobin levels in the lower target groups in National Hematocrit and CHOIR sufficient to form the basis for ESA dosage recommendations?*** Any such recommendation necessarily recognizes the difference in dosages between subcutaneous administration to patients not on dialysis and intravenous administration to patients on dialysis. If no, describe clinical study data or other considerations that should form the basis for the recommended ranges of ESA dosages and discuss whether the NH and CHOIR studies should be

factored into that determination. If yes, suggest how the product labels should be revised.

YES, by a vote of 14 Yes to 3 No, with 2 abstentions

QUESTION 5. Please suggest ways to identify ESA hyporesponders. For example, is failure to respond to a maximum ESA dose the most important consideration? Are sufficient data currently available to suggest how best to identify and dose these patients? If yes, provide recommendations for how best to define and dose this population and your basis for these recommendations.

No formal vote taken.

Panel members agreed that better dosing algorithms are needed and generally agreed that the labels should include some information warning hyporesponders of potential problems. The problems of cycling and hyporesponsive patients contribute to the muddle and should be addressed by conducting more studies, the FDA believes – and the panel generally agreed. An FDA official said, "A target of 12 g/dL may pose excessive risk to a patient with advanced renal disease and a low hematocrit who is poorly responsive to ESAs…The critical, unanswered question is whether poorly responsive patients might incur less cardiovascular risk if attempts were not made to raise their hemoglobin to this 'ideal' concentration, and/or if there were a recommendation for a maximum dose."

QUESTION 6. Discuss dosing algorithm hypotheses that could be tested in clinical studies. Considerations may relate to criteria for terminating a dose or reducing a dose by specific amounts/proportions in patients whose hemoglobin response exceeds the target or who experience an excessive rate of rise, or conversely who do not show an appropriate hemoglobin response or rate or rise. What should be the primary efficacy outcomes?

No formal discussion or vote taken.

FDA POST-MEETING REACTION

FDA officials were disappointed that the panel failed to provide any specific answers to the first two questions (both dealing with a ceiling on hemoglobin levels) or to even come to a consensus. Dr. Rieves said, "What I came away with was …the sense of the committee was that the language (in the current labeling) can be improved. There was a variety of opinions as to how that could be improved. A number of advisers thought we should go the route of target range. They were giving credence to some of the observational data to make that statement."

He said that the takeaway from the committee's answers to the first two questions was, "The committee was unsettled with respect to identification of a specific target. They were concerned about the lack of data. Nineteen years after initial approval, there was concern that there was not better dosing information. That was at the top of the list of our concerns – trying to get some specificity on this target range."

On the idea of changing dosing information, Dr. Rieves said that the panel "supported the conceptual approach and gave a lot of credence to the importance of CHOIR and the National Hematocrit Study. But…they did not define the optimum hemoglobin target. So it behooves us to work with Amgen to work with the committee's advice to improve directions, to identify a nominal target range or suggested target range…It was impressive that many of the committee members, if not the majority, did not feel comfortable with a single number, and clinicians in general don't like the single number. They like a range, and that take home message of towards a range is an important one, and we will take that to heart…I asked for a consensus, and there was no consensus. There were pockets of opinions. There was an important pocket that thought there should be a range of nominal hemoglobin targets. On the other hand, there was a pocket of opinions that felt strongly that randomized controlled trials had established that nominal target, and randomized clinical trials identified a single point."

As to a consensus on range, Dr. Rieves said, "I asked for a consensus on range, and there was no consensus…(That) reflects the state of the data. The committee was struggling with the first two questions, as we were, and that's why we came to the committee. We were hoping to walk away, ideally, with a clear consensus."

Asked how the panel matched up with the ODAC meeting in May, Dr. Richard Pazdur, director of the FDA's Office of Oncology Drugs, CDER, said, "These are two different situations, and we need to divide this into two different panels. There are totally different issues for oncology patients and renal patients…There are so many profound differences here that it's hard to bridge."

Dr. John Jenkins, director of the FDA's Office of New Drugs, CDER, said that the FDA will come out with final label revisions for ESAs for oncology and renal indications in the coming weeks, not months. He said that the FDA is working "full steam ahead" to get to a final product label as quickly as they can, "One of the issues to work through is that we didn't get a clear view from the committee on what their target recommendations are, and we have to work through that. What is the best data-supported labeling at this point?"

As for PRO labeling, Dr. Jenkins said, "It is important to clarify that for labeling claims we require substantial evidence, which is very different from clinical practice observations. We're looking at all the data we have available to provide substantial evidence. It's not as if we're throwing out or disregarding quality of life."

What will CMS do? Dr. Jenkins said that, although the FDA shares information with CMS, "at the end of the day, the FDA will decide what should be in the labeling, and CMS will decide about coverage decisions." ♦