EXHIBIT 3

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

Civil Action
No. 97-10814-WGY

* * * * * * * * * * * * * * * * * * * *

AMGEN, INC.,

Plaintiff,

v.

HOECHST MARION ROUSSEL, INC.
and
TRANSKARYOTIC THERAPIES, INC.,

Defendants.

* * * * * * * * * * * * * * * * * * * *

DAILY TRANSCRIPT OF
PROCEEDINGS ON REMAND
(Volume 6)

BEFORE: The Honorable William G. Young,
District Judge

APPEARANCES:

DAY CASEBEER MADRID & BATCHELDER, LLP (By Lloyd R. Day, Jr., Esq., David M. Madrid, Esq., Jonathan Loeb, Esq., and Robert M. Galvin, Esq.) 20400 Stevens Creek Blvd., Suite 750, Cupertino, California 95014
- and -
HOWREY, SIMON, ARNOLD & WHITE, LLP (By Edward M. O'Toole, Esq.), 321 North Clark Street, Chicago, Illinois 60610-4714
- and -
DUANE MORRIS, LLP (By D. Dennis Allegretti, Esq.), 470 Atlantic Avenue, Suite 500, Boston, Massachusetts 02210
- and -
STUART L. WATT, ESQ. and MONIQUE L. CORDRAY, ESQ., Amgen, Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799, on behalf of the Plaintiff

1 Courthouse Way
Boston, Massachusetts

November 3, 2003

A P P E A R A N C E S (Cont'd)

CHOATE, HALL & STEWART (By Eric J. Marandett,

Esq.), Exchange Place, 53 State Street, Boston, Massachusetts 02109
- and -
FISH & NEAVE (By Herbert F. Schwartz, Esq., Douglas J. Gilbert, Esq., Gerald J. Flattmann, Jr., Esq., Kenneth B. Herman, Esq. James F. Haley, Esq., Barbara A. Ruskin, Esq. and Katherine A. Helm, Esq.), 1251 Avenue of the Americas, New York, New York 10020, on behalf of the Defendants

I N D E X

WITNESS:	DIRECT	CROSS	REDIRECT	RECROSS
JOSEPH W. ESCHBACH				
By Mr. Madrid	644		757,	

640

THE CLERK: All rise. Court is in session, please be seated.

Calling Civil Action No. 97-10814, Amgen v. HMR/TKT.

THE COURT: Well, good morning, counsel.

COUNSEL: Good morning.

THE COURT: I have two motions before me, both of which I'm going to decide. I've read them carefully. I'm going to decide them without hearing.

First, I have Amgen's motion for judgment. That

plasma corrected the anemia of the sheep model that we created that had renal failure, and then we subsequently tried to do the same study in one patient with erythropoietin rich human plasma and it was unsuccessful in the sense that we could not treat that but, we did not have enough erythropoietin rich plasma to succeed, but we did show that it was effective in a sense in terms of a biological response. It wasn't until we had recombinant human erythropoietin that we've had the most experience in treating this anemia.

Q. In the context of your investigations have you measured reticulocytes?

A. Yes.

Q. For what purpose?

A. Reticulocytes were used to, primarily as an early indicator of a biological response to erythropoietin therapy. It wasn't clear as I mentioned whether uremic inhibitors would interfere with the action of

erythropoietin. And so we needed to have some clue as to whether this would, whether we were overcoming that uremic factor, and reticulocytes were one of those measures that we used.

Q. Did you measure ferrokinetic effects?

A. Yes.

Q. For what purpose?

A. For the same reason.

Q. Now, have you interacted with the Food and Drug Administration concerning any clinical studies?

A. Yes, several.

Q. Can you list what those are?
A. With recombinant human erythropoietin and also with intravenous iron gluconate.
Q. How did you first become involved in the study of the anemia chronic renal failure?
A. Over 40 years ago when I decided to become a nephrologist I was a research fellow with Dr. Belding Scribner at the University of Washington. He had just started doing, or keeping patients alive with chronic dialysis, and as a result of this a lot of complications were revealed, one of which was the significance of anemia chronic renal failure.
When I arrived he said, Joe, solve the anemia problem.

Q. Now, have you had any exposure to the field of hematology?
A. Yes. Very fortunately the hematology division at the University of Washington was just down the hallway. I was very fortunate to work with Dr. Clem Finch, head of the division of hematology, a world-renown hematologist.
MR. FLATTMANN: I object, your Honor. I don't believe any of this is in the report about hematological experience.
THE COURT: It seems to be somewhat background. What he's testified to will stand. Let's get to this case, Mr. Madrid.
MR. MADRID: Yes, your Honor.
Q. One final question with respect to background, Doctor.
Since the year 2000 have you become involved in

any professional organizations?
A. Yes.
Q. Please describe your involvement?
A. The organization was called National Anemia Action Council, and it's a group of subspecialists from various specialties that are interested in anemia and anemia in general and our aim is to educate not only the public but the profession at large about the significance of anemia and how important its treatment is.
Q. Doctor, I'm going to ask you some questions today with

respect to the Court's claim construction. Do you understand?
A. Yes, I do.
Q. Before I do that, I would like to ask a few brief background questions with respect to that subject.
Doctor, by or before November 1984 did you try to help or cure -- did you try to help to heal or cure any patients suffering from anemia?
A. Oh, yes.
Q. Approximately how many anemia patients did you try to help to heal or cure?
A. Several hundred.
Q. Were you successful in helping to heal or cure their anemia?
A. No.
Q. Why not?
A. We had no effective therapy at that time. The two therapies that we had available were androgens and red cell transfusions, both of which had their own problems.

Androgens resulted in a minimal increase in hematocrit and did not work in everybody, and complications were not very good for, particularly for female patients. Red cell transfusions was a temporary treatment, never resolving the anemia, and in the long run causing further complications that patients continue to have trouble with today.

Q. With the advent of recombinant human erythropoietin did you try to help to heal or cure any anemia patients?
A. Yes.
Q. How many?
A. Well over 500.
Q. Were you successful in helping to heal or cure their anemia?
A. Yes.
Q. How did you know you were successful?
A. Well, by two criteria. One, we were able to increase the hematocrit from 20's up to a target range of 35 to 40, which is near normal or normal levels, and because of their clinical response. Patients improved dramatically in their clinical overall well-being.
Q. Now, Doctor, if you could, please, I would like to direct your attention to Demonstrative Exhibit BTA.1. That's Tab 2 in the notebook.
Now, this is a reproduction of the Court's September 18, 2003 working construction. Are you familiar with the Court's September 18, 2003 working construction to determine therapeutically effective amount?
A. Yes, I am.
Q. I would like to direct your attention to the first

sentence of the Exhibit BTA.1, Tab 2, which reads: A therapeutically effective amount is a quantity that

652

produces a result that in and of itself helps to heal or cure.

Do you see that?

A. Yes, I do.

Q. Do you have an opinion regarding whether the ordinary skilled artisan in 1984 would have understood there to be a plain meaning for the term therapeutically effective amount?

A. Yes.

Q. What's that opinion?

A. That opinion in terms of the anemia of chronic renal failure would be that we would need to show not only an increase in the hematocrit in normal or near normal levels but to achieve a clinical improvement in the patient as demonstrated with quality of life and other measures.

Q. Now, why do you hold that opinion?

A. I'm sorry, why?

Q. Why do you hold that opinion? What are the bases?

A. Because that's the definition of being therapeutically effective.

Q. Doctor, do you have an opinion as to whether or not the ordinary skilled artisan would have understood that a sustainable increase in hematocrit was necessary in order to help heal or cure?

A. Yes.

653

Q. What is that opinion?
A. A temporary improvement in raising hematocrit is only temporary. You need to have a sustained response in order to achieve the therapeutically effectiveness that we're talking about.
Q. What is anemia?
A. Anemia is basically a reduction in the amount of circulating red cells in the body as determined by a hematocrit or hemoglobin concentration.
Q. Why do doctors use hematocrit or hemoglobin concentration to determine whether a patient has anemia?
A. They're standard techniques.
Q. How would --
A. Accepted, accepted by the profession.
Q. I'm sorry.
How would the ordinary skilled physician in 1984 have determined whether a treatment was helping to heal or cure the anemia of a patient?
A. We would be following the hematocrit or hemoglobin level.
Q. Do you have an opinion as to whether or not the ordinary skilled artisan would have considered a biologic effect in and of itself to be sufficient to heal or cure?
A. Yes.
Q. What is that opinion?

A. Biological effect in and of itself is not sufficient to determine whether there's healing or curing of a problem.
Q. Why is that?

A. Well, biological effect by definition is more or less a chemical, or something happening on the cellular level that shows you're getting a response to some therapeutic agent, in this case let's say erythropoietin. And so, this is usually an acute response and doesn't guarantee that you'll have a sustained, sustained response, nor that you'll have a sufficient amount to get to your target level.

Q. I would like to direct your attention now back to Exhibit BTA.1 in Tab 2, and specifically to the second sentence of the Court's working construction. And I'll read that for the record: A therapeutically effective amount is one that elicits in vivo biological activity of natural EPO such as those listed in the specification, column 33, lines 24 through 28. And then the listing: Stimulation of reticulocyte response, development of ferrokinetic effects, and erythrocyte mass changes, and one that increases the level of hematocrit.

Now, Doctor, I would like to also direct your attention to the Lin patent. This would be at Tab 3 of your notebook. This is Exhibit 1. And in particular, if you would turn to column 33 of the Lin patent.

Now, do you have an opinion as to how the ordinary

skilled physician would have understood column 33 of Dr. Lin's specification?

A. Yes.

Q. What is that opinion?

A. May I read through this?

Q. Yes, please.

A. Your Honor, I'm particularly focusing on the third

paragraph, column 33, and it starts off by talking about the in vitro biological activity of EPO isolates from natural sources that the patent shares with, and consequently are projected to have utility as substitutes for EPO isolates in culture media.

This is all in vitro effects of erythropoietin.

Q. Doctor, can you speak into the microphone, please.

A. Oh, I'm sorry. The first part of the paragraph refers to the in vitro effects, the biological activity of EPO isolates, affecting EPO isolates in culture media employed for growth of erythropoietin cells in culture.

Then it goes on and says: Similarly, to the extent the polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable to use in erythropoietin therapy procedures practiced in mammals, including humans, to develop any or all of the effects herefore attributed to in vivo EPO.

The here -- the, what it says, herefore, at this time in 1984 we knew what the biological effects were, but there was not anything available for therapy. So, the fact that we start with the in vitro effects of EPO, which were well-known, and move on to the in vivo biological activity, it then mentions stimulation of reticulocyte response, development of ferrokinetic effect, such as plasma iron turnover effects and marrow transit time effects, erythrocyte mass changes, stimulation of hemoglobin C synthesis, see Eschbach, et al., and as indicated increasing hematocrit levels in mammals.

So my review of this is that the specific effects that are listed here are clearly biological effects following the mention of the in vitro biological effects listed earlier.

And I amplify that further because the specific statement about stimulation of hemoglobin C synthesis, which I'm very acutely aware of having spent twelve years working with sheep, this is a phenomena seen only in certain sheeps and goats in which hemoglobin, a phenotype of hemoglobin A is shifted to hemoglobin C and can be, and is an indicator that erythropoietin has been acting. However, it has no, absolutely no effect upon hematocrit or therapy.

THE COURT: And the language you're just

explaining is the reference to stimulation of hemoglobin C synthesis?

THE WITNESS: Synthesis, correct.

THE COURT: That's something that you, and you're citing there --

THE WITNESS: Yes.

THE COURT: -- that's something that you found with respect to sheep?

THE WITNESS: Correct.

THE COURT: But have not found other than with respect to sheep?

THE WITNESS: No, it's in goats. But I didn't look at goats, sir. But it's not in humans.

THE COURT: Sheep and goats.

THE WITNESS: Yes.

THE COURT: And you're saying that was known then?
THE WITNESS: Yes.
THE COURT: Go ahead, Mr. Madrid.
Q. Doctor, have you finished with your answer?
A. Well, I could amplify more with ferrokinetics, too.
Q. Go ahead.
MR. FLATTMANN: I object, your Honor; form. Have a question and answer. I don't know what was answered.
THE COURT: No, I'm satisfied with the form, in the same form as we just had.

What about ferrokinetic effect?
THE WITNESS: Ferrokinetics is an investigational tool. It does not tell you what the hematocrit or tell you anything about therapeutic response. It clearly helps to determine how the bone marrow was functioning and particularly about iron metabolism. It helps to quantitate red cell production, but does not give you any indication as to what's happened to the hematocrit.
Q. Do you have an opinion with respect to the mention of erythrocyte mass changes in column 33?
A. Yes.
Q. What is that opinion?
A. Erythrocyte mass changes likewise are both, both biologic and if there's significant mass changes can be related to therapy.
Q. And column 33 makes reference to increasing hematocrit levels in mammals. Do you have an opinion with respect to the significance of that sentence?
A. Yes. Well, to continue on with my analysis of the

patent in column 33, we go from the in vitro effects to the in vivo biologic effects and then increasing hematocrit levels, both the biologic and eventually a therapeutic effect. And then it moves beyond that to the next sentence which talks about the various medical conditions that might be impacted and improved by such therapy.

So I think it shows an evolution of the use of erythropoietin from, in the laboratory to biological effects to, finally to potential therapy.

THE COURT: And roughly speaking, you think that the Court's construction, the second sentence -- well, put the Court's construction to one side. You're saying the second sentence talks about biologic effects and the third sentence is directed toward therapeutic effects?

THE WITNESS: Well, I would like to amplify that further, if I may, your Honor.

THE COURT: You may.

MR. MADRID: Tab 2 is the --

THE WITNESS: The thing I liked about your second sentence is that it provides a very natural transition, as does the patent, the first part of your second sentence in which you list simulation of reticulocyte response, development of ferrokinetic effects, and erythrocyte mass changes are biological responses. Then you say, and one that increases the level of hematocrit, which is moving on to showing that this is then going to become a therapeutic response, which then ties into your first sentence very nicely.

So I think your second sentence and the first

sentence are very much related.
THE COURT: But I did hear you say that

660

erythrocyte mass changes, if in sufficient quantity, have a therapeutic effect, correct?
THE WITNESS: Well, let me explain that. Yes. Erythrocyte mass changes really basically shows the hematocrit is increased.
THE COURT: It's another way --
THE WITNESS: It's another --
THE COURT: -- of getting at that?
THE WITNESS: Yes, exactly.
THE COURT: I take it that the key to you as a physician here, the key to treating humans who have anemia which causes other bad things to happen, is to get that hematocrit up?
THE WITNESS: That's correct.
THE COURT: Have I got that right?
THE WITNESS: Absolutely correct.
THE COURT: Go ahead, Mr. Madrid.
THE WITNESS: I'm talking about adult humans now. I've been talking mainly about the anemia chronic renal failure, but that's true of many other anemias as well.
THE COURT: Yes.
Q. Now, Doctor, do you understand HMR/TKT to contend that an increase in reticulocyte count or ferrokinetic effects is a result that helps to heal or cure anemia?
A. I understand that question.

661

Q. Do you agree?
A. No.
Q. Why not?
A. Well, as I mentioned, the reticulocyte response and ferrokinetic responses are biological effects, they're acute effects, and they do not have, they do not guarantee that you will have a sustained effect to result in helping to heal or cure the parent.
THE COURT: Let's just get at this, your concern about a sustained effect.
THE WITNESS: Uh-huh.
THE COURT: First of all, I heard you say that -- and you'll forgive me if my questions are foolish.
THE WITNESS: No.
THE COURT: I'm groping here.
You want to get, as a physician you want to get that hematocrit level out of the 20's as you mentioned --
THE WITNESS: Uh-huh.
THE COURT: -- up into the 30's.
THE WITNESS: Correct.
THE COURT: 30's is what, low normal?
THE WITNESS: Right. It's still anemia. Low 30's is still anemia.
THE COURT: But you're better off -- well, I shouldn't assume anything. Now, since we're talking about

a therapeutic effect, your concept of therapeutic effect falls to a sustained response.
THE WITNESS: Yes.
THE COURT: In other words, if you can get the

hematocrit to spike up that would certainly be interesting.
THE WITNESS: Yes.
THE COURT: But if it immediately went back down --
THE WITNESS: Right.
THE COURT: -- it wouldn't be much good to the patient. Correct?
THE WITNESS: Correct.
THE COURT: What do you mean by sustained then? Quantity sustained?
THE WITNESS: Could I use an analogy to --
THE COURT: Sure.
THE WITNESS: -- try to illustrate this with you?
And this is a bathtub. When we take a bath we like to have the tub up, water up so high. Let's think of that in terms of our body and red cells. The hematocrit being a measure of that level. Let's say 40 just for illustration purposes.
The patient that has renal failure -- can you hear me?
MR. MADRID: Yes.

THE WITNESS: The patient that has renal failure has a hematocrit, let's say of 20. It may be lower, it may be a little higher. So it's half full.
Now, our hematocrit is determined by two things. One is the amount of red cells being produced, and two, by the number of red cells being destroyed. And the destruction -- our red cells last up to 120 days. But in general there's a balance.

Now, in the patient with renal failure that balance may not be stable. Many times the hematocrit drops because red cell destruction exceeds the rate at which it's being produced.

Now, let's then, let me use the analogy that what's coming out of the spigot are reticulocytes. Those are early red cells. We have a drain that is analogous for red cell destruction, or loss. And there's a balance here, there's a rule.

Well, when we start erythropoietin stimulation we're actually turning the knob and increasing the amount of water or red cells coming out of the spigot, increase reticulocytes.

Now, initially there's very little change in that level of water, or blood, in the blood. Eventually it will start to fill. But there's no guarantee for that because a number of intervening effects can happen. And we've seen

this repeatedly, clinically. Number one, we can have iron deficiency which then results in basically turning that knob down. A more important one is an infection or inflammation which really blunts the action of EPO so you don't get much coming out. You have blood loss, the drain is going to be increased so you've got more blood coming out and you can't possibly overcome the amount losing with the amount coming in. And the red cells themselves can be destroyed quicker if there's more infection.

So, there's these intervening things that can affect then what's coming in. So just measuring the retics doesn't tell you whether you're going to get up here.

THE COURT: But -- well, I appreciate that answer and I think I understand it.
THE WITNESS: Uh-huh.
THE COURT: But if I, if I were a physician and I had a sure source --
THE WITNESS: Uh-huh.
THE COURT: -- of reticulocytes, which I take it this invention claims to give you --
THE WITNESS: Right.
THE COURT: -- while it would be true that in certain patients I would not get that sustained response --
THE WITNESS: Uh-huh.
THE COURT: -- I could then go looking for these

other causes, iron deficiency, too quick destruction of the red blood cells, infection, the things you've mentioned.
THE WITNESS: Yes.
THE COURT: And if I could stop them or take care of them then, since your analogy is to physics, if I've got a sure source of reticulocytes that hematocrit is going to come up, correct?
THE WITNESS: But you're assuming then that you have to measure both, the retics and the hematocrit. Measuring just the retics alone is not going to give you that answer.
THE COURT: That's fine. I think I understand. But my point as I grapple with the legal aspects --
THE WITNESS: Uh-huh.
THE COURT: -- of this is, you've introduced the, not introduced, but you've pointed out that in order to be

therapeutically effective you've got to have sort of a sustained effect.

THE WITNESS: Correct.

THE COURT: And then when I asked you about that you pointed out how complex the matter was because a number of things are going to, other things are going to --

THE WITNESS: Right.

THE COURT: -- be at play here.

How would you measure a sustained supply of, as

you call them, retics? Would you?

THE WITNESS: We know clinically that if the hematocrit is staying stable with erythropoietin therapy there has to be new retics coming out.

THE COURT: But I'm trying to get at what you mean by sustained.

THE WITNESS: Well, a sustained level of hematocrits have to be --

THE COURT: Isn't it a temporal concept? Over what period of time?

THE WITNESS: As long as you're treating, using that therapeutic agent.

THE COURT: And is that how it works? In other words, have you discovered that if you're using this therapeutic agent you can get those hematocrit levels up and you can hold them up, save for these other things?

THE WITNESS: Oh, yes. Been doing this for 18 years.

THE COURT: So for you sustained is a successful therapy?

THE WITNESS: Exactly.
THE COURT: You're saying this, this works unless I've got some other problem.
THE WITNESS: Exactly right.
THE COURT: Infection.

THE WITNESS: Yes.
THE COURT: Too quick destruction.
THE WITNESS: Right.
THE COURT: Iron deficiency. And I'm sure --
THE WITNESS: Yes.
THE COURT: -- there's others. But an array of problems --
THE WITNESS: Yes.
THE COURT: -- that physicians know.
THE WITNESS: Exactly.
THE COURT: Thank you. Go ahead, Mr. Madrid.
MR. MADRID: Thank you, your Honor.
Q. Doctor, do you have an opinion as to whether or not in the context of your bathtub analogy the erythropoietin preparation that you administer can have an effect with respect to accomplishing sustained increase?
A. Yes.
MR. FLATTMANN: I object, your Honor. It's not in the reports.
THE COURT: Yes.
MR. FLATTMANN: The analogy wasn't in the reports but it was in response to your Honor's question. This is clearly not --
THE COURT: There we are. I'll sustain it.

MR. MADRID: Your Honor, if I may?

668

THE COURT: Yes.
MR. MADRID: The reports address the Goldwasser study, in fact, address this very point as to whether or not --
THE COURT: Well, where is it? Just show me where it is.
MR. MADRID: Sure. If we look at the 10-03 report. And if one looks at Paragraph 32.
THE COURT: Just a moment.
MR. MADRID: Wait a minute. Sorry. Paragraph 33 of the 10-03 report. And Paragraph 23.
THE COURT: Yes. But my problem is, my ruling as to the untimely report was I would allow you to make reference to specific citations. Where in some earlier report is it?
MR. MADRID: Your Honor, I believe there may be a misunderstanding here. The 10-03 -- 10-3-03 report is filed and served timely. That's not contested. The earlier report, the 9-16 report, was filed timely but in the 9-16 report we did not specify specific pages that Dr. Eschbach was relying upon.
THE COURT: So, it's the correction of the 9-16 report. I'm following. All right, go ahead.
MR. MADRID: Okay. In the 10-3-03, Paragraph 23 --

669