UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC.,)
)
Plaintiff,)
)
vs.) Civil Action
)
F. HOFFMANN-LA ROCHE LTD., a Swiss) No. 05-12237 WGY
Company, ROCHE DIAGNOSTICS GmbH,)
a German Company, and HOFFMANN-LA)
ROCHE, INC., a New Jersey)
Corporation)
)
Defendants.)
_____)

DEPOSITION OF STEVEN G. ELLIOTT, Ph.D.
Thursday, March 29, 2007

- CONFIDENTIAL -

REPORTED BY:
JUDY SAMSON
CSR NO. 6916

to be.

Q We're talking about use in humans.

So can you know that something is going to work in humans until you do a clinical trial?

A When you say "work," there's different kinds of meaning to the word "work."

So can you actually demonstrate that there's the biological effect you want?

You know, you might be able to predictably say that's going to be true.

Would you have a safety profile associated with it that's acceptable? You may not know that.

So there's different kinds of things that we're doing when we're talking about predictability in humans.

There's more that goes into a successful commercial product then merely the biological activity assay.

So you could predict with high likelihood the likelihood that you'll see the in vivo response you need, but that does not mean that the threshold for approval by the FDA is going to happen because there's other variables that come into that that have nothing to do with the biology.

Q Are you familiar with any pegylated

erythropoietin molecules?

A I'm aware of some, yes.

Q Can you predict whether any of those will work in the clinic before testing?

MR. DAY: Objection.

THE WITNESS: Yeah, let's define what you mean by "work" first.

There's work in terms of increased half life, the work in terms of is it safe and effective, are there liabilities associated that would outweigh, you know, make it unapprovable.

BY MR. JAGOE:

Q All of these things.

A We don't have an approval for any pegylated erythropoietin yet.

Q Can you predict now whether you will or will not?

A I think that's up to the FDA to decide and the results of the clinical trials that are looking at safety.

So I think it's a safety, efficacy, cost. And there's a lot of variables that go into that decision that are beyond the scope of what is happening in the laboratory.

Q So in one of your answers you said, "we

don't have an approval for any pegylated erythropoietin yet."

When you say "we," who are you referring to?

Amgen?

A "We," meaning the scientific community.

There's, to my knowledge, nobody that has had an approval in the United States or Europe to sell commercially pegylated erythropoietin.

Q And based on what you know, are you able to predict whether there will be a safe and effective pegylated erythropoietin?

MR. DAY: Objection; irrelevant, lacks foundation, calls for expert testimony, beyond the scope of this deposition.

THE WITNESS: Yeah, I would agree with that.

There's a lot of variables that go into that that are political, let's say, financial that I could not comment on.

BY MR. JAGOE:

Q Based on the science --

A There's legal reason as well, which is why we're sitting here.

Q Based on your understanding of the science,

are you able to predict whether a pegylated erythropoietin will be a safe and effective compound for treating anemia?

MR. DAY: Same objections.

THE WITNESS: Yeah, "safe and effective" are terms that will require, you know, clinical trials.

And I think really it's going to come down to a safety issue with, you know, theoretical risks.

Whether it will be approved is going to be a consequence of a number of variables including legal ones.

BY MR. JAGOE:

Q Are you aware of Amgen clinical data on pegylated erythropoietin?

A That Amgen has done, I am not aware of any.

Q Do you know if Amgen has prepared any pegylated erythropoietin?

A We have made preparation of pegylated NESP.

There may have been early experiments to look at pegylated EPO.

Q Were you involved in any of the work on preparing pegylated EPO?

A Preparing pegylated EPO -- if you mean did I help construct or manufacture or make peg EPO, no,

I didn't do that.

Q Were you involved in any testing or analyzing of peg EPO?

A I don't recall specifically whether I tested preparations.

I may have.

Q What type of testing would you -- may you have done?

A If I did any, I might have done some receptor binding studies and/or in vitro studies or helped coordinate getting some samples into a mouse bioassay.

I recall doing something with a pegylated molecule. I'm not sure exactly what the preparation was.

Q What time frame are we talking about when you may have done those experiments?

A I don't recall exactly. This was a number of years ago.

Q Within the last five years?

A Probably before that.

Q And were you involved in the pegylation of NESP?

A I wasn't involved directly in making the preparations. I was aware of the project.

else to say.

Q Is there any way to predict whether a novel protein will be immunogenic in a human before testing it?

A It depends.

MR. DAY: Again, I'll object. It calls for expert testimony, lacks foundation.

BY MR. JAGOE:

Q What does it depend on?

A It depends on what else you know about the history of the molecule, and what you've done.

Sometimes you can make a change and there would be -- you would not predict that there would be antibodies; other times you would say there's a theoretical risk.

Q Do you know whether putting a peg molecule onto erythropoietin creates a potential risk of immunogenicity?

MR. DAY: Same objections.

THE WITNESS: Again, this depends on what kind of manipulation you're doing with pegs.

So peg, in general, putting on, it might.

Peg -- certain peg specific modifications to a specific kind of erythropoietin might not.

I'd have to know more.

way via expression from the NESP gene.

MR. JAGOE: I'm going to mark the next exhibit as Elliott Exhibit 10.

(Defendants' Exhibit 10 was marked for identification by the deposition reporter and is attached hereto.)

BY MR. JAGOE:

Q Can you identify Elliott Exhibit 10 for the record.

A Yes, this is an article I wrote for a book that I was one of the editors of.

Q And is it "Erythropoietin and Erythropoiesis"?

A Oh, the title -- yes, "Erythropoietin and Erythropoiesis."

Q And it was published in 2003?

A Yes.

Q And the title of your chapter is "new Molecules and Formulations -- sorry. "New Molecules and Formulations of Recombinant Human Erythropoietin"?

A Yes, that's the title.

Q And you're the sole author?

A Yes.

Q And you wrote this as an employee of Amgen?

A I wrote this while I was at Amgen.

Q And did this undergo internal Amgen review prior to the publication?

A I had people that read it, and it was approved, yes.

Q Okay. On page 246 of your chapter there's a section called "Pegylation."

A Yes.

Q The second sentence says:

"Pegylation involves chemical attachment of the polymer, polyethylene glycol (PEG), to reactive regions of proteins or carbohydrates."

Did I read that correctly?

A You read that correctly.

Q What did you mean by "chemical attachment of the polymer, polyethylene glycol, to reactive regions of proteins"?

A This is a chemical reaction whereby one would -- using an appropriate subtract and chemical environment -- allow the attachment of a peg to a particular reactive atom.

Q What types of atoms are reactive in proteins that you're aware?

A Well, it kind of depends on the chemistry

that you use. So there's different polyethylene glycol chemistries.

You can target any number of chemistry or reactive intermediaries depending on where and how you want to do the attachment.

So there's different way of putting peg onto erythropoietin.

Q Are all ways equivalent?

MR. DAY: Objection; lacks foundation, calls for speculation, expert opinion.

THE WITNESS: Yeah, let's talk about equivalent can mean many things.

So when you say "equivalent," what do you mean?

BY MR. JAGOE:

Q Can you chose any one of those chemistries to put on peg and end up with a molecule that has equivalent function?

A Again this depends. It depends.

I need to know more about the particular chemistry that you're talking about in order to make a conclusion about that.

Q On the next page you say that -- in the second paragraph:

"The current chemistries typically

target the reactive amino groups on lysine --"

A Where are you reading that?

Q The second paragraph starts --

A 247.

Q "One issue with drugs."

A Yes, I see.

Q And, then, in the middle of the paragraph there's a sentence:

"The current chemistries typically target the reactive amino groups on lysine or the amino terminal amine."

A Yes, I see that.

Q Then you say:

"Recombinant human EPO has eight lysines, some of which are part of the active site."

Right?

A Yes, that's what it says.

Q So if a peg group were attached to one of the eight lysines of human erythropoietin as opposed to another lysine of human erythropoietin, would you expect a difference in the biological activity of the product?

A There's several different kinds of

activities we are referring to.

So, you know, all things being equal, looking at a particular assay, you could see a differential effect of adding peg at one position than another one.

The properties that would be changed would depend on which assay we're talking about.

Q So if you're talking about an in vivo assay?

A Which one?

Q One that measure the ability of a compound to increase reticular sites in red blood cells in the body.

A So your question is if you had an assay where you're asking about increasing red blood cell formation, would you see what?

Q Differences depending on where a peg molecule were attached.

A Would I see differences in a given assay with polyethylene glycol attached at different positions, would I see a different relative amount of activity?

I think the answer is likely yes, you would see, under those specific conditions, a different relative activity.

Q And some would be relative to recombinant human erythropoietin, and some could have more activity than recombinant human erythropoietin and some could have less activity than recombinant human erythropoietin?

A Depending --

MR. DAY: Excuse me. Objection; lacks foundation. It's ambiguous and calls for expert opinion.

BY MR. JAGOE:

Q Now you can answer.

A Okay. Can you rephrase the question.

MR. JAGOE: Can you read it back.

(The record was read back.)

MR. JAGOE: Let me try it again.

BY MR. JAGOE:

Q You agree that there are eight reactive lysines on human erythropoietin.

A There are eight lysines.

The reactivity would depend on the context.

Q Right.

Do you know whether a peg molecule could be attached to any one of those lysines?

A It depends on the chemistry and on the folding status of a given molecule. And these are

probabilities.

Can you define a chemistry that would add peg to all of the lysines? You could find conditions that would do that.

Q So if you were able to make eight individual preparations, differing on where the peg was attached to the erythropoietin, each being attached to one of the eight lysines, you would expect a range of activities in an in vivo assay; correct?

MR. DAY: I'll object; lacks foundation, calls for an expert opinion.

THE WITNESS: Yeah, this experiment has never been done.

BY MR. JAGOE:

Q To your knowledge.

A To my knowledge, that experiment has not been done.

Q Would you be able to predict the result of such an experiment based on your work in studying the function-structure relationship of the amino acid in erythropoietin?

A Predict which result?

Q The results of the experiment that you say has not been done.

A There's a lot of experiments that haven't been done.

Q No, but you know we're talking about a particular experiment.

A No, we're not.

We're talking about in vivo activity, and there's a whole bunch of different kinds of assays that one could do.

So none of those experiments, to my knowledge, have been done in any assay.

So now we're getting into specifics. The result would depend on which assay we're doing.

Q Okay. Based on your work studying the structure and function of the amino acids of erythropoietin, are you able to predict the effect of adding a peg molecule to lysine 45 of human erythropoietin?

MR. DAY: Objection; vague and ambiguous, compound.

THE WITNESS: That is true. It's a pretty vague and ambiguous question because we have to define what we mean by activity and what experiment and for what use and how did you do it really depends on what the result is.

So how you add the peg has an impact on

this.

There's a whole bunch of different chemistries that one could do. And if you do a chemistry that inactivates the molecule, then you're going to lose in vivo activity.

If you do it differently, you might get a different result.

I can't answer the question without knowing more detail about it.

BY MR. JAGOE:

Q In your book chapter, you refer to current chemistries that are typical for targeting the amino groups on lysine; right?

A There are chemistries that use that -- that target the amino groups.

Q And what are those chemistries?

A I don't have the specifics of the particular chemistries and what they involve.

But I merely know that it's a reactive polyethylene glycol that would target an amino group.

Beyond that, I don't have the specific detail.

Q Would attaching a polyethylene glycol polymer to a lysine effect that equilibrium of

"Peg is thought to be relatively inert and non-immunogenic by itself, so it is a suitable starting material for protein-conjugate therapeutics."

A I'm not sure where that is so --

Q 247.

A Yes.

Q We talked about the paragraph that starts with "One issue."

A Yes.

Q The paragraph just above that ends with the sentence, "peg is thought."

A Ends with the sentence -- the sentence of that paragraph I'm seeing begins with "other peg related EPO molecules."

Are we going down further?

Oh, the paragraph above. I'm sorry.

Okay. Yes, I see the sentence.

What's your question?

Q Is that true, that peg molecules are relatively inert and non-immunogenic?

A It depends.

As a global statement, immunogenicity in a particular person can vary, and the peg molecule itself may or may not be immunogenic.

But to speak further than that, to say whether you add peg to a molecular, whether that molecule would be immunogenic, would depend on what molecule that is and how you measured it.

And then it also might depend on how long you wait to actually assess immunogenicity, because immunogenicity in a short term might show you something or may not show you an effect.

But if you wait long enough and have a large enough population of people, you might actually see some immune reaction against it.

Q So this would be another instance where you just have to do the test, the trial and see what happens?

A With a given molecule, looking at the variable nature of the human population and what we know, if we're going to speak about erythropoietin specifically --

Q Yes.

A -- we know that there's a potential for immunogenicity which is caused by whole bunch of variables, some of which have to do with manufacturing processes.

And so one could imagine that if you were to do pegylation of EPO, there might be some

conditions under which you pegylate that would result in immunogenicity and other conditions where it might be less likely to get immunogenicity.

It's a combination not only of whether peg is there or not, but also how you make the protein.

So because of all of these variables, one would need to do an experiment to find out.

And, then, even when you do the experiment, it's not necessarily conclusive because you might only have a limited number of samples or time that is involved in the experiment.

MR. JAGOE: I'm going to mark the next exhibit as -- Elliott Exhibit 11 is the PCT publication WO 95/05465.

(Defendants' Exhibit 11 was marked for identification by the deposition reporter and is attached hereto.)

BY MR. JAGOE:

Q Earlier this morning you spoke of a patent application on NESP.

Do you recall that?

A Yes.

Q Is this the patent application that discloses NESP?

A I'd have to look and see if NESP is