DR. NIYIKIZA

Dr. Niyikiza Testimony

8	Q. Dr. Niyikiza, do you hold a Ph.D.?
9	A. Yes.
10	Q. In what subject?
11	A. I hold a Ph.D. in mathematics and in statistics.

Dr. Niyikiza Testimony

Q. Did you at that point -- would you have any expertise in what doses of vitamins to give to patients?

A. No. I had to do the literature, and I did. And, Counsel, you asked me why I was thinking about what I was thinking. There was another important factor. The important factor was that we couldn't do it the same way we had been doing for the past five years, because it had failed. And if doing so was going to be the way we go about it, we were probably going to fail the next generation of patients.

So, it became an urgency, in my view, and I reviewed the literature, but I also had an interesting insight. When I went home some evening in that March timeframe, I found my wife in discussion with my young son about cereals that he wanted to make sure he has but they were not in the house. So we were living on the northwest side of Indianapolis, and my wife gave me clear executive orders to go and get those cereals.

So, I went to a Kroger pharmacy on 58th and Georgetown, and I was looking at the cereals, and there was also this supplements aisle. And then I saw bottles of 400 microgram of folic acid. I saw some other amounts in different tablets, but I also saw some pills of B12. And I had done some reading and realized that these are the kinds of interventions you can have in trying to restore the folate pools, restore this for patients in general. And actually, even normal human beings, you need that.

So, I figured that given that we had failed with five-milligram folic acid the way we're doing it in the previous programs, given that there was also concern that the biochemistry experts were telling me that if you give too much of folic acid, you will lose the efficacy of the drug --

DR. BLEYER

Dr. Bleyer's Testimony

69. Opinions concerning Hammond:

Lilly Interpretation to FDA (Exs. 2103, 2107)	**Lilly Interpretation to *The Oncologist* (Ex. 1047)**
Ex. 2103: "Ongoing LY231514 trials include a phase I study of LY231514 and folic acid. An interim report suggests that folic acid supplementation in this study permits dose escalation by ameliorating toxicity since heavily and minimally pretreated patients tolerate LY231514 at doses of 700 and 925 mg/m^2 respectively [10]." [10 = Hammond, Ann Oncol 1998] **Ex. 1075, 167:14-168:21** Q. The next paragraph starting with	Ex. 1047: "preliminary results indicate that the addition of folic acid ameliorates toxicities permitting dose escalations of pemetrexed up to at least 925 mg/m^2 in heavily pretreated patients [49]." [49 = Hammond, Ann Oncol 1998] ***Chabner disagrees that Hammond teaches a POSA that the addition of FA ameliorates toxicities thus permitting dose escalation.*** **Ex. 1075, 141:25-142:19**:

Source: Ex. 1077 at ¶69; Paper 48 at 8-9.

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Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
"ongoing LY231514 trials." That's where I am next. It says, "Ongoing LY231514 trials include a Phase I study of LY231514 and folic acid. An interim report suggests that folic acid supplementation in this study permits dose escalation by ameliorating toxicity since heavily and minimally pretreated patients tolerate LY231514 at doses of 700 and 925, respectively. Reference 10." Do you see that? BRUCE CHABNER A. I see that. Q. What is reference 10 -- A. That's -- Q. -- that is cited for that proposition? A. That is a Hammond paper. Not the abstract. Where do we have the list of the references? Q. Reference 10, if you go back. It's abstract 620, correct? A. I don't see it. Annals of oncology supplement 4. Yes. I guess that's the same. I -- I'm not sure. I guess it is the same abstract that we've looked at. Q. Yes. That reference 10 if you -- I think you have it in front of you. A. Yeah. Q. Reference 10 is Exhibit 1022 in this proceeding. A. Okay. All right. ***Chabner disagrees with everyone who thought Hammond was encouraging for FA pretreatment*** **Ex. 1075, 160:5-20**	Q. What did the person of ordinary skill BRUCE CHABNER in the art as of June of 1999, what would that person take from Hammond, from the Hammond disclosure? A. A person of ordinary skill would see the very poor response rate. The fact that -- the logic of the trial was that they could dose escalate with the drug and get a better response rate. That proved not to be the case. They began running into renal toxicity, which is a serious problem for a drug that undergoes renal clearance. So they couldn't dose escalate. I mean with methotrexate you can go up tenfold, even more in dose. They couldn't do that. And so they were -- the result was that they had one response in the 30-some patients that they studied. **Ex. 1075 143:9-145:2:** Will you turn to Page 371. A. I can't find -- oh, here we. Yes. Q. And if you look at the first full paragraph on the left-hand column -- A. Uh-huh. Q. -- starting "based on." A. Uh-huh. Q. "Based on these other preclincal findings, a Phase I study combining pemetrexed and high dose intermittent oral folic acid, 5 milligram on days minus two to day plus two of every cycle, has been initiated. While this trial is currently still ongoing, preliminary results indicate that the addition of folic acid ameliorate toxicities, permitting dose escalations of pemetrexed up to at least 925 milligrams per BRUCE CHABNER

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
Q. So you disagree with everyone who thought Hammond showed some encouraging signs towards folic acid pretrial? A. I disagree with everyone. I'm just stating what I think that a person of ordinary skill would conclude from happening. I think a lot -- you know, there was not -- also a prior trial at Lilly with lometrexol which -- which showed the same negative result. So I think it was a discouraging. I mean it was virtually the same result. It was one response in 30-some patients, and they -- they dropped lometrexol. So it didn't seem to me that was a promising avenue of approach. ***Chabner not aware of any art reading Hammond results like he does – rejects the teaching because Lilly did not use the Hammond regimen*** **Ex. 1075, 160:22-161:12** In preparing your declaration for the two or three years you've been working on this matter -- A. Yeah.	milliliter in heavily pretreated patients, reference 49." A. Where do you see -- I'm sorry, I'm not following you. Q. Do you see the paragraph -- A. Oh, this is on the left-hand side of the page. Q. Yes. A. Well, that actually didn't happen. But all of this is post facto. This is hindsight. Once the trials are done and the data is available to patients on the -- the supplementation business, you can say, well, it worked. Q. What is -- A. I was very surprised it worked, to tell you the truth. Q. What is reference 49? A. Oh, that's Hammond, I suppose. I don't know. Q. And what -- A. But that wasn't true, was it? Q. Well, how did you let this get published in The Oncologist if this wasn't BRUCE CHABNER true? **Ex. 1075 146:11-148:14** **(Q. This seems to be in conflict with your opinion that a person of ordinary skill in the art would have taken from Hammond failure?** **Q. Does it not?** **A. What -- yes. That -- my opinion is that people would look at the abstract and say it failed.** Q. Did your reviewers fail here by letting this through? A. Pardon?

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Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
BRUCE CHABNER Q. -- and studying it, have you ever identified anyone, any author in the prior art or after the prior art that characterizes Hammond like you do? A. You know, I haven't asked that question of any people, I'm sorry to say. I would say this, that the company didn't -- didn't use that regimen ever again. Q. The company didn't use that regimen. The company pretreated, used folic acid. A. They didn't use that regimen. ***Chabner admits that Hammond taught POSA it was possible that FA permitted a patient to remain on 500 dose rather than require dose reduction – and admits no evidence that anyone disagreed with Hammond conclusion that FA permitted dose escalation*** **Ex. 1075, 180:13-184:15:** Q. Sure. So we are on Exhibit 2035, which is a Hammond abstract. A. Yes, right. Q. And the last sentence of that abstract concludes, "These results indicate that folic acid supplementation appears to permit MTA dose escalation." Do you see that?	**Q. Did your reviewers fail by letting this through?** **A. What do you mean, did my reviewers fail? What a stupid question. Come on.** Q. Well how -- I mean you would agree that that – **A. I don't read -- I don't read every sentence in every paper that is published in that journal, do I?** **Q. Do you wish you would have so you could have corrected -** **A. I wish I would have corrected it, yes, sir.)**

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
A. It does. Q. And would a person of ordinary skill in the art as of June of 1999 have any reason to disagree with the conclusion of Hammond? BRUCE CHABNER A. Yes, they would, because we knew that there was a problem with creatinine clearance in these patients. Q. And have you cited or identified anywhere, Dr. Chabner, any publication in the prior art or otherwise that takes issue with the Hammond conclusion? A. Oh, my God. Why would -- I mean why would they argue with it? I don't think they would. I mean that is his conclusion. He is entitled to make his conclusion. He did dose escalate. It doesn't say that that was the dose they chose -- they could choose to study further. They didn't. I mean I think it's obvious that as of June 1999, they weren't studying 900 milligrams per meter squared with folate supplementation, unless I'm mistaken. Q. Does Hammond's abstract	

Source: Ex. 1077 at ¶69; Paper 48 at 8-9.

Dr. Bleyer's Testimony

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
state or imply to a person of ordinary skill in the art anything that was disappointing about the results of their study? A. No. Of course, the fact that they had BRUCE CHABNER one response was disappointing. If they had seen 10 responses, they would have jumping for joy. I wasn't there at this presentation so I don't know what -- what his feelings were about it. Q. Would a person of ordinary skill in the art as of June 1999 understand from this Hammond abstract that folic acid may permit a patient to take either additional cycles or a greater dose than they might otherwise tolerate? A. I think what a person of ordinary skill would know in June of 1999 is that folate supplementation was not associated with what appeared to be an improvement in response rates, and it may -- the data were unclear as to how much of a dose escalation was permitted because of this --	

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
this problem with impairment of creatinine clearance. And so they -- you know, it didn't work out that they would use dose escalation with folate supplementation. BRUCE CHABNER Q. Would -- A. It never did. Q. Sorry. You finished? A. They never did. Q. Would a person of ordinary skill in the art as of June 1999 understand from Hammond that folic acid may permit a patient that had to go from a 500 to a 350 dose could remain at the 500 amount if it was accompanied with folic acid pretreatment? A. That really wasn't proven, but, you know, it is still possible. And I think that what we don't know is that if that folate was added, whether that would reverse the antitumor activity. That was still in question. Q. Well, we know it didn't completely reverse the antitumor activity from Hammond, don't we? A. That's one patient.	

Source: Ex. 1077 at ¶69; Paper 48 at 8-9.

Dr. Bleyer's Testimony

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
Q. So is that a yes? A. There was one patient that responded. Q. And so we know that the administration of folic acid in Hammond did BRUCE CHABNER not eliminate antitumor activity – A. Did not completely eliminate, yes. Q. In fact, not only did it not completely eliminate it, there was a patient who took it and got a partial response, correct? A. Well, that's what I mean by did not completely eliminate it. We may have 90 percent eliminated it, but we don't know. But it certainly wasn't an encouraging result, you know. Q. Your opinion is that Hammond was not an encouraging result? A. Not at all. Ex. 2103: "As previously mentioned, a phase I study of LY231514 and folic acid (Study JMAS) has shown that folic acid supplementation permits dose escalation by ameliorating toxicity since heavily and minimally pretreated patients tolerate LY231514 at doses of 700 and 925 mg/m^2 respectively [10]."	

Source: Ex. 1077 at ¶69; Paper 48 at 8-9.

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Dr. Bleyer's Testimony

70. Opinions concerning Worzalla

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
Ex. 2103: "As with lometrexol, in vivo experiments with LY231514 have suggested that supplemental folic acid modulates its toxicity profile and antitumor activity. . . In these experiments, the antitumor activity of LY231514 was preserved [9]." [9 = Worzalla, Anticancer Res 1998] **Ex. 1075, 165:5-167:13**: Q. And do you understand, Dr. Chabner, that Lilly Exhibit 2103 is a Lilly submission to the FDA where Lilly is telling the FDA or -- or suggesting to the FDA that they want to add vitamins to the pemetrexed -- A. Yes. Q. -- regimen, correct? A. I do. Q. Now, you will see at the end of this brief, before the page that says "Dear JCMH Investigator." A. I don't. Q. And I can turn it for you. A. Yeah. Show me what you're talking about. (Document tendered.) Q. At the end of that brief, there is a section called "references." A. Gotcha.	Ex. 1047: "Concurrent with this analysis, preclinical data supported the notion that oral folate supplementation markedly reduced toxicities in mice while maintaining antitumor efficacy [48]." [48 = Worzalla, Anticancer Res 1998] ***Chabner disagrees that Worzalla taught FA can reduce toxicity and maintain antitumor efficacy.*** Ex. 1075, 157:5-159:20 (Q. Exhibit 1047, that sentence says, "Concurrent with this analysis, preclinical data supported the notion that oral folate supplementation markedly reduced toxicities in mice while maintaining antitumor efficacy, reference 48." Do you see that? A. I see that. Q. And what is reference 48? A. It's probably Dr. Worzalla, or Mr. Worzalla I should say. Q. Worzalla is attributed for that statement? A. Yes. Q. Do you disagree? A. I think if you take each element of it, you can -- you can say he did show this. He showed that you could reduce toxicity by giving the drug -- folic acid. That's not an issue. The issue is do you get a better therapeutic result. You get the same therapeutic result essentially until you get -- the only data that -- in that abstract that shows any possible advantages is at doses which you could never achieve in people, never.

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
Q. And do you see that reference 9 is BRUCE CHABNER Worzalla, which is Exhibit 1005 in our proceeding. And reference 10 is Hammond, which is Exhibit 1022 in our proceeding. Do you see that? A. I see them both. Q. Now, if you would turn back to the -- to the brief, which is Page 3 of 20. It says that in the bottom left-hand corner. A. Got it. Q. There is a -- first full paragraph on Page 3 is a sentence that starts "as with lometrexol." A. Yes. Q. And if you could read that paragraph. A. "In vivo experiments with, I guess, pemetrexed have suggested that supplemental folate modulates its toxicity profile in antitumor activity. The LD 50 of the drug occurred at 60 to 200-fold lower doses of this drug in DBA/2 and CD1 nu/nu mice maintained on a low folate diet compared with those fed standard diets. In these experiments the antitumor activity of the drug was preserved." BRUCE CHABNER Q. And the drug that they're talking about that was, the antitumor activity was	**Q. Do you think this is a wrong -- an inaccurate citation to Worzalla?** **A. Is it inaccurate?** **Q. Do you think this wrong, miscited?** **A. I don't think it's absolutely correct, that's right. And I was the editor, but I don't read every paper. And I don't endorse every sentence in every paper in my journal. There is certain freedom that people have to make statements, which they're -- it's fine with me if, you know, they interpret it a different way. But that's my interpretation.** I think that a person of ordinary skill would have the same interpretation.) *Id.* at 219:23-221:5 (Q. And then it goes on, "Concurrent with this analysis, preclinical data supported the notion that oral folates supplementation markedly reduce toxicities in mice while maintaining antitumor efficacy," and that cites to Worzalla prior art, correct? A. Yes. And as I pointed out previously, you take apart that sentence, it certainly did reduce toxicities. It shifted the curve, the dose-response curve far to the right. And you did get the same efficacy but at a much higher dose, and that begins to be a problem -- not begins to be. It confronts a problem, and that is, you can't escalate the dose of pemetrexed indefinitely in patients. **So the relevance of this is questionable.** **Q. And did you raise any of these issues at the time that this article --** **A. I didn't -- I don't believe --** **Q. -- was published in the journal --** **A. I don't believe I reviewed the paper --** **Q. -- that you're editor -** **A. I don't think I reviewed this paper in detail. I thought it was worth publishing,**

Source: Ex. 1077 at ¶70; Paper 48 at 8-10.

Dr. Bleyer

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Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
preserved is LY231514? A. That's correct. Q. And that's pemetrexed? A. Right. Q. And the reference cited to substantiate the argument that Lilly was making to the FDA is reference 9? A. Yes. Q. And what is reference 9? A. Worzalla. Ex. 2107: "Preclinical and clinical studies evaluating the impact of dietary folic acid on the toxicity or efficacy of antifolates such as LY231514 and lometrexol have been reported. Because tumor tissue and normal tissue, such as bone marrow, presumably have different folate requirements, it is possible to decrease the toxicity to healthy tissue while maintaining antitumor effect through careful adjustment of folic acid intake. This has been shown in experimental systems for LY231514 and another antifolate, lometrexol (**Worzalla et al. 1998**; Alati et al. 1996) and in clinical trials with lometrexol (Young et al. 1992; Laohavinij et al. 1996)." ***Chabner disagrees with Lilly's statement to the FDA that Worzalla taught a POSA that FA can reduce toxicity and maintain antitumor activity.*** Ex. 1075 249:12-250:20	**obviously. It got published but, you know, I don't -- I don't conduct a deposition with each of my authors, if that's what you're saying.)**

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
(Q. "Because tumor issue and normal tissue such as" -- sorry -- "because tumor tissue and normal tissue, such as bone marrow, presumably have different folate requirements, it is possible to decrease the toxicity to healthy tissue while maintaining antitumor effect through careful adjustment of folic acid intake. This has been shown in experimental systems for LY231514 and another antifolate, lometrexol," citing to Worzalla and Alati. Do you see that? A. I do. Q. And is the -- and, Worzalla, is that the same -- is that the same Worzalla that we've been -- we have looked at today? A. Yes. Q. Worzalla 1998, correct? A. Right. **Q. And so Lilly told the FDA that the prior art Worzalla document showed that LY has shown for LY231514 that it is possible to decrease the toxicity to healthy tissue while maintaining antitumor effect through careful adjustment of folic acid intake."** **Q. Do you agree with that?** **A. I, you know, I wouldn't have said that. No, I don't agree with that. I'm sorry.)** *Id.*, 251:19-24 **(Q. And are you aware of any publication that sides with your interpretation of Worzalla and not the one that is disclosed in The Oncologist article -- or these FDA reports?** **A. No.)**	

Source: Ex. 1077 at ¶70; Paper 48 at 8-10.

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Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
Ex. 2107: "**Worzalla and coworkers** have studied the effects of folic acid on the toxicity and antitumor activity of LY231514 in the in vitro and in vivo settings. In a number of human tumor cell lines, folic acid protected cells from cytotoxicity at concentrations 100- to 1000-fold higher than those required for folinic acid protection, indicating that the action of LY231514 is less sensitive in vitro to folic acid than it is to folinic acid. They also found that in mice fed a low folate diet (LFD), tumor growth inhibition was complete at LY231514 doses of 0.9 to 3.0 mg/m2 with 100% lethality occurring at LY231514 doses of 9.0 mg/m2 or higher. Mice receiving the same 121) who were supplemented with high doses of folic acid at 15 mg/kg/day (a dose approximately 10-fold greater than that in the normal diet) experienced complete tumor growth inhibition at LY231514 doses of 90 to 3000 mg/m2 without any lethality. Mice on the standard diet (approximately one tenth of the folic acid given to the supplemented mice) saw a virtually identical dose response, but greater lethality, with 100% lethality occurring at 2400 mg/m2 (**Worzalla et al. 1998**). These data show that antitumor activity is virtually identical in mice receiving a standard diet to that in mice receiving a 10-fold increase in daily folk acid. Mice receiving the extra folic acid also showed a decreased lethality at higher	

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
doses of LY231514. These data support the hypothesis that folic acid supplementation can protect healthy tissue from the toxic effects of LY231514 with retention of antitumor activity." **Ex. 1075, 269:3-277:2:** Q. All right. So I want to go to Page 12, the second page of this discussion. And do you see that the data -- there is a cite Worzalla et al. 1998.□A. Yes.□Q. Do you see that that's the□Worzalla --□ A. Now, wait a minute. What page are you going to?□ Q. Page 12, the next page right above the table.□ A. Wait a minute. Page -- yeah. We are switching pages here unfortunately. Okay.□**Q. Okay. You with me?□And you see where it says Worzalla et al. 1998?□ A. Yeah.□ Q. And that's the same Worzalla that's at issue in this case, correct?□ A. Right.□ Q. And there is a table and the sentence or the paragraph below the table Lilly wrote to the FDA, "These data" -- and this is a reference to prior data --□ A. Right.□ Q. "These data show that antitumor activity is virtually identical in mice receiving a standard diet to that in mice receiving a 10-fold increase in daily folic acid. Mice receiving the extra folic acid also showed a decrease lethality at higher□doses of LY231514. These data support the hypothesis that folic acid supplementation□can protect healthy tissue from the toxic effects of LY231514 with retention of antitumor activity." Do you see**	

Source: Ex. 1077 at ¶70; Paper 48 at 8-10.

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Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
where Lilly --□ A. I do see that.□ Q. -- said that to FDA?□ A. Yeah. Right.□ Q. Do you think Lilly misled the FDA about what the prior art did --□ A. I don't think they -- I'm not.□ A. I'm not in a position to judge whether they misled it. My interpretation of this is, first of all, the standard diet is a high folic diet. It's not the human diet. So this moves the doses way up. Then they add a much larger□increment of folate with a low folate plus 15 milligrams per kilogram. Do you realize for a human being that would be like 60 to 100 milligrams of folate a day. We wouldn't take that. It□would turn our urine like iridescent yellow.□ And at doses of maximum□activity -- I'm looking at the table. I hope you can see that. 90 to 3,000 milligrams per meter squared. I mean there is no way you could give that on a daily basis to an animal – a human and even come close to those doses. I mean this is irrelevant. You're dealing with a mouse that has a creatinine clearance like 50 times that of a human. He is able to cure -- eliminate the drug fast and has a tolerance for drugs which is much greater than humans. So I don't know how to interpret that data. I don't think it's -- it tells me that I can do this in people because I can't get to those kinds of doses. The 3 -- 3 grams per meter squared in a human would be like 12 grams per meter squared -- 3 grams per meter squared in a mouse would be in the range of 12 grams per meter squared in humans. There is no way you can do that. I mean you're starting to get creatinine changes at	

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
600. **So, you know, I think they interpreted the experiment accurately**, and what they said in this experiment, with this tumor, a very disabled mutant tumor, which doesn't resemble any human tumor I've ever□seen, and with these high doses in mice and with this extremely, extremely high folate□supplementation, they can actually get away with these high doses. **And they may have□seen a broader window for the therapeutic ratio, yes. But, you know, whether this could□be done in people, I think it's highly, highly dubious.**□ Q. Would a person of ordinary skill in the art in June of 1999 disagree -- agree or disagree that the Worzalla '98 data support□the hypothesis that folic acid□supplementation can protect healthy tissue from the toxic effects of LY231514 with□retention of antitumor activity?□ A. I would look to the Hammond trial. I wouldn't -- I would say, "Look, this is a□really weird regimen in mice with a disabled tumor." I would look to the human trials to see what that says. In the human trials Hammond showed that you couldn't escalate. I mean you□couldn't go to -- from 500 to 5,000 milligrams per meter squared like they did in the mouse. And, you know, you're using once -- a one-day regimen rather than a constant daily regimen. And you're treating□human tumors. You're not treating this disabled poor tumor that they used in mice, which has, you know, a hypersensitivity to□TS inhibitors. **So I would say, "Show me the human**	

Source: Ex. 1077 at ¶70; Paper 48 at 8-10.

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Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
data. What did it do in people?" And I found that, you know, totally unconvincing that I should go forward with it. Now, why they did this with the FDA, I don't know. Things happened between 1999 June and when this document went in. They had their reasons for doing it. I'm not privy to that. I suspect it was that their regimen was very toxic, that they were testing a mesothelioma and they were eager to find a way to keep going. They had a big investment in this so they did it. A. They used a regimen which had never been tried in people, as far as I know. And that was folic acid and B12. I've never seen any paper prior to '99 where that combination was used to ameliorate pemetrexed toxicity. So their reasons for doing this and their rationale for suddenly changing their trial, I think that's their business. Q. Just to be clear, so I understand your opinion -- A. Yeah. Q. – your opinion, Dr. Chabner, is that a person of ordinary skill in the art in June of 1999 would conclude that the Worzalla data does not support the hypothesis that folic acid supplementation can protect healthy tissue from the toxic effects of pemetrexed with retention of antitumor activity; is that right? A. I would – I would say because you have the Hammond trial, you have data in people. You have to specify whether you're talking about a mouse with this tumor or with people. And if you are asking me to support that statement, I would say in Worzalla's mouse it	

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
seemed to work, at the very highest dose, in a dose which is not achievable in people. And you can't point out to me any instance where they've gone even close to these doses in people. Q. So your opinion is that a POSA in June 1999 would conclude that the Worzalla data does not support the hypothesis that you can have antitumor activity and reduced toxicity? A. My – I -- you say it was in 1999. In 1999, I know Hammond. And so I have doubts about this data, yes. Q. And when Lilly wrote to the FDA that the data support that hypothesis, they, of course, knew about Hammond too, didn't they? A. You know, I'm not sure exactly what they – what they told the FDA. This is not part of my testimony.	

Source: Ex. 1077 at ¶70; Paper 48 at 8-10.

Dr. Bleyer's Testimony

71. Opinions concerning Morgan:

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
Ex. 2107: "In addition, it has been clinically observed that the efficacy of low dose methotrexate used in the treatment of rheumatoid arthritis is not negatively affected by folio acid supplementation, while an improvement in toxicity is seen (**Morgan et al. 1998**). Ex. 2107: "Thirty-two patients with rheumatoid	Ex. 1047: "Studies with other antifolates inhibiting DHFR and TS have suggested that poor nutritional status contributes to the likelihood that a patient will experience severe toxicity when exposed to these drugs [41-44]. More specifically, these studies have investigated the relationship between folic acid and the toxicity of these agents and have concluded that the addition of folic acid significantly reduced toxicity while preserving the antitumor activity of

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
arthritis completed a 24-week, placebo-controlled, double-blind trial of folic acid (FA) supplementation during low-dose methotrexate (MTX) therapy (**Morgan et al. 1990**). Administration of the daily FA supplement significantly lowered toxicity scores without affecting efficacy, as measured by joint counts, joint indices, and physician evaluation of disease activity. Fifteen patients experienced some sort of toxicity; 67% in the placebo group, and 33% in the FA supplement group. Four patients in the placebo group had toxicity levels serious enough to require discontinuation of the MTX, while no patients in the FA supplement group discontinued MTX because of toxicity. It was concluded that a daily supplement of 1 mg of FA during low-dose MTX therapy is useful in lessening toxicity without altering efficacy during the first 6 months of treatment." Ex. 2107: "One of the principal routes of homocysteine metabolism is the folate-dependent mechanism. Through this route, homocysteine is converted to methionine by the enzyme methionine synthase, which is dependent on vitamin B12 and incorporates a methyl group from 5-methyltetrahydrofolate into homocysteine, giving methionine. Therefore, a folate deficiency will result in lowered methionine synthase activity and lead to an elevation of plasma homocysteine levels. Indeed, homocysteine has been found to be a sensitive	the drug. In a study conducted by *Morgan et al.* [41], patients with rheumatoid arthritis who were given a combination of MTX and folic acid experienced less than half the toxicities as compared to those toxicities seen in the placebo group." [41 = Morgan 1990 42 = Smith et al, Cancer Res 1995 43 = Alati, Cancer Res 1996 44 = Mendelsohn, Adv Enzyme Regul 1996] ***Chabner disagrees that Morgan et al teach a POSA that FA can significantly reduce toxicities while maintaining the antitumor activity of the drug.*** Ex. 1075 210:3-211:25 (Q. If you go down around, about a little more than halfway down, that column under that heading there's a sentence that starts "studies with other." A. Yes. Q. And that says, "Studies with other antifolate inhibiting DHFR and TS have suggested that poor nutritional status contributes to the likelihood that a patient will experience severe toxicity when exposed to these drugs." A. Yes. Q. "More specifically, these studies have investigated the relationship between folic acid and the toxicity of these agents, and have concluded that the additional" -- "that the addition of folic acid significantly reduces toxicity while preserving the anti-tumor activity of the drug." Do you see that? A. I see that, and I would like to look at the

Source: Ex. 1077 at ¶71; Paper 48 at 8-9.

Dr. Bleyer

Dr. Bleyer's Testimony

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
marker for folic acid as well as B12 deficiency (**Morgan et at. 1991**; Seihub and Miller 1991)." **Ex. 1075, 279:22-282:20**: **Q. And in the first paragraph after some text, there -- the last sentence, the first paragraph, Lilly wrote to the FDA, "Indeed, homocysteine has been found to be a sensitive marker for folic acid as well as B12 deficiency."** **A. Uh-huh.** **Q. And that cites Morgan et al. 1991?** **A. Yeah. Right.** **Q. And Selihub and Miller 1991. Do you see that?** **A. Right. Right.** **Q. Was it known to a person of ordinary skill in art as of June of 1999 that homocysteine is a sensitive marker for folic acid as well as B12 deficiency?** **A. Well, I think what was known is that homocysteine elevations were found in folic acid/B12 deficiency, and that at least a subset of those patient had either folic acid deficiency or B12, but it didn't distinguish between the two until you did methylmalonic acid assessment.** And then there were other causes of homocysteine elevation. There's an inborn error of cysteine metabolism. Cysteine -- cysteine thio -- what is it? Anyway, it's one of the top metabolic steps in homocysteine metabolism.	references. (Witness reviews document.) Q. 41 to 44, is that what you're looking at? A. Yeah. Q. 41 is Morgan 1990? A. It's not in -- it's not in cancer, Morgan isn't. And I would like to discuss Morgan if you would like. Q. Sure. A. Morgan, the use of a methotrexate in rheumatoid arthritis, there's -- the evidence, then and even stronger now, is that it exerts its effect through a totally different pathway. Not -- not sensitive to folate supplementation. **Q. So you think that citation does not support the proposition --** **A. It doesn't. It doesn't.** **Q. So you think the authors miscited that and the reviewers at The Oncologist missed the mis-citation?** **A. Well, they let him put it in there, but it -- I don't think it's right. I mean I'm -- I didn't write the paper.)**

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
Renal failure, diabetes. So various things can cause it aside from folic acid and B12. **But most patients, most patients with folic acid deficiency or B12 deficiency will have elevated homocysteine. So that's the complete story**. Now, whether it's a sensitive marker, it's -- while it may be a sensitive marker, it's not specific for either one of those. So you have to rule out the other causes. And between folic acid and B12, you have to do methylmalonic acid. Q. And -- and I understand what you said. I don't understand, though, whether you agree or disagree that the person of ordinary skill in the art as of June of 1999 would understand homocysteine to be a sensitive marker for folic acid and B12 deficiency? A. Well, I tried to explain it. I'm wasting my voice. Q. Was your explanation -- is your explanation no, they wouldn't because what you just said, or yes, they would because --- it's not entirely clear? **A. Well --I would say the statement is incomplete in the sense that it should explain that it doesn't distinguish between the two and it doesn't rule out other causes of homocysteine elevation. So my statement was that it is sensitive for both folic acid and for B12, yes.** But it's not specific for -- it isn't a specific test for those or the other causes. ***Id.*, 283:13-284:18**:	

Source: Ex. 1077 at ¶71; Paper 48 at 8-9.

Dr. Bleyer's Testimony

Lilly Interpretation to FDA (Exs. 2103, 2107)	Lilly Interpretation to *The Oncologist* (Ex. 1047)
Q. There's another heading on this page towards the bottom, and the heading is "Safety analysis and rationale for programmatic intervention: Synopsis of safety analysis findings." Do you see that? A. Yes. Q. And the first safety analysis synopsis is -- references multivariate and multiple logistic regression analyses carried out Niyikiza and coworkers. Do you see that? A. Wait a minute. Where is it? What sentence? Q. It's right below "synopsis of safety analysis" -- A. Oh, I'm sorry. I'm on the wrong page. Wait a minute. Where is it? Synopsis. I don't see it. Q. Are you on Page 15? **A. Oh, 15. Oh, okay. Right. Got it. Q. And so the question is: Do you agree that a person of ordinary skill in the art in June of 1999 would understand that a patient's pretreatment serum homocysteine is a statistically significant predictor of his or her risk -- his or risk of developing serious toxicity during the course of treatment with pemetrexed? A. Yes.**	

Source: Ex. 1077 at ¶71; Paper 48 at 8-9.

Dr. Bleyer's Testimony

16. As Dr. Chabner admits, "as of June 1999, the POSA would understand that pemetrexed was the most promising antifolate to be developed since the introduction of methotrexate." (Ex. 2120 ¶ 51.) For this reason, a POSA would have focused on controlling the drug's known toxicities so more patients could tolerate this treatment.

Source: Ex. 1077 at ¶16; Paper 48 at 8-9.

Dr. Bleyer's Testimony

a. I disagree. A POSA in 1999 would have known that pemetrexed is "a very potent inhibitor for human DHFR (Ki = 7.0 nM)," as further explained below. (Ex. 2078 at 142; *see* Ex. 2120 ¶ 179.) As such, a POSA would have understood that pemetrexed acts, in part, by decreasing the amount of tetrahydrofolate ("FH_4") available for DNA synthesis.

b. As shown in Figure A below (modified from Ex. 1014 at 5), a POSA in 1999 also would have understand that folic acid ("FA" in the diagram) is not a folate usable by the body until it has been reduced twice to tetrahydrofolate ("FH_4" in the diagram)—a process for which DHFR is required. (Ex. 1014 at 3, 5.)

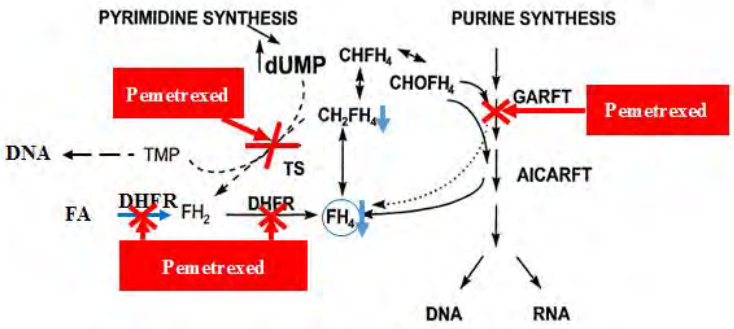


Figure A

c. A POSA in 1999 would have further understood that, because pemetrexed is a potent DHFR inhibitor, once pemetrexed is administered, it will prohibit folic acid from being reduced into a usable form ("FH_4"), no matter how much folic acid is given while pemetrexed is inhibiting DHFR, folic acid cannot compete with pemetrexed and interfere with its effect on impairing DNA synthesis.

Source: Ex. 1077 at ¶¶19(a-c); Paper 48 at 8-9.

Dr. Bleyer's Testimony

a. I disagree. As I stated during my deposition, a POSA in 1999 would have understood that, "because folinic acid is a reduced folate that is downstream of DHFR in the folic acid pathway, administration of folinic acid would be expected to circumvent the action of an antifolate such as pemetrexed or methotrexate that inhibits DHFR (Fig. B, below). By contrast, as [I] explained, because folic acid is upstream from DHFR, it would not reverse the effect of pemetrexed (Fig.A). Bleyer Dep. (Part II) at 334-339." (Ex. 2120 ¶ 179.)

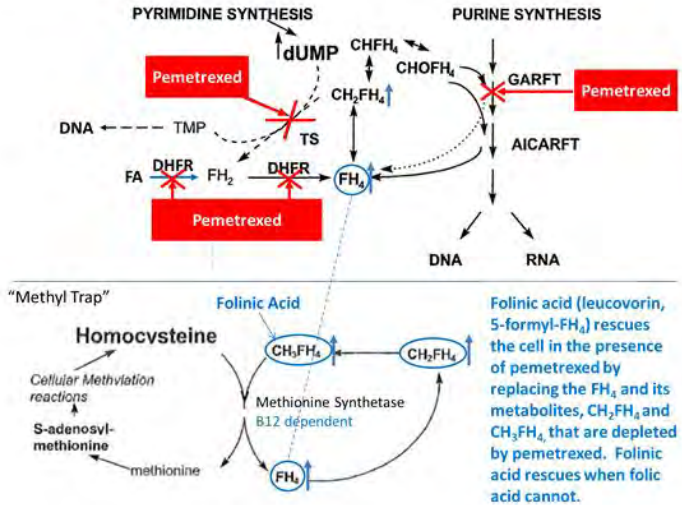


Figure B

b. Dr. Chabner relies on the assumption that pemetrexed is primarily a TS inhibitor to support his contention that folic acid would, like folinic acid, antagonize the efficacy of pemetrexed ("while pemetrexed does inhibit DHFR, it was primarily understood to be a TS inhibitor, i.e., its primary effect was on the TS enzyme, and the contribution against DHFR was more limited." (Ex. 2120¶ 179-113). This is incorrect. A POSA in 1999 would have known that, while pemetrexed inhibits three enzymes (Fig. A) (thus its name, MTA = multi-targeted antifolate), pemetrexed is a potent DHFR inhibitor, as described above. Ex. 1014-7 ("MTA was developed by Eli Lilly and Company (Indianapolis, IN), initially as a TS inhibitor. However, it rapidly became clear that, unlike any of the other antifolates discussed, MTA is capable of inhibiting two other enzymes involved in folate metabolism, GARFT and DHFR (see Mendelsohn et al, this supplement).") (Fig. A). In 1999, a POSA would not have assumed that because pemetrexed was first discovered to be a TS inhibitor that its inhibition of DHFR would be less significant ("more limited") than its effect on TS.

Source: Ex. 1077 at ¶¶20(a-b); Paper 48 at 8-9.

Dr. Bleyer's Testimony

c. Additionally, I disagree with Dr. Chabner's assumption that leucovorin rescue would work for pemetrexed just as for methotrexate. A POSA in 1999 could not assume this. Because pemetrexed is a multi-targeted enzyme (Fig. A), pemetrexed's inhibition of folate-requiring enzymes is more potent and complicated than for DHFR and TS inhibitors alone. As Dr. Chabner admits "[a]s of June 1999, the POSA would recognize that different antifolates had different properties with respect to, for example, affinity for enzyme targets, polyglutamation, and intracellular transport, as well as other properties such as pharmacokinetics. The POSA would therefore understand that, while antifolates can share common properties, the effects of one antifolate (such as efficacy or toxicity) cannot necessarily be used to predict the properties of another compound simply because it is also an antifolate." (Ex. 2120 ¶ 48.) For example, because pemetrexed is a multi-targeted enzyme, pemetrexed's inhibition of folate-requiring enzymes is more potent and complicated than classical DHFR-only and TS-only inhibitors.

d. In summary, leucovorin's mechanism of action is very different from that of folic acid. For example, folic acid requires DHFR to be reduced to dihydrofolate and tetrahydrofolate in order to be in a form usable by the body, whereas leucovorin (5-formyltetrahydrofolate) is already reduced, and its conversions to 5,10-methenyltetrahydrofolate, 5-methyltetrahydrofolate, and tetrahydrofolate do not require DHFR (Fig. B). (*See* Ex. 1014 at 3, 5.) Additionally, because pemetrexed does not inhibit the conversion of folic acid to dihydrofolate and tetrahydrofolate, but do not inhibit the conversion of folinic acid to its active, reduced folate that takes place downstream of DHFR.

Source: Ex. 1077 at ¶¶20(c-d); Paper 48 at 8-9.

Dr. Bleyer's Testimony

a. I disagree. A POSA in 1999 would have understood that after pemetrexed and its polyglutamate metabolites have had their desired effect on the malignant cells, folic acid supplementation is then able to improve pemetrexed's therapeutic index by allowing better recovery of normal tissue. This benefit can occur with folic acid given prior to, on the day of, or shortly after pemetrexed administration.

b. A POSA in 1999 also would have understood that Dr. Chabner's declaration ignores the fact that my opinion included folic acid and B12 *pretreatment*, and so the action of folic acid (and therefore its ability to ameliorate toxicity) can occur *prior to* pemetrexed treatment, and so would not be blocked by the action of pemetrexed itself. Indeed, the fact that pemetrexed can block the action of folic acid is one of the reasons that a POSA would have known that folic acid and B12 can be given to a patient prior to pemetrexed treatment.

Source: Ex. 1077 at ¶¶22(a-b); Paper 48 at 8-9.

Dr. Bleyer's Testimony

b. Second, the increase in reduced folates that occurs with folic acid pretreatment cannot not prevent the inhibition of either DHFR or TS by pemetrexed (Fig. B). The increase in reduced folates may allow the cell to recover faster after pemetrexed and its polyglutamates are cleared from the cell, but that is the essence of the selective effect of pemetrexed being able to kill more cancer cells than normal cells. Normal cells survive the interval of pemetrexed inhibition and recover more rapidly if the reduced folate pool is increased prior to pemetrexed treatment. A POSA in 1999 would understand this selective advantage (therapeutic index).

c. Even if folic acid is administered shortly before pemetrexed, a POSA in 1999 would have understood that pemetrexed has a higher affinity for DHFR than folic acid, and thus pemetrexed will effectively bind to DHFR in the presence of folic acid, as discussed above in paragraph 19 and further explained below.

d. A POSA in 1999 also would have known that the estimated average requirement of folate is 320 µg/day, and recommended nutrient intake is 400 µg/day. (Ex. 1062 at 228; Ex. 1076 at 83:18-20.) Because the claimed single dose of folic acid approximates the normal daily dietary level of folic acid, a POSA would have been even less concerned about interfering with pemetrexed.

e. And, because pemetrexed exhibits high affinity for the target enzymes (i.e., TS, DHFR, GARFT), a POSA in 1999 would have known that pemetrexed can displace any folic acid derivatives that are bound to the target enzymes. In fact, Dr. Chabner states, "Antifolates competitively bind to, and displace a folic acid derivative from, the catalytic site on a folate-requiring enzyme …." (Ex. 2120 ¶ 45.)

f. Dr. Chabner also ignores the fact that, in the competition between pemetrexed and reduced folate for enzyme binding sites, pemetrexed will still be effective, based on its higher binding affinity for DHFR than folic acid. In fact, as Dr. Chabner points out, pemetrexed binds DHFR in the presence of folic acid and also displaces folic acid that is bound to DHFR. (Ex. 2120 ¶ 62 ("an antifolate is designed to compete with folic acid and disrupt DNA synthesis.").) In the very journal for which Dr. Chabner was then (as now) the editor-in-chief, pemetrexed and its polyglutamate forms were reported by a colleague at the National Cancer Institute to be a potent inhibitor of DHFR (Ex. 1082 at 72.)

Source: Ex. 1077 at ¶¶23(b-f); Paper 48 at 8-9.

Dr. Bleyer's Testimony

a. A POSA in 1999 would have known that both the efficacy of pemetrexed in killing cancer cells and the ability of a patient to tolerate more and/or higher doses of pemetrexed play significant roles in pemetrexed's therapeutic index—the treatment window in which a patient receives doses of pemetrexed that kill more cancer cells than normal cells.

b. A POSA in 1999 would not have focused purely on pemetrexed's efficacy, but instead would have had as a goal increasing the therapeutic index of the drug.

c. The prior art in 1999 would have taught a POSA that administering folic acid along with pemetrexed was likely to increase the therapeutic index of pemetrexed. (Ex. 2035 at 225a ("Since preclinical studies indicated the folic acid supplementation increases the therapeutic index of MTA, the feasibility of administering folic acid 5 mg daily for 5 days starting 2 days before MTA in minimally- and heavily-pretreated pts was evaluated to determine if folic acid supplementation ameliorates the toxic effects of MTA, permitting significant dose-escalation above the recommended phase II dose of MTA alone. … Thus far, heavily- and minimally-pretreated patients have tolerated MTA at 600 and 800 mg/m^2 and accrual continues at 700 and 900 mg/m^2, respectively. These results indicate that folic acid supplementation appears to permit MTA dose escalation."); Ex. 1011-1195 ("dietary supplementation with folic acid may improve therapeutic index by reducing toxicity"); Ex. 1022-129 ("supplementation increases the therapeutic index of MTA" by "permit[tin] MTA dose escalation by ameliorating toxicity.".)

d. Additionally, a POSA in 1999 would have known that a randomized, double-blinded clinical trial had been reported that concluded that folic acid supplementation could protect patients with rheumatoid arthritis from antifolate toxicity while preserving the efficacy of the antifolate. (Ex. 2085 at 833, 839.) Although the disease studied was not cancer and the antifolate was methotrexate, a POSA would have considered the trial relevant for cancer treatment with pemetrexed since the trial demonstrated that with folic acid supplementation, the beneficial cellular mechanism of the antifolate could be maintained while the antifolate's toxicity on normal tissue could be reduced or prevented. (Ex. 2085 at 833, 839.)

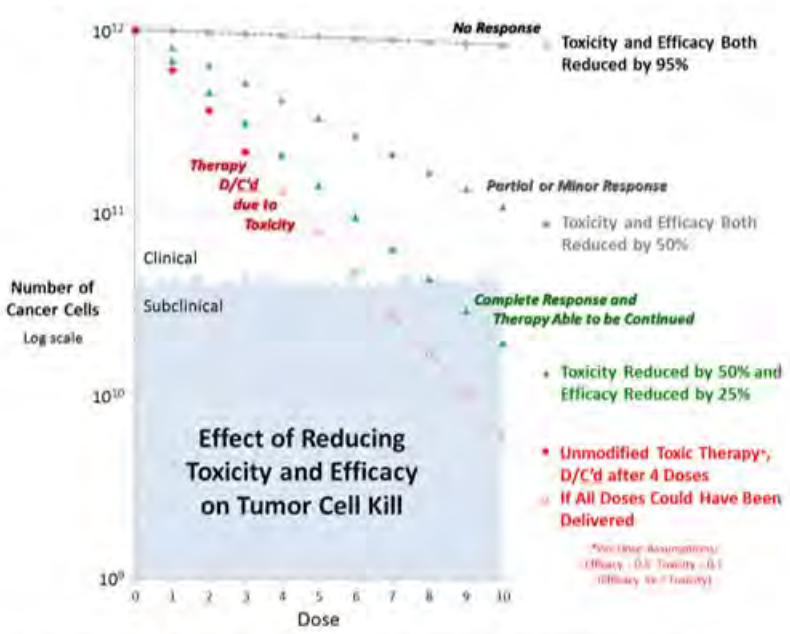
Source: Ex. 1077 at ¶¶24(a-d); Paper 48 at 8-9.

Dr. Bleyer's Testimony

e. Specifically, a POSA in 1999 would have understood that the overall therapeutic index of a cancer chemotherapy agent depends on the extent to which the planned course of treatment can be completed, and not just the initial dose(s). Since a POSA would have known that 10 of 33 patients in the Rusthoven trial had to discontinue pemetrexed therapy prematurely due to toxicity (Ex. 1011 at 1194), the implication was clear that folic acid intervention could have enabled continuation of therapy. This was indicated by a report published the previous year that minimally- and heavily-pretreated patients tolerated both dose escalation and continuation with pre/post folic acid treatment. (Ex. 2035 at 225a ("Thus far, 21 patients with solid cancers have received 55 courses at the following dose levels: 600, 700, and 800 mg/m^2.").) Dr. Chabner does not mention the ability to continue prescribed therapy with folic-acid-supplemented pemetrexed therapy.

f. A POSA in 1999 would have understood that decreasing a drug's toxicity can allow a patient to receive higher/more doses of the drug, which can improve the drug's overall response, even if the toxicity reduction results in a lower efficacy per mg of drug administered.

g. The following graphic demonstration, which a POSA in 1999 would have understood, further explains a greater cancer cell kill by an antifolate or a chemotherapy drug when the reduction in efficacy is less than the reduction in toxicity.



h. In the above figure, by dose #10, reducing both the toxicity and efficacy by 40% decreases the cell kill by 1 log, whereas decreasing the toxicity by 40% and the efficacy less, by 25% instead of 40%, decreases the loss in cell kill from 1 log to 1/3 of a log. The number of cancer cells left after 10 doses with the less-reduced efficacy regimen is 35% that left by the regimen with equivalent toxicity and efficacy reduction.

Source: Ex. 1077 at ¶¶24(e-h); Paper 48 at 8-9.

Dr. Bleyer's Testimony

i. Specifically, every effective antitumor agent has toxic effects in addition to its efficacy in killing cancer cells more selectively than normal (host) cells. If the agent is too toxic by itself, and an intervention is needed to reduce the toxicity, the efficacy in cancer cell kill is compromised to the extent that efficacy is also reduced by the intervention. However, if toxicity is reduced more than efficacy, clinical benefit can be preserved, albeit not to the same extent that the agent may have been able to achieve by itself if it could be tolerated. In the graphic example above, reducing the toxicity by 50% allows an antitumor agent that otherwise cannot be tolerated (red items) to be tolerated and repeated (gray and black items). If the efficacy is also reduced by same degree as the reduction in toxicity, clinical benefit is not achieved (black items) or is limited (e.g. partial or minor response) (gray items). However, if efficacy is reduced less than is toxicity, a complete response (and the ability to continue dosing until cure) may be achieved (green items).

Source: Ex. 1077 at ¶¶24(i); Paper 48 at 8-9.

Dr. Bleyer's Testimony

a. A POSA does not rely on the PDR, since it is neither peer-reviewed nor the source of original report, and it frequently lags current clinical thinking and practice. Also, the PDR states that folic acid "may" decrease efficacy, not that it does. (Ex. 2020 at 1398.) Since the therapeutic index balances a drug's response with toxicity, this reference is at best inconclusive regarding folic acid's effect on methotrexate's therapeutic index. Additionally, a POSA would not have ignored prior art teachings specific to pemetrexed in favor of contrary teachings relating to methotrexate.

b. In fact, the PDR entry for methotrexate states that "[f]olate deficiency states may increase methotrexate toxicity," which teaches a POSA to pretreat a cancer patient on antifolate with folic acid. (Ex. 2020 at 1399.)

38. Dr. Chabner goes on to state, "Similarly, the guidelines for administration of raltitrexed-a TS inhibitor that was marketed in Europe for cancer under the name Tomudex- stated, 'Folinic acid, folic acid or vitamin preparations containing these agents must not be given immediately prior to or during administration of Tomudex, since they may interfere with its action.'" (Ex. 2120 ¶ 65.) Dr. Chabner cites "ABPI Compendium of Data Sheets at 1544" as the reference, which is not an obvious reference source known to a POSA. (*Id.*) And, unlike pemetrexed, Tomudex is not a DHFR inhibitor that prevents folic acid reduction. Additionally, a POSA would not have ignored prior art teachings specific to pemetrexed in favor of contrary teachings relating to Tomudex.

Source: Ex. 1077 at ¶¶37(a-b)-38; Paper 48 at 8-9.

Dr. Bleyer's Testimony

a. I disagree. Because Hammond II is a phase I study, and a POSA would not compare efficacy in Hammond II to the prior phase I study (Rinaldi I). Hammond II continued the phase I dose escalation (with folic acid supplementation) at the same phase I schedule of patients in the prior phase I study to determine a new maximally tolerated dose ("MTD"). (Compare Ex. 2022 at 489 with Ex. 2035 at 225a.)

b. In fact, Hammond's investigators came to the opposite conclusion of Dr. Chabner—who describes Hammond's outcome as "clearly negative therapeutic results"—a conclusion that a POSA in 1999 would not reach based on phase I studies alone. (Ex. 2120 ¶ 33b.) By contrast, Hammond's investigators concluded that folic acid pretreatment "appears to permit MTA dose escalation" which may increase "the therapeutic index of MTA." (Ex. 2035 at 225a ("Since preclinical studies indicated the folic acid supplementation increases the therapeutic index of MTA, the feasibility of administering folic acid 5 mg daily for 5 days starting 2 days before MTA in minimally- and heavily-pretreated pts was evaluated to determine if folic acid supplementation ameliorates the toxic effects of MTA, permitting significant dose-escalation above the recommended phase II dose of MTA alone. … Thus far, heavily- and minimally-pretreated patients have tolerated MTA at 600 and 800 mg/m^2 and accrual continues at 700 and 900 mg/m^2, respectively. These results indicate that folic acid supplementation appears to permit MTA dose escalation.").) However, because Hammond II was only a phase I study, its investigators properly limited their conclusions to the topic being investigated—the maximum safe and efficacious dose—concluding that "folic acid supplementation appears to permit MTA dose escalation," and stating no conclusions about efficacy at this phase I stage. (*Id.*)

c. Further, a POSA would not have drawn conclusions about the efficacy of Hammond II beyond the investigators' stated conclusions because it appears that, at the time the abstract was written, the study was not yet complete. (Ex. 2035 at 225a ("Thus far, heavily- and minimally-pretreated patients have tolerated MTA at 600 and 800 mg/m^2 and accrual continues at 700 and 900 mg/m^2 respectively.") (emphasis added).)

Source: Ex. 1077 at ¶¶28(a-c); Paper 48 at 8-9.

Dr. Bleyer's Testimony

d. However, from the Hammond II investigators' conclusion that "folic acid supplementation appears to permit MTA dose escalation," a POSA in 1999 would have understood this conclusion to have been consistent with an improvement in the therapeutic index with folic acid supplementation. (Ex. 2035 at 225a.) That is, the ability to continue taking the drug (when 30% of patients in a trial had to discontinue it due to unacceptable toxicity) and/or take the drug at a higher dose, with folic acid supplementation, is consistent with an improvement in therapeutic index. (*See, e.g.*, Ex. 1022 at 129; Ex. 1011-1195.)

e. Second, while a POSA would not compare the efficacy of the Hammond and Rinaldi studies because they are phase I studies, a POSA would further decline to compare the studies, not only because the abstracts contain insufficient information to compare the treatment regimens, but because what information is present would suggest to a POSA that their treatment regimens are different. For example, although Hammond II and Rinaldi I both speak to treating patients with solid tumors, Rinaldi I discloses that patients with advanced, refractory, solid tumors were treated with MTA, whereas Hammond II discloses that minimally pretreated patients were included in the patient population. So, it would appear to a POSA that there were differences in the patient population between Hammond II and Rinaldi I. (Compare Ex. 2022 at 489 with Ex. 2035 at 225a.)

f. A POSA additionally would not know the dose or schedule of MTA given to each of the patients in Hammond II versus Rinaldi I, and so would not compare them for that reason. (*Id.*) Rinaldi I states that escalating doses were administered every 21 days, with dose escalation based on the modified continual reassessment method, whereas Hammond II is silent on treatment schedule or how dose escalation proceeded. Neither Rinaldi I nor Hammond II discloses the dose and schedule received by any individual patient, let alone all patients, so a POSA would be unable to determine whether there was a treatment difference associated with responders versus non-responders.

Source: Ex. 1077 at ¶¶28(d-f); Paper 48 at 8-9.

Dr. Bleyer's Testimony

g. Third, although a POSA would not compare efficacy between Hammond II and Rinaldi I for the above-stated reasons, a POSA would understand nonetheless that the putative response rates were neither clinically nor statistically different. For example, Rinaldi I reported 4 objective responses[3] (all partial responses) out of 37 patients: in 2 patients with pancreatic cancer and in 2 patients with advanced colorectal cancer; Hammond II reported 1 objective response out of 21 patients.[4] (Ex. 2022 at 489; Ex. 2035 at 225a.)

[3] A POSA in 1999 would understand that investigators frequently only report objective responses, which consist of partial or total responses, since less-than - objective responses are uncertain, unclear, or subjective. The definition of *objective* response was established many years before 1999 to be defined in quantitative, measurable terms, such as a ≥30% decrease in the sum of the longest diameters of target lesions, taking as reference the baseline sum longest diameter, without progression in any other tumors. Minor responses are not considered objective responses. For this reason, a POSA reading a report of responses would not assume that there were no minor responses, just because none were listed.

[4] Six of the ten responses in the Rinaldi report were minor responses, but a POSA in 1999 would understand that minor responses may not have been reported in Hammond since they are not considered objective (only partial and complete responses are considered objective) and so minor responses are not typically accepted by a POSA when reading a report. (*See* Ex. 2035 at 225a.)

A POSA in 1999 would understand that the difference in the number of objective responses, 1 in 21 reported in Hammond II and 4 in 37 in Rinaldi, is not statistically significant (Chi-Square p-value = 0.43; i.e., nearly 50-50 probability). In other words, the "4 of 43" rate in Rinaldi could have had 1 or 2 more responses purely by chance, especially given that it had twice as many patients than Hammond. Reciprocally, Hammond could have had, by chance 1 less response. Either way, the rates would then have been entirely comparable. The p-value suggests that there was an equal chance that it could have gone either way. And, both studies lacked the controls necessary for comparisons and showing statistical significance.

Source: Ex. 1077 at ¶28(g); Paper 48 at 8-9.

Dr. Bleyer's Testimony

50. Dr. Chabner also states, "Even if the POSA considered using folic acid and vitamin B12 in a cancer patient receiving pemetrexed in order to address toxicity or lower homocysteine levels, the POSA would still not take the risk of pre-treating a cancer patient with vitamin B12 and folic acid before administering pemetrexed. At most, the POSA would employ leucovorin rescue, an approach that the POSA would understand could be used to lower homocysteine levels (including with methotrexate in cancer patients), but which would avoid the risk of the vitamin therapy undermining the efficacy of the chemotherapy before the chemotherapy was even administered to the cancer patient. And even if the POSA was further interested in also treating with vitamin B12, for the same reasons, at most the POSA would administer it after chemotherapy was completed." (Ex. 2120 ¶ 33e.) As I discuss above, Dr. Chabner assumes that folic acid and vitamin B12 can inhibit pemetrexed. Once again, as a potent inhibitor of the enzymes that activate folic acid and allow vitamin B12 to facilitate methionine synthesis, pemetrexed could have been expected to be effective in patients treated with either vitamin before or after pemetrexed treatment.

Source: Ex. 1077 at ¶50; Paper 48 at 8-9.

Dr. Bleyer's Testimony

> 45. And, as I noted earlier, Rusthoven specifically discusses that dietary supplementation with folic acid may improve the therapeutic index of pemetrexed by reducing toxicity. (*Id.*)

Source: Ex. 1077 at ¶45; Paper 48 at 8-9.

Dr. Bleyer's Testimony

27. I disagree. A POSA would not compare the results described in the Hammond abstracts and Rinaldi I to reach Dr. Chabner's conclusion.

a. First, a POSA would not compare the results described in the Hammond abstracts and Rinaldi I at all. This is because these are both phase I trials, and a POSA would not quantify the responses seen in phase I trials, which are designed to establish a safe and effective dose, and not to evaluate efficacy, as mentioned above. (Ex. 2043 at 274 ("A key question that remained was how much folic acid was required to achieve optimal amelioration of toxicity, accepting that any effects on efficacy could only be evaluated in a phase II setting."); Ex. 2031 at 325 ("[I]t has not been possible to perform Phase II studies to evaluate the potential efficacy of lometrexol.").) Dr. Chabner confirmed this in his deposition, stating: "[i]n a phase I trial, you're just trying to find a safe and effective dose to carry on." (Ex. 1075 at 172:23-25.) Although a POSA might be encouraged by responses occurring during a phase I study, a POSA would not evaluate a drug's efficacy in humans prior to a phase II study. (Ex. 2043 at 277 ("Any effect on efficacy can of course not be evaluated except in the context of a phase II study. However, it is encouraging to note that a number of partial responses were observed in the phase I clinical development in those patients who received folic acid supplementation.").) Specifically, in 1999, a

POSA would have known that although noting and reporting responses in a phase I trial is important, quantitating them is neither reliable nor the purpose of phase I trials, based on their trial design.

Source: Ex. 1077 at ¶¶27(a); Paper 48 at 16.

Dr. Bleyer's Testimony

29. Dr. Chabner states that "the POSA would recognize that there was a significant risk that pre-treatment with folic acid would cause the tumor to progress." (Ex. 2120 ¶ 33b.) For this proposition, Dr. Chabner relies on early observations by Dr. Farber circa 1948 (and an out of context citation to another study citing Dr. Farber) that when he gave folic acid to children with leukemia, the leukemia appeared to accelerate (Ex. 2120 ¶¶ 66-67.) A POSA would understand, well before 1999, that the 1948 experience was by then no longer relevant:

Source: Ex. 1077 at ¶29; Paper 48 at 17.

Dr. Bleyer's Testimony

a. A POSA would have known that cancer growth has never been reported to be caused by folic acid supplementation *in conjunction with any antifolate*.

b. The 1948 Farber study cited by Dr. Chabner actually treated leukemia patients with an antifolate (aminopterin, the precursor to methotrexate), with folic acid, and B_{12} (in the form of a liver extract), and were able to achieve temporary remissions of the leukemia in 10 children. (Ex. 2042 at 787; Ex. 1064 at 4022.) Although two patients in the 1948 Farber study initially displayed an acceleration of their disease, it was following administration of folic acid conjugates, not folic acid itself. The patients improved following treatment with aminopterin and liver extract, and there was no evidence of leukemia progression during administration of folic acid and liver extract along with the antifolate. (Ex. 2041 at 788 and 791-792).

c. A POSA in 1999 would also have known that since Dr. Farber's original observation in children with leukemia, reported in 1947, cancer growth accelerated by folic acid has never been reported since. No other cancer and no other population of cancer patients since 1948 have been identified to have their cancer progress with folic acid treatment, whether or not with an antifolate as part of the regimen.

d. By 1999, it was well-recognized that the cancer at issue in the 1948 Farber article (acute lymphoblastic leukemia) was well known to be among the most, if not the most, sensitive to antifolate therapy (with methotrexate). The lowest doses— milligrams per week—used in cancer chemotherapy are effective in this cancer but not in the vast majority of others and in virtually no solid tumors such as those for which pemetrexed is used. The concept of metronomic (very low doses at frequent intervals) was first shown effective in childhood leukemia and rarely since then in any other cancer.

e. Acute lymphoblastic leukemia is rare in the cancer spectrum, not typical of the cancers, and pemetrexed (generally used with solid tumors) has never been indicated as a treatment for it. In 1999, acute lymphoblastic leukemia accounted for 0.3% of all cancer in the United States.

Source: Ex. 1077 at ¶¶29(a-e); Paper 48 at 17.

Dr. Bleyer's Testimony

f. The tumor growth acceleration for which Dr. Chabner cites Dr. Farber's 1948 study (Ex. 2120 ¶ 66) actually occurred in his *1947* study following treatment with the folic acid conjugates diopterin and teropterin (not folic acid itself) (*See* Ex. 2042 at 787, 2nd paragraph (citing Ex. 1066).) This acceleration was observed in children with advanced leukemia, and they were undoubtedly malnourished and likely folate and B12 deficient, given how much longer their diagnosis would have taken to be made back then. At that time, leukemia was just being established as a diagnosable entity and the patients were far more emaciated, malnourished, and cachectic than after Dr. Farber's discovery and subsequent availability of aminoperin and its successor, methotrexate. In fact, Farber, a pathologist, thought they had a vitamin deficiency and treated them with a liver extract. When he saw that their leukemia process in viscera and marrow worsened (instead of improved, as he had hoped) he attributed the acceleration to folic acid deficiency. Since then, leukemia had been established as a diagnosis, patients have not had the long delays experienced by patients in the 1940s, and the "acceleration phenomena" with folic acid conjugates seen by Dr. Farber in 1948 has not been seen. That degree of malnutrition five decades later (1999 vs. 1948) would not be expected by a POSA.

g. Moreover, when Dr. Farber and colleagues added folic acid to the antifolate therapy they were administering, they did not see a repeat of the tumor growth acceleration that Dr. Farber described in 1947. (*See* Ex. 2042.)

h. It was a sentinel observation that led to antifolate therapy but it was the one and only report that folic acid conjugates could accelerate cancer. By 1999, many malnourished cancer patients had been treated with supplemental vitamins, including folic acid and vitamin B12, before their anticancer treatment began, without having been reported to have progressive disease prior to their anticancer therapy.

i. The children were given up to 300 mg of the folic acid conjugates diopterin and teropterin. (Ex. 1066 at 620.)

j. The liver extract with a variety of other nutrients that could have contributed to the occurrence and certainly muddled the conclusion regarding folic acid.

Source: Ex. 1077 at ¶¶29(f-j); Paper 48 at 17.

Dr. Bleyer's Testimony

30. I note that Dr. Chabner quotes the Laohavinij article out of context, stating: "As one publication (Laohavinij) regarding pre-treatment with folic acid prior to administration of lometrexol to phase I patients with a variety of solid tumors observed, 'One cause for concern is that the administration of folic acid prior to lometrexol and during treatment could potentially supplement the folate requirements of the tumour, and thereby circumvent the activity of lometrexol or, worse still, aid tumour progression.' Laohavinij at 333 (citing Farber)." (Ex. 2120 ¶ 67.)

Source: Ex. 1077 at ¶30; Paper 48 at 18.

Dr. Bleyer's Testimony

31. In fact, despite being aware of the Farber studies, the express purpose of the Laohavinij investigators was a study of folic acid combined with an antifolate: "The objective of the present clinical study was to identify a safe dose of lometrexol when given with folate supplementation so as to allow Phase II trials, in an attempt to reproduce the efficacy of lometrexol seen in folate-deficient mice receiving folate supplementation." (Ex. 2031 at 330.) Further, after undertaking their study, the Laohavinij investigators did not warn against tumor proliferation when combining folic acid with an antifolate, but instead stated that "[t]he work described in this report has demonstrated that lometrexol toxicity can be modulated by folic acid supplementation in patients," and encouraged others to use "the information obtained from this study [to] facilitate the future development and evaluation of this class of compounds [antifolates] in the treatment of human cancer." (Ex. 2031 at 330-31.) By 1996, Laohavinij et al recommended folic acid pretreatment with lometrexol. Thus, like the Laohavinij investigators, not only was a POSA in 1999 undeterred by the 1947 Farber study from using folic acid to mediate the toxicity of antifolates, but actively considering it as a promising method for managing toxicity.

Source: Ex. 1077 at ¶31; Paper 48 at 18.

Dr. Bleyer's Testimony

40. Additionally, by 1999, the prior art included suggestions and recommendations to supplement pemetrexed-receiving patients with folic acid in order to reduce dose-limiting toxicity, and thus improve the therapeutic index:

a. Ex. 1005 at 3237-39: "In this paper, we demonstrate that mice fed a low folate diet for a short period (2 weeks) became 60- to 250-fold more sensitive to the lethality of LY231514 than observed in mice fed standard laboratory diet (Figure 1). The antifolate GARFT inhibitor, lometrexol has previously been shown to accumulate in the livers of folate-deficient mice, and this accumulation was diminished by the administration of folic acid to these animals (16). These investigators hypothesized that the substantial and unexpected toxicity of lometrexol in humans not given concurrent folic acid and in folate-deficient mice is due to the sequestration of drug in hepatic tissue, with the subsequent slow release of drug to the circulation at toxicologically relevant concentrations. … A similar mechanism probably exists for the potentiation of LY231514 toxicity by folate-deficient diet, since this compound is an extremely efficient substrate for mouse liver FPGS (1). In addition, LY231514 requires polyglutamation for cytotoxic potency (3). … The combination of folic acid with LY231514 may provide a mechanism for enhanced clinical antitumor selectivity."

b. Ex. 1013 at 39: "Trials are also planned to investigate the effect of folates on the toxicities seen with MTA, based on the observation that animals given folate supplements were better able to tolerate treatment with MTA, with fewer side-effects."

Source: Ex. 1077 at ¶¶40(a-b); Paper 48 at 18, 20.

Dr. Bleyer's Testimony

c. Ex.1014 at 7-9: "The clinical toxicity of many antifolates is, not surprisingly, affected by the pretreatment folate status of the patient. In the case of the GARFT inhibitors, the effect of the folate status is particularly marked, with the maximum tolerated dose being at least 10-fold higher in patients who have received folate supplementation compared with those who have not. … Although the effect of folic acid supplementation on reducing the toxicity of antifolate drugs (particularly the GARFT inhibitors) is clear, it always has been difficult to correlate antifolate induced toxicity with pretreatment folate levels. One possible explanation for this is that the folate levels do not adequately reflect the functioning of folic acid within proliferating cells at the time of measurement. In addition to the pathways discussed so far, folic acid is also involved in cellular methylation reactions by virtue of its role in methionine synthesis. CH_2FH_4 can be reduced to 5-methyltetrahydrofolate (Fig 1). This is a substrate for the enzyme methionine synthase, which uses the methyl group to convert homocysteine to methionine. Methionine in turn takes part in cellular methylation reactions regenerating homocysteine. Methionine synthase is B_{12}-dependent but also uses 5-methyltetrahydrofolate as the co-substrate. Thus, any functional deficiency either in B_{12} or folate will result in reduction in the flux through methionine synthase and a consequent increase in the plasma level of homocysteine … (Fig 8). The measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA."

d. Ex. 1022 at 129: "Myelosuppression precluded dose escalation above 500-600 mg/m^2. As preclinical evaluations indicate that FA supplementation increases the therapeutic Index of MTA, this study was initiated to determine if FA supplementation permits significant dose-escalation above the recommended phase II dose of MTA alone. … Conclusions: FA supplementation appears to permit MTA dose escalation by ameliorating toxicity. Heavily- and minimally-pretreated pts tolerate MTA at 700 and 925 mg/m^2 and accrual continues at 800 and 925 mg/m^2, respectively."

Source: Ex. 1077 at ¶¶40(c-d); Paper 48 at 18, 20, 22.

Dr. Bleyer's Testimony

e. Ex. 2035 at 225a: "Initial phase I trials demonstrated major antitumor responses when MTA was given as a 10 min i.v. infusion, however, myelosuppression precluded dose escalation above 500-600 mg/m^2. Since preclinical studies indicated the folic acid supplementation increases the therapeutic index of MTA, the feasibility of administering folic acid 5 mg daily for 5 days starting 2 days before MTA in minimally- and heavily-pretreated pts was evaluated to determine if folic acid supplementation ameliorates the toxic effects of MTA, permitting significant dose-escalation above the recommended phase II dose of MTA alone. … Thus far, heavily- and minimally-pretreated patients have tolerated MTA at 600 and 800 mg/m^2 and accrual continues at 700 and 900 mg/m^2, respectively. These results indicate that folic acid supplementation appears to permit MTA dose escalation."

f. Ex. 1011 at 1195: "Early studies have suggested that dietary supplementation with folic acid may improve the therapeutic index by reducing toxicity in mice."

Source: Ex. 1077 at ¶¶40(e-f); Paper 48 at 18, 20, 22.

Dr. Bleyer's Testimony

a. To state that there is no indication that a cancer patient on antifolate therapy was "ever" pretreated with vitamin B 12 is an excessive presumption. Dr. Chabner may not have had a nutritionist on his team in 1999, but other medical oncologists had, and for them a nutritionist could have recommended B12, especially if the patient was in danger of B12 deficiency. It is not a "novel regimen" in such patients to administer B12 with folate. On the contrary, it is recommended practice. (*See, e.g.*, Ex. 1107 at 431-432; Ex. 1101 at 2696.)

b. As further discussed above, the prior art taught a POSA to be concerned about a patient's pretreatment nutritional status, so it would have been obvious for a POSA to supplement a patient with vitamin B12 prior to treatment with pemetrexed in order to assure that the patient's B12 stores were sufficient:

c. Ex. 1008 at 127: "Toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels (≥10μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA." (emphasis added)

Source: Ex. 1077 at ¶¶47(a-c); Paper 48 at 20.

Dr. Bleyer's Testimony

d. Ex.1014 at 7-9: "The clinical toxicity of many antifolates is, not surprisingly, affected by the pretreatment folate status of the patient. In the case of the GARFT inhibitors, the effect of the folate status is particularly marked, with the maximum tolerated dose being at least 10-fold higher in patients who have received folate supplementation compared with those who have not. … Although the effect of folic acid supplementation on reducing the toxicity of antifolate drugs (particularly the GARFT inhibitors) is clear, it always has been difficult to correlate antifolate induced toxicity with pretreatment folate levels. One possible explanation for this is that the folate levels do not adequately reflect the functioning of folic acid within proliferating cells at the time of measurement. In addition to the pathways discussed so far, folic acid is also involved in cellular methylation reactions by virtue of its role in methionine synthesis. CH_2FH_4 can be reduced to 5-methyltetrahydrofolate (Fig 1). This is a substrate for the enzyme methionine synthase, which uses the methyl group to convert homocysteine to methionine. Methionine in turn takes part in cellular methylation reactions regenerating homocysteine. Methionine synthase is B_{12}-dependent but also uses 5-methyltetrahydrofolate as the co-substrate. Thus, any functional deficiency either in B_{12} or folate will result in reduction in the flux through methionine synthase and a consequent increase in the plasma level of homocysteine … (Fig 8). The measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA."

e. Ex. 1015 at 104: "Work by Zervos et al supports the position that toxicity may be increased in patients with poor nutritional status."

Source: Ex. 1077 at ¶¶47(d-e); Paper 48 at 20.

Dr. Bleyer's Testimony

f. Ex. 1016 at 225a: "Studies in animal models and humans have revealed that folate nutritional status may be correlated with toxicity and antitumor activity of antifolates. Supplemental folic acid may play a role in protecting against the toxicities associated with antifolate drugs. LY231514 is a multi-targeted antifolate that inhibits Thymidylate synthase, Dihydrofolate reductase and Glycinamide ribonucleotide formyltransferase. Functional folate status, based on serum concentrations of homocysteine (HCYS), cystathione (CYSTAT); and methylmalonic acid (MMA), was assessed in 116 patients participating in Phase 2 studies of LY231514. This drug was administered as a 10-minute infusion once every 21 days. Samples were taken prior to initiation of therapy and prior to the start of each cycle. CTC toxicity scores (hematologic and non-hematologic) were assigned at the end of each cycle of therapy. Eight pts were found to be folate deficient (elevated HCYS and CYSTAT and normal MMA). All experienced CTC grade 3 or 4 toxicity which was primarily hematologic. From this data, we would conclude that functional folate status appears to be a reliable prognostic indicator of hematologic toxicity that may be experienced from treatment with LY231514. Further investigation is warranted to support this conclusion."

g. Ex. 2015 at 558a: "Because earlier studies with other antifolates had suggested that nutritional status may play a role in the likelihood that a patient will experience severe toxicity, levels of the vitamin metabolites homocysteine, cystathionine and methylmalonic acid were measured at baseline and once each cycle thereafter. A multivariate statistical analysis of the data was conducted. … There was a strong correlation between baseline homocysteine levels and the development of the following toxicities at any time during the study: CTC Grade 4 neutropenia (57 pts, $p < 0.0001$), Grade 4 thromobcytopenia (13 pts, $p < 0.0001$), Grade 3 or 4 mucositis (8 pts, $p < 0.0003$), and Grade 3 or 4 diarrhea (8 pts, $p < 0.004$). … No correlation between toxicity (CTC Grades as defined above) and the remaining pre-specified predictors were seen. Toxicity was seen in all patients with homocysteine levels above a threshold concentration of 10 µM. A correlation over time between homocysteine levels and CTC Grade 4 neutropenia and thrombocytopenia and CTC Grade 3 or 4 mucositis was also observed but only in the first two cycles of treatment. Maximum homocysteine levels did not appear to change from baseline during treatment with MTA."

Source: Ex. 1077 at ¶¶47(f-g); Paper 48 at 20.

Dr. Bleyer's Testimony

h. Ex. 2033 at 2800: "Folate deficiency, either by diet or drug, increases plasma homocysteine (Hcy). Hcy damages cerebrovascular endothelium, and hyperhomocysteinemia is a risk factor for stroke. Hcy is metabolized to excitatory amino acid (EAA) neurotransmitters, such as homocysteic acid (HCA) and cysteine sulfinic acid (CSA), which may cause seizures and excitotoxic neuronal death. We postulated that excess Hcy and EAA neurotransmitters may partly mediate methotrexate (MTX)-associated neurotoxicity. … The [methotrexate] treatment group had a significantly (P=.0255) greater concentration of Hcy in cerebrospinal fluid (CSF) (0.81 uM ±0.215 [mean ±SEM], n=23) than the control group (0.210 uM ±0.028, n=34). HCA and CSA were not detected in CSF from control patients (n=29); however, MTX caused marked accumulation of CSF HCA (119.1 uM ±32.0, n=16) and CSA (28.4 uM ±7.7, n=16) in the treatment group. Pts with neurologic toxicity… had many of the highest concentrations of Hcy, HCA, and CSA. … These data support our hypothesis that MTX-associated neurotoxicity may be mediated by Hcy and excitotoxic neurotransmitters." (emphasis added)

Source: Ex. 1077 at ¶47(h); Paper 48 at 20.

Dr. Bleyer's Testimony

51. In addition to concern about a patient's pretreatment B12 status because of their nutritional status, the prior art also rebuts Dr. Chabner's B12 opinions because the prior art provided numerous motivations to pretreat a pemetrexed patient with B12.

a. First, when supplementing a pemetrexed patient with folic acid—already documented in the prior art at reducing pemetrexed toxicity—a POSA would also want to supplement with B12 in order to avoid masking the serious and well-known condition that occurs when folate supplementation appears to alleviate the symptoms of a B12 deficiency, thus hiding the B12 deficiency and allowing it to worsen and result in dangerous conditions such irreversible neuropathy. (Ex. 1054 at 1720; Ex. 1076 at 98:4-17.)

b. Second, a POSA in 1999 would have known that elevated homocysteine highly correlated with pemetrexed toxicity, and so a POSA naturally would want to address the causes of elevated homocysteine—and a POSA would have known that low levels of B12 were a cause of elevated homocysteine—in an attempt to also address the cause of increased pemetrexed toxicity. (Ex. 1008 at 126-27; Ex. 1014 at 8; Ex. 1076 at 40:10-19, 41:5-12.) Although Dr. Chabner states that "the POSA would understand that methylmalonic acid—not homocysteine—was the unique marker for a vitamin B12 deficiency. Niyikiza II taught that no correlation was identified between methylmalonic acid levels and toxicity." (Ex. 2120 ¶ 33d.) Patent Owner's nutritionist expert, Dr. Zeisel, disagrees. Specifically Dr. Zeisel maintains that Niyikiza merely teaches that you cannot tell one way or another whether B12 deficiencies were involved in the Niyikiza elevated homocysteine. (Ex. 1076 at 116:12-20.) Additionally, a POSA in 1999 would know that approximately 10% of B12 deficient patients cannot be detected via MMA because they will have high homocysteine levels but normal MMA levels. (Ex. 1017 at 97; Ex. 1075 at 324:21-25; Ex. 1076 at 95:11-12.) Moreover, Dr. Chabner's position that a POSA viewing Niyikiza would not believe B12 deficiencies were involved in the observed elevated homocysteine is inconsistent with his concern that pemetrexed patients should not receive B12 supplements due to a methyl trap concern—which is admittedly only a concern when B12-deficient patients are involved. (Ex. 2120 ¶ 143; Ex. 1076 at 105:7-108:4.)

Source: Ex. 1077 at ¶51(a-b); Paper 48 at 20-27, 29.

Dr. Bleyer's Testimony

c. Third, a POSA in 1999 would have been particularly sensitive to B12 deficiencies causing elevated homocysteine and pemetrexed toxicity since patients being treated with pemetrexed were more likely to suffer from B12 deficiencies, especially with repeated pemetrexed administrations (recall that 30% of patients in the Phase II trial reported by Rusthoven had to stop therapy due to toxicity. (Ex. 1011 at 1194, 1198.) There are several reasons for this likelihood:

i. The cancers for which pemetrexed is a treatment (e.g., lung and pancreatic cancer) are more likely to occur in older adults, and the elderly have a higher incidence of B12 deficiencies than the general population. (Ex. 1072 at 277; Ex. 1075 at 348:4-8; Ex. 1076 at 149:25-150:3.)

ii. Patients with cancer are also more likely to suffer from B12 deficiencies, as are patients undergoing chemotherapy (such as cisplatin, which is often given in conjunction with pemetrexed) that causes nausea and malnutrition. (Ex. 1074 at 208; Ex. 1061 at 810.)

iii. Dr. Chabner's concern regarding the methyl trap assumes that a portion of the patients receiving pemetrexed would be B12 deficient since the methyl trap is only a concern in B12 deficient patients. (Ex. 2120 ¶ 123; Ex. 1076 at 105:7-108:4.)

d. Fourth, a POSA in 1999 would have wanted to provide as low a folic acid dose as possible in order to alleviate pemetrexed toxicity while maintaining pemetrexed's competitive advantage over any folic acid that has been reduced through methionine synthase. (Ex. 1076 at 136:25-137:5.) A POSA in 1999 would know that supplementing a patient with B12 (and possibly B6) in addition to folic acid would have a synergistic effect in lowering the patient's toxicity-predicting homocysteine levels. (Ex. 1010 at 11, 18; Ex. 1076 at 136:11-136:24.) For example, Brönstrup teaches that "the addition of vitamin B-12 to supplements containing 400 µg folic acid or to enriched foods maximizes the reduction of tHcy [homocysteine] through the synergistic potential of both vitamins." (Ex. 1019 at 1109.) Also, EP005 teaches that the triple agent supplementation (folic acid, vitamin B12, and vitamin B6) showed synergistic effect and more effective than folic acid alone (Ex. 1010 at 18.) Thus, a POSA in 1999 would have known that supplementing a patient with both folic acid and B12 was significantly more efficacious than supplementing with either folic acid or B12 alone. And, EP '005 further teaches that the vitamin supplementation should be administered for the prophylaxis. Therefore, a POSA would have pretreated a patient receiving pemetrexed with B12 in addition to folic acid.

Source: Ex. 1077 at ¶¶51(c-d); Paper 48 at 20-27, 29.

Dr. Bleyer's Testimony

a. Whereas the hematologic toxicity of antifolates was considered in 1999 not to be mediated by homocysteine elevation, the neurotoxicities of antifolates (fatigue, lethargy, somnolence, etc. … all of which were reported with pemetrexed before 1999) were. Hence, there was reason to lower homocysteine levels to reduce some of the toxicities of pemetrexed. That's precisely what Quinn et al recommended in 1998 after demonstrating the classic antifolate, methotrexate, elevated the neurotoxic homocysteine metabolites. (Ex. 2033.)

b. While a POSA in 1999 could not be certain that the underlying causes of the elevated homocysteine levels in Niyikiza were the same underlying causes of pemetrexed toxicity, this would be the most likely conclusion for a POSA to draw from Niyikiza's disclosed correlation between elevated homocysteine and pemetrexed toxicity. (*See* Ex. 1076 at 40:10-19, 41:5-12; Ex. 1075 at 280:10-20; Ex. 1015-104; Ex. 2015-558a; Ex.1014-8-9; Ex. 1016-256a.) Moreover, Dr. Chabner admits that a POSA in 1999 would have known that folate supplementation could decrease both pemetrexed toxicity and homocysteine levels, so there is no reason that a POSA's first instinct should not be to explore the underlying causes of elevated homocysteine as the same underlying causes of pemetrexed toxicity. (*See* Ex. 1075 at 153:25-158:11-14, 270:12-18, 283:3-12; Ex. 1076 at 41:5-19.)

c. Moreover, as of June 1999, it was well known in the art that pretreating with folic acid and vitamin B_{12} (low levels of which are two common causes of elevated homocysteine) would reduce pretreatment homocysteine levels. It was also well known that the primary purpose for administering folic acid and/or B_{12} is to reduce a patient's homocysteine level. Further, as Dr. Chabner admitted in his deposition (Ex. 1075 at 158:11-13), the POSA would have readily understood that administering folic acid reduced pemetrexed toxicity. Therefore, from the POSA's perspective, it would naturally follow that there is a reasonable correlation between reducing homocysteine levels and reducing pemetrexed toxicity. This correlation would have been readily apparent to a POSA irrespective of whether Niyikiza taught the cause of the pemetrexed toxicities. For that reason, the cause of the pemetrexed toxicity seen in Niyikiza is irrelevant to a POSA's motivation to try to lower homocysteine based on Niyikiza.

Source: Ex. 1077 at ¶¶62(a-c); Paper 48 at 20.

Dr. Bleyer's Testimony

a. In 1999, there were only a few identifiable causes of homocysteine elevation. Dr. Zeisel identified four: low folate, low B12, low B6, and low betaine. (Ex. 1076 at 34:16-23.) Niether B6 nor betaine deficiencies would have been as likely as folate and vitamin B12 deficiency, either on a nutritional basis or induced by antifolate therapy in patients scheduled for or on treatment with pemetrexed.

b. Both Dr. Chabner and Dr. Zeisel agree that it was common in the art in 1999 to use a combination of B12, B6, and folic acid to lower homocysteine levels. (Ex. 1010 at 18; Ex. 1075 at 322:10-323:3; Ex. 1076 at 35:18-21.) Moreover, Dr. Zeisel admits that "based on the knowledge of the biochemical pathways that remove homocysteine, betaine would have been … as reasonable as folic acid, to try to lower homocysteine." (Ex. 1076 at 72:2-6.)

Source: Ex. 1077 at ¶¶64(a-b); Paper 48 at 20.

Dr. Bleyer's Testimony

53. Additionally, contrary to Dr. Chabner's view, a POSA in 1999 would know that approximately 5-10% of B12 deficient patients cannot be detected via MMA testing because they will have high homocysteine levels but normal MMA levels. (Ex. 1017 at 97; Ex. 1075 at 324:21-25; Ex. 1076 at 95:11-12.) A POSA would have also understood that elevated homocysteine due to a B12 deficiency (or even low normal) would not be expected to respond to folic acid alone. (Ex. 1063 at 1277S (because patients "with moderate homocysteinemia (>16.3µmol/l) in most cases had suboptimal plasma vitamin B-12 (<200 pmol/l) *and* folate (<5 nmol/l) concentrations …. Most but not all responded to folic acid, with the mean homocysteine concentration decreased from 28.8 to 16.8 µmol/l (-42%), a posttreatment value, however, still above normal … whereas cyanocobalamin [B_{12}] decreased plasma homocysteine by a mean of 15%. In contrast, all responded to the combination by a mean homocysteine reduction of 50% ….").)

Source: Ex. 1077 at ¶53; Paper 48 at 21.

Dr. Bleyer's Testimony

14. I disagree. A POSA in 1999 would understand that when toxicity limits either dose or schedule, it is not being adequately addressed.

a. Calvert 1998 discloses that dose-limiting and even life-threatening toxicities had been observed, despite the availability of "the typical means of combating antifolate toxicities" touted by Patent Owner. (Ex. 1013 at 38.) For example, in a pancreatic cancer study (Miller et al. 1997), dose reductions were required in 17% of patients and grade 3+4 granulocytopenia was seen in 42% of patients (grade 3 toxicity is considered serious, grade 4 is considered life-threatening, and grade 5 is fatal.). (*Id.*) In a breast cancer study (Smith et al. 1997), grade 3+4 thrombocytopenia was seen in 41% of patients and grade 3+4 neutropenia was seen in 18% of patients. (*Id.*) In non-small cell lung cancer studies (Rusthoven et al. 1997), the starting dose was reduced from 600 mg to 500 mg after only three patients had been treated, with grade 3+4 neutropenia seen in 32% of patients in one study, and 42% of the patients exhibiting grade 3+4 neutropenia in a similar study. (*Id.*) In a colorectal cancer study (John et al. 1997), 56% of patients experienced grade 3+4 neutropenia, 16% of patients experienced grade 3+4 thrombocytopenia, and 12% of patients experienced grade 3+4 anemia, with the dose again being reduced to 500 mg after dose-limiting toxicities were observed. (*Id.*) In a Canadian colorectal cancer study (Cripps et al. 1997), "[g]rade 3+4 neutropenia was seen in 45% of patients," "3+4 thrombocytopenia in 12% of patients," and "[g]rade 3 rash was seen in 40% of patients." (*Id.*) In fact, Calvert 1998 specifically discusses that these toxicities needed to be addressed, and for that reason taught that "[t]rials are also planned to investigate the effect of folates on the toxicities seen with MTA, based on the observation that animals given folate supplements were better able to tolerate treatments with MTA, with fewer side-effects." (Ex. 1013 at 39.)

b. In April 1999, Rusthoven reported in the preeminent Journal of Clinical Oncology that 39% of patients on a phase II trial had grade 3+4 febrile neutropenia (including "severe systemic infection considered related to protocol therapy") and 30% of the patients "stopped protocol therapy because of toxicity." (Ex. 1011 at 1194, 1198 (emphasis added).) Rusthoven also specifically discusses that these toxicities needed to be addressed, and for that reason disclosed to a POSA that "studies have suggested that dietary supplementation with folic acid may improve therapeutic index by reducing toxicity." (Ex. 1011 at 1195.)

Source: Ex. 1077 at ¶¶14(a-b); Paper 48 at 22.

Dr. Bleyer's Testimony

> c. Both Calvert 1998 and Rusthoven state that only non-hematological toxicities *only* are manageable, not hematological toxicities. (Exs. 1013 at 37; 1011 at 1194.) Thus, these statements have no bearing on whether a POSA would have considered the hematological toxicities to be adequately addressed (they would not have considered them to be adequately addressed).

Source: Ex. 1077 at ¶14(c); Paper 48 at 22.

Dr. Bleyer's Testimony

52. Although Dr. Chabner states that "the POSA would understand that methylmalonic acid—not homocysteine—was the unique marker for a vitamin B12 deficiency, but Niyikiza II taught that no correlation was identified between methylmalonic acid levels and toxicity," Patent Owner's nutritionist expert, Dr. Zeisel, disagrees. (Ex. 2120 ¶ 33d.) Specifically, Dr. Zeisel maintains that Niyikiza merely teaches that you cannot tell one way or another whether B12 deficiencies were involved in the Niyikiza elevated homocysteine. (Ex. 1076 at 116:12-20.) Moreover, Dr. Chabner's position that a POSA viewing Niyikiza would not believe B12 deficiencies were involved in the observed elevated homocysteine is inconsistent with his concern that pemetrexed patients should not receive B12 supplements due to a methyl trap concern—since a methyl trap will only occur in the case of a B12 deficiency. (Ex. 2120 ¶ 123; Ex. 1076 at 105:7-108:4.)

Source: Ex. 1077 at ¶52; Paper 48 at 23.

Dr. Bleyer's Testimony

a. A POSA in 1999 would not have ignored the then known benefit of specifically lowering homocysteine level with vitamin therapy. On the contrary, it would have been incumbent on the POSA to offer a specific antidote for the ominous homocysteine elevation. In the next section, Dr. Chabner goes on to suggest using betaine or vitamin B6, which in fact are examples of antidotes more specific than reducing the dose of pemetrexed, using GCSF, or rescuing with folinic acid. A POSA would not have considered betaine as effective, however, as further described below.

b. A POSA in 1999 would have been aware of the principle that preventing possibly life-threatening toxicity in cancer patients is much more valuable and effective than trying to save the patients from that toxicity once it has occurred and have to delay, reduce, or abandon the next dose(s).

c. Further, a POSA in 1999 would have known that rescue therapy "can only be used to prevent *further* [antifolate] toxicity and has no effect on cells already damaged by the drug." (Ex. 1073 at 79.)

Source: Ex. 1077 at ¶¶63(a-c); Paper 48 at 25.

Dr. Bleyer's Testimony

65. Finally, in 1999, a POSA would have addressed chemotherapy toxicities using all available tools at their disposal. A POSA administering a chemotherapeutic agent would have been focused on managing dose-limiting toxicities and keeping the patient on the dose and schedule as planned. For these reasons, a POSA would rather prevent a dose-limiting toxicity from happening in the first place, than deal with one after it had happened. And either, as mentioned above, delay or reduce subsequent doses or more detrimentally have to stop pemetrexed therapy altogether, as occurred in 30% of the patients on the trial reported by Rusthoven. (Ex 1011 at 1198.) There is no reason why a POSA would choose to ignore a tool at their disposal—such as folic acid and B12 supplementation—particularly when there was evidence that it worked for pemetrexed.

Source: Ex. 1077 at ¶65; Paper 48 at 25.

Dr. Bleyer's Testimony

a. First, the claimed doses are routine dosages of folic acid and B12 and neither exceptional nor discovery. (Ex. 1070 at 100-01, 103, 105; Ex. 1076 at 83:18-20; 88:7-91:11.)

b. Second, by administering a dose of folic acid that approaches that of the normal dietary level of folic acid, a POSA would be even less concerned about possibly interfering with the action of pemetrexed.

67. Dr. Chabner states that "even if, contrary to my opinions, the POSA (1) wanted to lower the homocysteine levels of a cancer patient who was to receive pemetrexed (whether to reduce toxicity or to avoid cardiovascular problems); (2) wanted to avoid masking a vitamin B12 deficiency that could be caused by administering folic acid alone; and (3) thought to add vitamin B12 to the regimen in the Hammond abstracts in order to lower homocysteine levels or to reduce toxicity, the POSA would still not pre-treat with folic acid or vitamin B12. Rather, the POSA would, at most, employ leucovorin rescue." (Ex. 2120 ¶ 94.) I completely disagree. Leucovorin would be used to end the interval of time pemetrexed is active (as with high-dose methotrexate therapy) when the patient develops renal failure and can't eliminate pemetrexed or an over dose is given. Once given, the next dose of pemetrexed would have to wait until the increased pool of reduced folates generated by leucovorin has normalized; otherwise the pemetrexed would be ineffective, since it prevents reduction of folic acid to reduced (active) folates. That's why folic acid is preferable as pretreatment and leucovorin is reserved for post treatment when needed.

Source: Ex. 1077 at ¶¶66(a-b), 67; Paper 48 at 25.

Dr. Bleyer's Testimony

54. Dr. Chabner posits that consultation with "nutritionists as of June 1999 typically arose in circumstances involving treatment of individual patients for whom food intake was compromised and significant weight loss had occurred (such as a patient with head and neck cancer who was unable to take food by mouth)." (Ex. 2120 ¶ 24.) I differ.

a. First, head and neck cancer was one of seven cancers that by 1999 was shown to respond to pemetrexed. The other six include those also associated with cachexia, weight loss and malnutrition (lung cancer, pancreatic cancer, colorectal cancer, bladder cancer, cervix cancer, and mesothelioma). Anorexia is a common symptom of all these cancers that results in malnutrition, not just the inability to take food by mouth.

b. Second, I submit that nutritionists were by 1999 an integral part of the oncology teams which with I worked at academic medical centers. They made inpatients rounds with us, where nearly all newly-diagnosed patients were initially evaluated and decisions made as to their nutritional status and specific nutritional needs. They assisted in writing hyper- and enteral-alimentation orders, were available in the clinic, and attended Tumor Board. When 4 years later I moved to a community hospital and private practice environment in rural Oregon, I experienced nutritionists who had for years served similar roles in non-academic settings, where more than 80% of adult cancer patients in the U.S. are treated. Hence, I submit that a POSA in 1999 would have done the same.

c. Finally, with respect to Dr. Chabner's stated concern that administering B12 to a B12 deficient patient has the potential to cause an unknown quantity of reduced folate to be released from its 5-MTHF form, a POSA would have understood that by pretreating the patient with folic acid and B12, metabolite levels would be expected to have normalized before treatment with pemetrexed. For this reason, a POSA wanting to supplement a pemetrexed patient with folic acid and B12 would want to ensure that the patient was *pretreated* with these vitamins, in order to release reduced folate from the methyl trap prior to pemetrexed treatment so that, by the time of pemetrexed treatment, excess reduced folate would have been used up or excreted by the patient's body and therefore unavailable to compete with pemetrexed. (Ex. 1065 at 88 ("Elevated MMA and HCYS concentrations fell substantially within 5 days after only two injections [of folate, B12, and B6], with a maximum effect seen by day 12.").)

Source: Ex. 1077 at ¶¶54(a-c); Paper 48 at 27.

Dr. Bleyer's Testimony

57. For this proposition, Dr. Chabner has cited four references: McLean (Ex. 2058), Arsenyan (Ex. 2055), Sofyina (Ex. 2041), and Vidal (Ex. 2059). However, McLean contains only *in vitro* studies outside of the antifolate context. (Ex. 2058.) As far as Arsenyan and Sofyina go, they are both 1970s references from a single research group in Russia, that studied the same specific tumor lines and mice strains, and the results have never been reproduced or shown to be generally applicable outside of the particular tumor cell lines and mice strains studied. (Exs. 2041, 2055.) In April of 1999, a POSA would have considered it to be "impossible to study the action of vit. B_{12} using artificially deficient human model systems." (Ex. 2089 at 28; Ex. 1075 at 274:8-9.)

Source: Ex. 1077 at ¶57; Paper 48 at 28.

Dr. Bleyer's Testimony

41. Additionally, by 1999, the prior art included suggestions and recommendations to supplement pemetrexed-receiving patients with folic acid in order to reduce dose-limiting toxicity, and thus improve the therapeutic index:

a. Ex. 1005 at 3237-39: "In this paper, we demonstrate that mice fed a low folate diet for a short period (2 weeks) became 60- to 250-fold more sensitive to the lethality of LY231514 than observed in mice fed standard laboratory diet (Figure 1). The antifolate GARFT inhibitor, lometrexol has previously been shown to accumulate in the livers of folate-deficient mice, and this accumulation was diminished by the administration of folic acid to these animals (16). These investigators hypothesized that the substantial and unexpected toxicity of lometrexol in humans not given concurrent folic acid and in folate-deficient mice is due to the sequestration of drug in hepatic tissue, with the subsequent slow release of drug to the circulation at toxicologically relevant concentrations. … A similar mechanism probably exists for the potentiation of LY231514 toxicity by folate-deficient diet, since this compound is an extremely efficient substrate for mouse liver FPGS (1). In addition, LY231514 requires polyglutamation for cytotoxic potency (3). … The combination of folic acid with LY231514 may provide a mechanism for enhanced clinical antitumor selectivity."

b. Ex. 1013 at 39: "Trials are also planned to investigate the effect of folates on the toxicities seen with MTA, based on the observation that animals given folate supplements were better able to tolerate treatment with MTA, with fewer side-effects."

Source: Ex. 1077 at ¶¶41(a-b); Paper 48 at 29.

Dr. Bleyer's Testimony

c. Ex.1014 at 7-9: "The clinical toxicity of many antifolates is, not surprisingly, affected by the pretreatment folate status of the patient. In the case of the GARFT inhibitors, the effect of the folate status is particularly marked, with the maximum tolerated dose being at least 10-fold higher in patients who have received folate supplementation compared with those who have not. … Although the effect of folic acid supplementation on reducing the toxicity of antifolate drugs (particularly the GARFT inhibitors) is clear, it always has been difficult to correlate antifolate induced toxicity with pretreatment folate levels. One possible explanation for this is that the folate levels do not adequately reflect the functioning of folic acid within proliferating cells at the time of measurement. In addition to the pathways discussed so far, folic acid is also involved in cellular methylation reactions by virtue of its role in methionine synthesis. CH_2FH_4 can be reduced to 5-methyltetrahydrofolate (Fig 1). This is a substrate for the enzyme methionine synthase, which uses the methyl group to convert homocysteine to methionine. Methionine in turn takes part in cellular methylation reactions regenerating homocysteine. Methionine synthase is B_{12}-dependent but also uses 5-methyltetrahydrofolate as the co-substrate. Thus, any functional deficiency either in B_{12} or folate will result in reduction in the flux through methionine synthase and a consequent increase in the plasma level of homocysteine … (Fig 8). The measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA."

d. Ex. 1022 at 129: "Myelosuppression precluded dose escalation above 500-600 mg/m^2. As preclinical evaluations indicate that FA supplementation increases the therapeutic Index of MTA, this study was initiated to determine if FA supplementation permits significant dose-escalation above the recommended phase II dose of MTA alone. … Conclusions: FA supplementation appears to permit MTA dose escalation by ameliorating toxicity. Heavily- and minimally-pretreated pts tolerate MTA at 700 and 925 mg/m^2 and accrual continues at 800 and 925 mg/m^2, respectively."

Source: Ex. 1077 at ¶¶41(c-d); Paper 48 at 29.

Dr. Bleyer's Testimony

e. Ex. 2035 at 225a: "Initial phase I trials demonstrated major antitumor responses when MTA was given as a 10 min i.v. infusion, however, myelosuppression precluded dose escalation above 500-600 mg/m^2. Since preclinical studies indicated the folic acid supplementation increases the therapeutic index of MTA, the feasibility of administering folic acid 5 mg daily for 5 days starting 2 days before MTA in minimally- and heavily-pretreated pts was evaluated to determine if folic acid supplementation ameliorates the toxic effects of MTA, permitting significant dose-escalation above the recommended phase II dose of MTA alone. … Thus far, heavily- and minimally-pretreated patients have tolerated MTA at 600 and 800 mg/m^2 and accrual continues at 700 and 900 mg/m^2, respectively. These results indicate that folic acid supplementation appears to permit MTA dose escalation."

f. Ex. 1011 at 1195: "Early studies have suggested that dietary supplementation with folic acid may improve the therapeutic index by reducing toxicity in mice."

Source: Ex. 1077 at ¶¶41(e-f); Paper 48 at 29.

Dr. Bleyer's Testimony

42. Dr. Chabner supports his argument that a POSA would not have supplemented a patient with folic acid immediately prior to or during administration of an antifolate by stating that "the clinical trial protocol in Rusthoven specified that patients were not allowed to take folic/folinic acid supplements." (Ex. 2120 n. 9.) I disagree.

Source: Ex. 1077 at ¶42; Paper 48 at 29.

Dr. Bleyer's Testimony

147. And, as explained above, it would have been obvious to a POSA to adjust the amount, method (i.e., oral or intramuscular administration), and duration (i.e., the length of time for which folic acid alone or in combination with vitamin B12) of administration of folic acid and vitamin B12, depending on the clinical condition of the patient, without undue experimentation.

152. Additionally, *EP 005* teaches that the *triple agent therapy* containing the folate and vitamin B12 "dosage regimen is time programmed, providing for different dosage rates during different periods of a course of treatment," it would have been obvious to a POSA that the dosage and time program would be adjusted according to the clinical condition of a patient. (Ex. 1010 at 5, 19, 20 (emphasis added).)

158. Like the *'974 Patent*, which discloses pretreatment with folic acid before antifolate therapy, *EP 005* discloses a dosage regimen for prophylactic treatment of elevated homocysteine levels, as explained above with respect to Claim 12(a). (*See* Ex. 1010 at 5, 8, 9.)

159. Thus, upon reading these *'974 Patent* and *EP 005* disclosures, it would have been obvious to a POSA to administer folic acid "1 to 3 weeks" prior to pemetrexed treatment, as required by **Claims 6 and 19**. (*See* Ex. 1004 at 7, 21-22.)

Source: Ex. 1025 at ¶¶147, 152, 158-159; Paper 48 at 30.

DR. MASON

Dr. Mason's Testimony

22. In his declaration, Dr. Zeisel provides information that purportedly "reflects the understanding of the folic acid pathway and pathways related to the metabolism of vitamin B12". (Ex. 2118, Zeisel Dec. ¶¶ 20 et. seq.) Dr. Zeisel then uses his explanation of the pathways to arrive at the crux of his opinion that "because pemetrexed is an antifolate, the POSA would be concerned that its efficacy against cancer would be diminished by pretreatment with folic acid, vitamin B12, or both." (Ex. 2118, Zeisel Dec. ¶ 48). For the reasons I provide herein, I disagree with Dr. Zeisel's opinion that a POSA in 1999 would not have pretreated a cancer patient with folic acid and/or vitamin B12.

23. In my opinion, Dr. Zeisel's explanation of the "folic acid pathway and pathways related to the metabolism of vitamin B12" overlooks several important issues that are highly relevant to this deliberation, and which absolutely need to be considered if one is to arrive at an accurate, balanced, and truthful assessment of this debate. By disregarding these finer points, Dr. Zeisel's declaration lacks the necessary level of detail needed to adequately understand one-carbon metabolism and, concurrently, how pemetrexed, folic acid and vitamin B12 affect these metabolic pathways. Accordingly, it is my opinion that a POSA in 1999 would not have avoided pretreating a cancer patient with folic acid and/or vitamin B12.

24. First, one-carbon metabolism is necessary for the synthesis and interconversion of several amino acids, the building blocks of proteins. Additionally, one-carbon metabolism is absolutely essential for the synthesis of nucleotides, the building blocks of RNA and DNA. Encoded in DNA is the information that serves as the blueprint from which all cells carry on their lives. Moreover, once a DNA molecule is synthesized, supplementary information is encoded into the DNA (and its closely-associated proteins, called histones) by attaching additional one-carbon units called 'methyl groups' at particular sites on the DNA and histones, which is another function dependent on one-carbon metabolism. When a cell divides it must make a new copy of its DNA, and therefore rapidly dividing cells (such as cancer cells) have heightened requirements for folate. One-carbon metabolism also provides for the methylation of other important molecules, such as proteins, RNA, and lipids.

25. Each of the biochemical reactions discussed herein, was known as of June 1999. These reactions all fall within the category of '1-carbon metabolism', which includes methionine and folate metabolism.

26. Each chemical reaction in methionine and folate metabolism is facilitated by an enzyme especially suited for that reaction. Vitamin B12 and folate assist these enzymes as helpers (in which case they are called a 'co-factor') or as a substrate that is converted by the reaction.

Source: Ex. 1078 at ¶¶22-26; Paper 48 at 12.

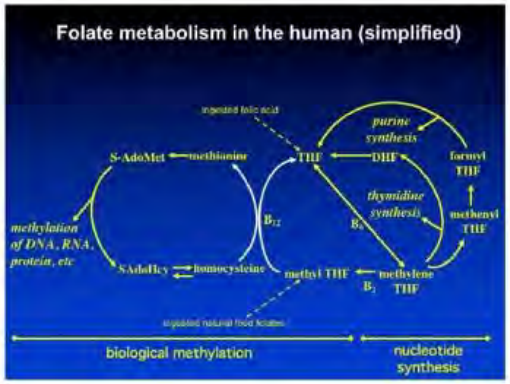
Dr. Mason's Testimony

27. One set of reactions in one-carbon metabolism is responsible for the synthesis of the DNA and RNA building blocks--the nucleotides--and another set of reactions is responsible for methylation reactions. These two sets of reactions intersect in single, shared reaction in which the amino acid homocysteine is converted to methionine. This reaction requires a form of folate called 5-methyltetrahydrofolate (which provides the methyl group that is donated to homocysteine) and a form of vitamin B12 called cob(I)alamin. The enzyme that catalyzes this reaction is called methionine synthase. Since the inter-conversion of compounds in both the nucleotide synthesis and methylation reactions operate in a circular fashion, the two sets of reactions are often (in a simplified manner) depicted as two intersecting circles, depicted in the diagram below.

28. Within the nucleotide synthesis cycle is the conversion of a form of folate called 5,10 methylenetetrahydrofolate to another form called 5-methyltetrahydrofolate (5-methylTHF). This reaction is irreversible and thereby carries important consequences since the re-conversion back to the 5,10 methylene form of folate can only occur through the roundabout means depicted in the diagram that is dependent on vitamin B12. If the methionine synthase reaction is blocked by B12 deficiency or other means such as inhalation of nitrous oxide ('laughing gas'), cellular folate accumulates in the form of 5-methylTHF and becomes unavailable for other purposes, including nucleotide synthesis, since the only way it can be recycled back to a form usable by other reactions (THF) is via the methionine synthase reaction.

29. Further, homocysteine, which is a cellular toxin when it accumulates, can be disposed of by one other pathway (which does not appear in the diagram below). In this additional pathway homocysteine is converted to cystathionine in a reaction that utilizes a form of vitamin B6 called pyridoxal phosphate as a co-factor. Deficiencies of either folate or vitamin B12 prevent the disposal of homocysteine from taking place and lead to elevations in the cellular and blood levels of homocysteine. The plasma concentration of homocysteine is therefore sometimes used as an indication that depletion of one or both of these vitamins exists, although an elevation in homocysteine is not entirely specific for folate and vitamin B12 deficiency, since other factors can also raise plasma levels of the compound.

30. Accordingly, a diagram of the two nucleotide synthesis and methylation cycles follow:



Source: Ex. 1078 at ¶¶27-30; Paper 48 at 12.

Dr. Mason's Testimony

31. Folic acid is a fully oxidized form of folate that is present only in miniscule amounts in nature. Nevertheless, it is the form used in vitamin supplements and fortified foods since it is very shelf-stable. When folic acid is ingested it cannot function in one-carbon metabolism in that form and must therefore first be reduced to dihydrofolate (DHF) and tetrahydrofolate (THF), utilizing the enzyme dihydrofolate reductase (DHFR). THF and DHF enter the one-carbon pathway and are converted to other forms of folate. Thus, as indicated in the figure, folate that is ingested in the form of folic acid enters the cycle via a different avenue than folate that is ingested in one of its more natural forms, such as 5-methylTHF. Blockade of DHFR therefore impairs the ability of folic acid to be effectively utilized within the folate metabolic network by preventing folic acid, which is unusable by the body in DNA synthesis, from being reduced to its useable form, tetrahydrofolate.

32. THF is converted to 5,10 methylene-THF (5,10-MTHF), via a reaction that utilizes vitamin B6 as a cofactor. This is either used as such for the synthesis of thymidine utilizing thymidylate synthase (TS), which is incorporated into DNA, reduced to 5-methylTHF, or converted into another form of folate for synthesis of other nucleotides. 5-methylTHF is used to add a methyl group to homocysteine to form methionine, a reaction that is catalyzed by methionine synthase. Much of the methionine that is formed is converted to S-adenosylmethionine (SAM), a universal donor of methyl groups, including for methylation of DNA, RNA, hormones, neurotransmitters, membrane lipids, proteins and others.

Source: Ex. 1078 at ¶¶31-32; Paper 48 at 12.

Dr. Mason's Testimony

33. Given the centrally-important functions performed by one-carbon metabolism, it is not surprising that many disease conditions are associated with interruptions in this metabolic network.

34. Interruptions in the nucleotide synthesis cycle interferes with DNA synthesis and repair. Since cancer cells have heightened requirements for DNA synthesis, pharmacologic blockade of this cycle has often been exploited as the basis for cancer chemotherapy agents that kill cancer cells.

35. As a result of bypassing certain facts about one-carbon metabolism, Dr. Zeisel concludes that a POSA "would have understood folates such as folic acid to serve as antidotes to antifolates such as pemetrexed." (Ex. 2118, Zeisel Dec. Zeisel Dec. ¶ 48). Accordingly, Dr. Zeisel opines that it would not be possible to treat a patient with folic acid before treating with pemetrexed without causing a negative effect on its efficacy against cancer cells. (Ex. 2118, Zeisel Dec. ¶ ¶ 50-53.) I disagree.

Source: Ex. 1078 at ¶¶33-35; Paper 48 at 12.

Dr. Mason's Testimony

46. Accordingly, a POSA in 1999 would have understood that the blockage of DHFR by pemetrexed impairs the ability of folic acid to be effectively utilized within the folate metabolic network by preventing folic acid (unusable by the body in DNA synthesis) from being reduced to its useable form, tetrahydrofolate. Consequently, pemetrexed affects and reduces the amount of tetrahyrofolate available for cellular activity in individuals who are consuming some of their folate in the form of folic acid. This is in contrast to leucovorin (folinic acid), so-called "rescue" treatment, which is introduced into the body as an already reduced form of folate and so does not need DHFR to act upon it. Accordingly, pemetrexed treatment should not diminish that portion of THF in cells that is contributed by the ingestion of leucovorin, as would be the case among those consuming folic acid.

Source: Ex. 1078 at ¶46; Paper 48 at 12-13.

Dr. Mason's Testimony

40. Dr. Zeisel's opinion fails to evaluate or consider binding affinities. In fact, prior to June 1999, it was well known that all cells add bulky 'polyglutamate tails' onto folates once the folates are taken up into the cell via an enzyme called folylpolyglutamyl synthetase (FPGS). It was also known prior to June 1999 that the same mechanism applied to the antifolates as well. This is a very important means by which cells prevent folates (and antifolates) from leaking back out of the cell, thereby enabling them to accumulate high concentrations of folates inside the cell, which is where folates and antifolates exert all their actions. (Ex. 1084, Chabner 1985.) One of pemetrexed's advantageous features is that it has a particularly high affinity for FPGS. Literature shows that pemetrexed's affinity for FPGS is 100-fold greater than methotrexate. (Ex. 1085, Habeck 1995 at 326-33, Table 1.) Therefore, pemetrexed briskly accumulates in cancer cells much more so than other antifolates since it is more avidly polyglutamated.

41. The chemical structure of pemetrexed is similar enough to the folate structure to 'fool' cells into using it instead of natural folates. It thereby acts as a folate enzyme inhibitor (or "antifolate"), preventing or slowing cell division and cell viability.

42. I disagree with Patent Owner's claims that "[a]t a therapeutically effective dose for treating cancer, the POSA would have no reason to believe that pemetrexed would inhibit DHFR sufficiently to block the conversion of folic acid to other folates and thus to stop it from reversing the pemetrexed's efficacy." (See, e.g., POR IPR2016-00237 at 26.) It is patently false that as of June 1999, the POSA would have no reason to believe that DHFR wouldn't be inhibited by pemetrexed 'at a therapeutically effective dose used for cancer'. In fact, "it [was] not known whether the anti-tumour activity of MTA [pemetrexed] depends on its TS inhibition . . ." (Ex. 1013, Calvert 1998 at 35; *see also* Ex. 2078, Shih 1998 at 136 ("TS is only partially responsible for the antiproliferative action of [pemetrexed].")

Source: Ex. 1078 at ¶¶40-42; Paper 48 at 13.

Dr. Mason's Testimony

43. As of June 1999, the dosing of pemetrexed was 600 mg/m2, reduced to 500 mg/m2 due to toxicity. (Ex. 1011, Rusthoven 1999 at 1194; Ex. 1015, O'Dwyer 1999.) At a dose of 500 mg/m2, plasma concentrations of the drug reach 310 micromol/L. (Ex. 1086, Li 2007 at 1071–76.) In fact, cancer cells concentrate pemetrexed in its polyglutamate form above the concentrations of pemetrexed found in the plasma. (Ex. 2075, Shih 1997 at 1121.) Nevertheless, even if one assumes that an intracellular concentration of pemetrexed is no greater than the plasma levels of pemetrexed achieved, 310 micromolar exceeds the concentration needed to inhibit one-half of DHFR activity by over a thousand-fold, a fact proven by Lilly's own scientists in 1997 and 1998. (Ex. 2075, Shih 1997 at 1116-23; and Ex. 2078, Shih 1998 at 135-52.) Thus, at concentrations achieved using standard dosing guidelines in 1999, pemetrexed was a highly effective inhibitor of DHFR.

44. Indeed, these studies demonstrate that in its polyglutamated form pemetrexed is nearly as inhibitory of DHFR as it is of TS. The inhibitory constant, or Ki, is an indication of how potent an inhibitor is and defines the concentration required to produce half maximum inhibition: the Ki of DHFR by pemetrexed pentaglutamate is 7.2 nmolar versus 1.3 nmolar for thymidylate synthase, which in terms of enzyme kinetics is nearly an equivalent level of inhibition. (Ex. 2078, Shih 1998 at 143; Ex. 1013, Calvert 1998 at 2.) A subsequent review of the drug indicates that not only is the [pemetrexed] compound a TS inhibitor, but it also inhibits dihydrofolate reductase (DHFR). (Ex. 2078, Shih 1998 at 136; Ex. 2075, Shih 1997 at 1118; Ex. 1013, Calvert at 35; Ex. 1076, Zeisel Tr. 22:4-9 (stating, when questioned, that pemetrexed has "some activity against DHFR."). Dr. Zeisel, admittedly, did not consider the inhibitory constants when rendering his opinions. (Ex. 1076, Zeisel Tr. 22:18-24 (testifying that he "d[id]n't recall the binding affinity [of pemetrexed]"; 24:16-23 (indicating that he "ha[dn't] looked more deeply into that literature because it wasn't part of what he was asked to consider.").)

45. It is therefore my opinion that a POSA in 1999 would have understood that pemetrexed inhibits DHFR nearly as equally as it inhibits thymidylate synthase (TS) and that pemetrexed does not and cannot select and act only upon TS.

Source: Ex. 1078 at ¶¶43-45; Paper 48 at 13.

Dr. Mason's Testimony

84. Dr. Zeisel states that folic acid "masking" a vitamin B12 deficiency is not generally a concern. (Ex. 2118, Zeisel Dec. ¶78.) I disagree. In June 1999, a POSA would have also been well aware that treatment with folic acid alone in order to reduce homocysteine levels will not be effective where there is an underlying vitamin B12 deficiency. (Ex. 1070, Lindenbaum 1990; Ex. 2065, Brattstrom 1996 ("in vitamin B12 deficiency, erroneous treatment with folic acid may correct the hematological abnormalities but elicit and deteriorate vitamin B-12 neuropathy."; Ex. 1076, Zeisel Tr. at 93:22-94:4 ("Giving folate, folic acid, to a B12 patient can help to correct the anemia without correcting the underlying B12 problem. And that meant that physician had to be more alert and not assume that, because they gave folate and it got better, that this was folate deficiency.").)

85. A POSA in June 1999, would also have understood and retained common knowledge that folic acid supplementation may mask underlying vitamin B12 deficiencies. Left untreated, it was well known that a vitamin B12 deficiency can result in megaloblastic anemia and irreversible neuropathy. Accordingly, many experts felt it was important to treat these elevated homocysteine levels not only with folic acid, but also with vitamin B12. (Ex. 1102, Boushey 1995 at 1049, 1056; Ex. 2082, Omenn 1998 at 423 (recommending daily intakes of folic acid and vitamin B12).)

86. Dr. Zeisel opines that using folic acid and vitamin B12 as a pretreatment in a cancer patient in order to lower homocysteine in the cancer patient was not obvious. (Ex. 2118 ¶72.) Since many experts in that era were recommending B-vitamin supplementation, including folic acid and vitamin B12 on a proactive basis to reduce the risk of cardiovascular events in the same way that we now routinely administer therapy for high cholesterol level, I would disagree with Dr. Zeisel. (Ex. 1102, Boushey 1995 at 1049, 1056 (discussing risk factor of tHcy levels and arteriosclerotic vascular diseases and indicating that supplementation with folic acid and cobalamin would correct vitamin B12 deficiencies and lessen concern about possible masking effects of folic acid); Ex. 2082, Omenn 1998 at 423 (finding the linking of folic acid, homocysteine and cardiovascular disease "risk as remaining strong" and recommending daily intakes of folic acid and vitamin B12).)

Source: Ex. 1078 at ¶¶84-86; Paper 48 at 20, 22.

Dr. Mason's Testimony

87. A POSA in June 1999, would have known that treating a patient with vitamin B12 and folic acid was an effective means of treating elevated homocysteine levels and that vitamin B12 and folic acid, when administered together, were much more effective in lowering homocysteine levels than folic acid alone. This was well-known as early as 1992, with publications showing that supplementation with B6, B12 and folic acid had been successfully used to reduce hyperhomocysteinemia. (Ex. 1049, Mason 1992 at 201; Ex. 1019, Bronstrup 1998 at 1109 ("The results of this study suggest that the addition of vitamin B-12 to supplements containing 400 mg folic acid or to enriched foods maximizes the reduction of tHcy through the synergistic potential of both vitamins."); Ex. 2082, Omenn 1998 at 423 (finding the linking of folic acid, homocysteine and cardiovascular disease "risk as remaining strong" and recommending daily intakes of folic acid and vitamin B12).; Ex. 1076, Zeisel Tr. 133:21-134:4 testifying that "I believe you're asking were there in the public domain papers and information [in 1999] that said when you combine some of the B6, B12 and folate that you might get a bigger reducing in homocysteine than if you used any one alone . . . And that was true for a number of reasons.").)

94. In sum, in June 1999, a POSA would also treat elevated homocysteine levels with both folic acid and vitamin B12.

Source: Ex. 1078 at ¶¶87, 94; Paper 48 at 20, 22.

Dr. Mason's Testimony

80. Dr. Zeisel states that a POSA would not assume that an elevated homocysteine level would necessarily warrant treatment, partially because there is no strict definition of what is considered an elevated homocysteine level and results can vary. (Ex. 2118, Zeisel Dec. ¶ ¶ 64-66.) I disagree. Homocysteine, an intermediary compound in methionine metabolism, produces adverse health outcomes when greatly elevated in the plasma. By the early and mid-1990s compelling evidence had accrued which indicated that elevated homocysteine levels, even of a modest degree, conveyed an increased risk of stroke and heart attack. (Ex. 1102, Boushey 1995 at 1049, 1056; Ex. 2082, Omenn 1998 at 42-23; Ex. 1049, Mason 1992 ("enhanced risk of cardiovascular disease can arise with only modest elevations in plasma levels of homocysteine.).)

81. Additionally, it was well known in 1999 that elevated pretreatment levels of homocysteine highly correlated with the toxicity of pemetrexed. (Ex. 1008, Niyikiza 1998 at 126-127 (elevated baseline homocysteine levels highly correlate with severe hematologic and nonhematologic toxicities following treatment with pemetrexed).) Accordingly, a POSA in June 1999, would have been highly motivated to lower even modestly elevated levels of homocysteine in a patient scheduled to receive treatment with pemetrexed.

82. A POSA, in June 1999, would have been well aware that elevated homocysteine levels could be caused by low folate and that supplementing a patient with folic acid would reduce the elevated homocysteine levels. (Ex. 2065, Brattstrom 1996 at 1277S-78S (treatment of elevated homocysteine levels with a combination of folic acid and cyanocobalamin is "wise"); Ex. 1076, Zeisel Tr. 37:20-22 ("Q: It wasn't rare, in 1999, for high homocysteine to be caused by low folate? A: It was not rare."); Ex. 1076, Zeisel Tr. 34:15-20 ("Q: What were the combination nutrients that people with high homocysteine were treated with? A: Folate would have been a treatment that they used . . . B6, B12.").)

Source: Ex. 1078 at ¶¶80-82; Paper 48 at 22.

Dr. Mason's Testimony

> 91. In 1999 a POSA would identify those patients that are B12 deficient and would have repleted them prior to initiating chemotherapy. A POSA would therefore not leave a deficiency to linger due to the risk of irreversible damage and the very short delay in chemotherapy (approximately one week) that would be required to replete the patient. (Ex. 2069, Naurath 1995 at 87 (normal concentrations of homocysteine and MMA were achieved following five days of vitamin and folate supplements).)

Source: Ex. 1078 at ¶91; Paper 48 at 22.

Dr. Mason's Testimony

58. In June 1999, a POSA would have been aware that vitamin B12 deficiency is by no means rare, and in fact is common in certain patient populations.

59. The susceptibility of vegetarians and vegans to vitamin B12 deficiency was well-recognized before 1999. (Ex.1088, Herbert 1994 at 1213S (dietary deficiency of vitamin B12 results from vegan diet); Ex. 1089, Markle 1996 (vegetarians have long been known to be at risk of cobalamin deficiency) Ex. 1090, Gleeson 1974 (vegans susceptible to vitamin B12 deficiency); Ex. 1091, Mann 1999 at 898 (proportion of low and deficient vitamin B12 subjects disproportionately high in a population skewed to higher percentage of vegetarians); Ex. 1076, Zeisel Tr. 149:18-150:9 ("Q: So low levels of B12 is more common in, you said, the elderly and in vegetarians and vegans, is that correct? A: Yes.").) First, vegetarians and vegans are vulnerable to and are at heightened risk for vitamin B12 deficiency. This is particularly true of those vegetarians who strictly avoid all animal products (so-called 'vegans'). This is because vitamin B12 is found almost exclusively in animal products, making vegans and vegetarians particularly susceptible to vitamin B12 deficiency. (Ex.1088, Herbert 1994 at 1213S.)

60. As a result, a POSA, in June 1999, would have likely checked vitamin B12 status in those patients following a vegan or vegetarian diet and pretreated with vitamin B12 or, alternatively, would have empirically treated all vegans and vegetarians to replete the patient before administering an antifolate therapy, including pemetrexed.

61. In June 1999, a POSA would have also known that B12 deficiency is common among elderly individuals. (Ex. 1089, Markle 1996 "significant number of elderly and HIV-positive individuals are also at increased risk of deficiency."). It is generally accepted that this is due to atrophic gastritis, or the thinning of the lining of the stomach, the prevalence of which increases rapidly with age beginning in the 50s, afflicting ~40% of people in their 80's. (Ex. 1092, Carmel 1997 at 750; Ex.1093, Krasinski 1986 at 800.) 'Elderly' is a loosely-defined term but generally refers to individuals 60-65 years of age and above. (Ex.1088, Herbert 1994 at 1213S ("the most frequent cause of omnivore vitamin B-12 deficiency is genetically predetermined age-dependent loss of gastric secretory function, i.e. pernicious anemia.").)

Source: Ex. 1078 at ¶¶58-61; Paper 48 at 26.

Dr. Mason's Testimony

62. It is common knowledge that gastric juices are needed to properly cleave the bonds holding vitamin B12 to protein so that it can be processed by the body. (Ex. 1076, Zeisel Tr. at 77:5-8 ("Some people can absorb B12 from a vitamin well but not from meat, where B12 is located, because it's bound to proteins and they have trouble pulling it off.").) As an individual ages their gastric juices also decline, thereby interfering with the absorption of B12 from foodstuffs.

63. In fact, this information was well-recognized in medical circles well before June 1999. For example, in a 1994 study of over 500 free-living elder individuals aged 67-96, 11.3% were found to be B12 deficient, as defined as having both low plasma B12 and elevated methylmalonic acid levels. (Ex. 1094, Lindenbaum 1994).

64. As a result, it would have been common for a POSA, in June 1999, to possess a high index of suspicion for B12 deficiency among elderly patients and pretreat many with vitamin B12 before administering an antifolate therapy, including pemetrexed.

65. Additionally, a POSA would have known that any patient with a history of stomach surgery, certain intestinal diseases that are not rare such as celiac sprue and Crohn's Disease, and any patient taking acid-suppressant drugs such as Prilosec over the long-term would be at a higher risk for vitamin B12 deficiency due to their inability to absorb enough vitamin B12 from food. (Ex. 1095, MacLean 1983 at 352, fig. 4 (stomach surgery); Ex. 1103, Saltzman 1994 (Prilosec).

66. It is also important to recognize that cancer patients suffering from nausea due to chemotherapy (a common side effect of cisplatin, which in 1999 was commonly given in conjunction with pemetrexed) are more susceptible to vitamin B12 deficiency due to their overall nutritional issues. (Ex. 1095, MacLean 1983 at 353 (vomiting on a daily basis is an excellent indicator of nutritional depletion and can result in both malnutrition and diminished vitamin status); Ex. 1061, Cubeddu 1990 ("Cisplatin ... produces the most severe nausea and emesis of any chemotherapeutic agent."; Ex. 1074, Vu 1993 (early negative B12 balance evidenced in chemotherapy patients that in some instances was induced by the treatment itself).) Thus, the risk factors for B12 deficiency described above would be even more likely to result in a genuine state of deficiency since the depletion of B12 is exacerbated by nausea and vomiting, which results in inadequate consumption of foodstuffs containing B12 or oral intake of vitamin supplements.

Source: Ex. 1078 at ¶¶62-66; Paper 48 at 26.

Dr. Mason's Testimony

> 67. As a result, it would have been common for a POSA, in 1999, to pretreat such patients with vitamin B12 to replete them before administering an antifolate therapy, including pemetrexed.

Source: Ex. 1078 at ¶67; Paper 48 at 26.

Dr. Mason's Testimony

76. The '209 patent claims that vitamin B12 should be administered via intramuscular injection in doses ranging between 1000 µg or 500 - 1500 µg every 6 to about every 12 weeks during treatment. (Ex. 1001, '209 patent at claims 3-5, 12, 14-15). The Patent Owner argues that a POSA would not use the doses and schedules claimed in the patent. (POR IPR 2016-240 at 52.) I disagree. In my opinion, once repleting a cancer patient with vitamin B12, a POSA in June 1999, would have repeated intramuscular injections of 1000 µg of B12 every several weeks, particularly during chemotherapy treatment. Although B12 repletion (and resolution of the methyltrap) typically occurs within five days, a patient undergoing chemotherapy treatments, particularly in the presence of cisplatin (recommended to be administered with pemetrexed), is at additional risk of recurrent deficiency of vitamin B12 during chemotherapy treatment since the nausea and vomiting commonly induced by cisplatin would discourage oral intake of both foodstuffs containing B12 or oral vitamin supplements, depleting his or her vitamin B12 during chemotherapy treatment. (Ex. 2069, Naurath 1995 at 87 (in vitamin treated patients, a normal concentration was achieved by day 5); Ex. 1061, Cubeddu 1990 ("Cisplatin … produces the most severe nausea and emesis of any chemotherapeutic agent."; Ex. 1074, Vu 1993 (early negative B12 balance evidenced in chemotherapy patients that in some instances was induced by the treatment itself); Ex. 1076, Zeisel Tr. at 46:12-47:12 (testifying that "cancers in which the treatment makes people unable to eat, a POSA would have realized that they developed nutritional deficiencies. And some of those cancers where eating properly was difficult, a part of the cancer itself, a POSA would have realized that there was a potential for developing – malnutrition, yes.").) Dr. Zeisel also testified that 1 mg (1000 µg of vitamin B12) would be depleted by a patient in a matter of weeks, requiring additional and repeated intramuscular injections. (Ex. 1076, Zeisel Tr. 90:8-91:4 ("when you give an [intramuscular] dose, you don't have to give it to them daily. You give them something more than the few micrograms they need so that they can draw on that does that's sitting in the muscle that you stick it in for a period of time. And so a standard dose, probably, you know, a milligram would have been enough to last them weeks before they run it down.").)

77. Therefore, a POSA in June 1999 would likely recommend continued repeated treatments with vitamin B12 every several weeks to those patients undergoing chemotherapy. Most commonly the treatment interval is every four weeks. However, I have had patients over the years who dislike monthly injections, in which case I have successfully stretched out their injections to 6-12 weeks by confirming with MMA levels that they are not becoming vitamin B12 deficient after four weeks. Thus, a POSA in 1999 would have, in some instances, treated patients with vitamin B12 intramuscular injections every several weeks, including treatment intervals between 4 and 12 weeks, depending on the patient.

Source: Ex. 1078 at ¶¶76-77; Paper 48 at 26.

Dr. Mason's Testimony

73. A POSA in 1999 would have also known that even though taking vitamin B12 orally is possible, a medical professional overseeing vitamin B12 supplementation would most likely have administered vitamin B12 through an intramuscular injection and would not have administered it orally. This is in part because some patients who are vitamin B12 deficient would be unable to absorb the vitamin if taken orally. Accordingly, Dr. Zeisel stated during his deposition that: "A patient who can't absorb an oral dose would get an intramuscular dose . . . For patients with pernicious anemia, this subset of patients we've just been talking about, their problem is is they do not make a protein in the gut needed to intramuscular B12. So they cannot absorb B12. And you treat people with that problem with intramuscular dose." (Ex. 1076, Zeisel Dep. 88:9-19.) Furthermore, administering vitamin B12 through a 1000 ug intramuscular injection prevents the need to treat the patient daily, ensuring that the patient can draw on the vitamin B12 injected into the muscle for a period of weeks before undergoing additional B12 treatments. (Ex. 1076 Zeisel Tr. 90:8-91:4 ("when you give an [intramuscular] dose, you don't have to give it to them daily. You give them something more than the few micrograms they need so that they can draw on that does that's sitting in the muscle that you stick it in for a period of time. And so a standard dose, probably, you know, a milligram would have been enough to last them weeks before they run it down.").)

Source: Ex. 1078 at ¶73; Paper 48 at 26.

Dr. Mason's Testimony

52. First, a POSA in 1999 would not avoid supplementing cancer patients with vitamin B12 because of concerns that it might accelerate tumor growth since even the theoretical concern about releasing folates newly converted to the useable THF form with the vitamin B12 pretreatment would only apply to those individuals who are vitamin B12 deficient.

54. The fact that administering vitamin B12 supplements releases no additional folate for DNA synthesis and other functions once a person is B12-replete is well demonstrated by a paper from 1998. (Ex. 1087, Kuzminski 1998 at 1191-1198; see figure 3 at 1196 (demonstrating that once a state of B12 repletion is achieved the decrease in homocysteine levels off).) In the Kuzminski et. al. study, the homocysteine level is a valid proxy measure of the methyl trap. The fact that homocysteine does not further decline once B12 repletion is achieved indicates that, following repletion, the additional 'release of folate trapped as 5-methylTHF' to the more utilizable form (THF) is no longer occurring. In fact, in paragraph 53 of the Zeisel declaration, Dr. Zeisel acknowledges that the effect is confined to individuals who are B12 deficient.

Source: Ex. 1078 at ¶¶52, 54; Paper 48 at 27.

Dr. Mason's Testimony

75. In my opinion, a POSA in June 1999, would have identified those patients who were vitamin B12 deficient and would have repleted those individuals via intramuscular injections of 1000 µg of B12 prior to initiating chemotherapy. Further, it is likely that the POSA would have similarly chosen to treat those identified as being at high risk of vitamin B12 deficiency. Accordingly, a POSA in June 1999, would not have been concerned that pemetrexed efficacy would be negatively impacted by the vitamin B12 pretreatment, particularly since the methyl-trap issue (cited as the primary concern by Dr. Zeisel, Ex. 2118 ¶ 56) would resolve quickly and prior to treatment.

Source: Ex. 1078 at ¶75; Paper 48 at 27.

Dr. Mason's Testimony

53. Though only a minority of all patients undergoing cancer treatment are vitamin B12 deficient, vitamin B12 deficiency is common amongst certain patient populations, including the elderly. Accordingly, the POSA would not refrain from using B12 in non-B12 deficient patients over concerns for those that are vitamin B12 deficient. Further, what concerns a POSA might have for the minority of all patients would be eliminated since the POSA would almost certainly have identified those patients presenting with a vitamin B12 deficiency and repleted them before initiating chemotherapy. This is especially true since the training of oncologists always includes a great deal of hematology education as well, so these specialists are very attuned to attending to causes of anemia.

55. Dr. Zeisel states in paragraph 55 that "…as of June 1999, vitamin B12 was understood to be able to enhance the activity of methionine synthase and to increase the amount of the enzyme." (Ex. 2118 ¶55.) Dr. Zeisel cites Ex. 2038, Gulati et. al. But that study compared B12-deficient cells (cultured in media estimated to be 125 pM=167 pg/mL) with fully repleted cells, so one would expect nothing else than an increase in activity of methionine synthase since it is an experiment where deficient cells are being supplemented with B12.

56. Thus, in June 1999, a POSA would not be concerned with the release of folates due to the vitamin B12 pretreatment and therefore would not avoid pretreating a patient with vitamin B12 prior to administering antifolates, including pemetrexed.

Source: Ex. 1078 at ¶¶53, 55-56; Paper 48 at 27.

Dr. Mason's Testimony

70. A standard initial treatment of vitamin B12 deficiency in June 1999, would have consisted of an intramuscular injection 1000 µg of vitamin B12 rather than the very small amount suggested by Dr. Zeisel. One demonstration of this appears in the 1999 Vidal reference cited by Dr. Zeisel, in which it states the recommended treatment of vitamin B12: "Initial treatment: 1mg (one 1,000µg vial) per day or three times per week by intramuscular injection, i.e. 10mg (10 x 1,000µg vials) in total." ((Ex. 2059, Vidal 1999 at 3): Ex. 2032, Vidal 1998 at 28) (Forms of vitamin B12 described as "1,000 ug/ml intramuscular injectable solution: 1ml vials.".)

Source: Ex. 1078 at ¶70; Paper 48 at 30.

Dr. Mason's Testimony

68. Dr. Zeisel states that even in those vitamin B12 deficient patients a POSA would have avoided treating them with vitamin B12 because a patient "who has low levels of vitamin B12, and therefore would be understood to have a significant amount of folate 'trapped' in the 5-methylTHF form, administering even a small amount of vitamin B12 would be understood to have the effect of releasing potentially large amount of folate from the 'trap.'" (Ex. 2118 ¶ 53.) As a result, Dr. Zeisel states, a POSA would therefore believe "that even a small dose of vitamin B12 [2-3 µg] would be sufficient to overcome methyl trapping of folate, and thus release potentially large amount of any 'trapped' 5-MTHF in a person's cells for use in the form of other folates." (Ex. 2118 ¶ 55.) I disagree since I believe the POSA would not have avoided administration of B12 for all the reasons I described above. Moreover, I believe the POSA would have administered a dose of 1000 µgs as opposed to the 2-3 µgs proposed by Dr. Zeisel. In fact, 1000 µgs was one of the standard treatments of vitamin B12 supplementation in June 1999.

71. The fact that 1000 µgs of intramuscular B12 was a standard treatment in 1999 is further shown in Barker, et. al., Principles of Ambulatory Medicine, 4th Ed. (1995), in which it states that: "The usual treatment for B12 deficiency is monthly intramuscular administration of 1000 ug of B12…" (Ex. 1097, Barker 1995 at 600.) Vitamin B12 was also, in June 1999, provided in 1000 µg ampules, further demonstrating that 1000 µg was a well-known and accepted dose at that time. Additionally, Dr. Chabner testified in his deposition that "[t]he patent sort of gives some flexibility to the physician, but I can tell you in practice everybody uses 1000 [µg]." (Ex. 1075, Chabner Dep. at 352:7–9; *see also* Ex. 1076, Zeisel Tr. 90:8-91:4 ("when you give an [intramuscular] dose, you don't have to give it to them daily . . . And so a standard dose, probably, you know, a milligram would have been enough to last them weeks before they run it down.").)

Source: Ex. 1078 at ¶¶68, 71; Paper 48 at 31.

Dr. Mason's Testimony

90. Because of the irreversible damage caused by untreated vitamin B12 deficiency and the likelihood that a vitamin B12 deficiency may be masked by the supplementation of folic acid, practice dictated for many years (including the decades preceding 1999) that vitamin B12 deficiency--once identified or suspected --needs to be treated promptly and thoroughly. (Ex. 2065, Brattstrom 1996 ("in vitamin B12 deficiency, erroneous treatment with folic acid may correct the hematological abnormalities but elicit and deteriorate vitamin B-12 neuropathy. Therefore, before start of therapy, vitamin B-12 deficiency must be excluded, and the combination must contain a dose of cyanocobalamin high enough to prevent the occurrence of vitamin B-12 deficiency".) This is why therapy is always begun with an intramuscular injection such as the 1000 µg dose of vitamin B12 described above.

Source: Ex. 1078 at ¶90; Paper 48 at 31.

DR. FEIGAL

Dr. Feigal's Testimony

27. For most drugs, Phase 1 trials are small, closely monitored studies, in normal healthy volunteers, although for conditions such as cancer, patients with advanced disease are often recruited for these trials. In Phase 1 the goal is to learn how a drug is absorbed and eliminated from the body and to determine safe doses for further testing. Typically, fewer than 100 subjects participate in Phase 1. If patients are studied in Phase 1, initial evidence of effectiveness may be available from those short-term studies, but these small trials are not designed or large enough to reliably quantify efficacy.

28. Phase 2 trials are the first trials to evaluate the effectiveness of the drug for patients with a particular condition. The studies often involve several hundred patients. They are used to learn enough about the drug to plan the larger trials in Phase 3 that will study the safety and effectiveness of the drug for one or more indications. The studies in these phases can sometimes overlap.

Source: Ex. 1080 at ¶¶ 27-28; Paper 48 at 16.

Dr. Feigal

Dr. Feigal's Testimony

39. In my opinion, the record reflects instead a recognition that vitamin supplementation indeed was obvious, based on the mechanism of action of pemetrexed, but that to introduce folate and B12 supplementation at an interim point in an ongoing phase 3 randomized clinical trial ran the risk of jeopardizing the interpretation of the results of the trial. The concern stemmed from several issues:

a. First, statistical inference upon the completion of a randomized trial requires formal specification of when and how the trial would be analyzed. Interim analyses are planned events, as the safety analysis by Lilly may have been, but stopping or modifying a trial based on knowledge of those results must be done in a way that does not bias the final result. This concern was reflected in Dr. White's comments about a lack of a statistical plan. This has nothing to do with obviousness.

b. When a trial is modified and the treatment in the first part of the trial is not the same as the treatment in a second part—as Lilly proposed to FDA—it may not be statistically justifiable to pool the two parts of the trial, and the trial may fail for lack of power. This has nothing to do with obviousness.

c. If the treatment is changed for some or all participants after randomization, based on post-randomization observations of the primary end-point, i.e., survival—as Lilly proposed—then the comparability of the two randomized arms is compromised and the study may not be interpretable. This has nothing to do with obviousness.

d. FDA's long standing policies, as reflected in the combination drug regulations cited above, are to demonstrate the need for the combination with a randomized comparison of the combination to at least one of the drugs alone. This also has nothing to do with obviousness.

Source: Ex. 1080 at ¶¶39(a-d); Paper 48 at 33.

Dr. Feigal's Testimony

40. Dr. White was also not convinced that the data from the annual report was consistent with Lilly's new analyses, and that lack of consistency, in my opinion, was a reasonable basis for him to disagree with Lilly's proposed change. It was not that folate or B12 supplementation were unexpected to provide a clinical benefit, or that there was a reason not to study the contribution. Dr. White, in my opinion, was objecting to how Lilly was proposing to introduce the addition of vitamin supplementation, and suggesting that Lilly should do so in a way that would document the contribution of vitamin supplementation to both safety and effectiveness. Once Lilly submitted to the FDA data regarding the impact (or lack thereof) of vitamin supplementation on efficacy, including the prior art that I understand is at issue in this matter, I do not see any evidence that he questioned the obviousness that these vitamins would be beneficial to both the safety and effectiveness of the drug.

41. In short, FDA requires clinical trial evidence in many settings where the outcome is confirmation of the obvious. But in a phrase FDA borrows from Demming: "in God we trust. Everyone else must submit data." In my opinion, FDA's comments to Lilly regarding Lilly's proposed vitamin supplementation were manifestations of this policy—FDA was not expressing skepticism as to the benefits of vitamin supplementation, but was merely performing its statutory duty in requiring that Lilly submit data providing justification for introducing folate and B12 supplementation at an interim point in an ongoing phase 3 randomized clinical trial ran the risk of jeopardizing the interpretation of the results of the trial.

Source: Ex. 1080 at ¶¶40-41; Paper 48 at 33.

PETITION

Petition

-00240 Petition

Fig. 2. L-methylmalonyl-CoA mutase (left) and methionine synthetase (right) are the two mammalian Cbl-dependent enzymes. In Cbl deficiency, L-methylmalonyl-CoA accumulates and is converted to D-methylmalonyl-CoA, which is hydrolyzed to methylmalonic

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> Because folate and vitamin B-12 have a synergistic function as cofactors of methionine synthase, sufficiency of both seems to be important to increase enzyme activity, whereas a higher availability of only one cofactor, especially in subjects with an already good supply

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(*See e.g.*, Ex. 1008 at 126; *see also* Ex. 1017 at 93.) For example, in 1998, *Niyikiza* reported that 139 patients in a phase II study with pemetrexed treatment were monitored for homocysteine and methylmalonic acid levels, and the monitoring established that there was a strong correlation between elevated homocysteine levels and pemetrexed toxicity. (Ex. 1008 at 126–27.)

PATENT OWNER'S RESPONSE

Patent Owner's Response

I. Background

A. Antifolates and Folates

Folates, such as folic acid, are a class of compounds that the body needs to make DNA. Ex. 2120 ¶ 34; Ex. 2118 ¶ 21. DNA is required in order for cells, both normal and cancerous, to divide and grow. Ex. 2120 ¶ 34. Various enzymes in the human body convert various forms of folate to other forms; this cycle or pathway of folates being converted from one form to another is the folic acid pathway. Ex. 2120 ¶ 34; Ex. 2118 ¶ 22. For example, one such enzyme in the

¶¶ 24-25. Pemetrexed inhibits three enzymes in the folate pathway. Its principal effect is on TS; it also inhibits to some extent enzymes known as DHFR and GARFT. Ex. 2120 ¶ 35, 46; Ex. 2118 ¶ 25. By interfering with the binding of

folates to these enzymes, antifolates like pemetrexed interfere with DNA synthesis and thereby hamper cell division, ultimately killing cells that are dividing. Ex. 2120 ¶ 45; Ex. 2118 ¶¶ 25-26. It is this mechanism that allows antifolates to be effective in treating cancer: cancer cells divide rapidly and have a high demand for DNA precursors and are thus particularly susceptible to antifolates. *Id.*

Source: Paper 33 at 5; Paper 48 at 16.

Patent Owner's Response

trial; however, a phase I clinical trial of this regimen, published by Laohavinij in 1996, showed that the regimen led to only one response—far fewer than had been observed in trials of lometrexol unsupplemented by folic acid. Ex. 2031 at 333.

During the 1990s, Lilly was also developing pemetrexed. As of April 1999, phase II studies of pemetrexed had shown anticancer responses in six different tumor types, and pemetrexed's anti-tumor activity was considered "remarkable and unusual." Ex. 2120 ¶¶ 51-52; Ex. 2034 at 107; Ex. 2029 at 103–04; Ex. 1011 at 1194; Ex. 1013 at Table 3; Ex. 2022. This promising efficacy in killing cancer was

participating in pemetrexed clinical trials. Dr. Niyikiza published the results from this analysis in two abstracts in 1998. Ex. 1008 (Niyikiza I) at 609P, Ex. 2015 (Niyikiza II) at 2139. The abstracts explained that there was a correlation between pemetrexed toxicity and the level of homocysteine in the patients' blood prior to

Source: Paper 33 at 10; Paper 48 at 12.

Patent Owner's Response

acid—accompanied the labeling for the antifolate raltitrexed, a TS inhibitor (like pemetrexed, but unlike methotrexate) that was approved in Europe: "[F]olinic acid, folic acid, or vitamin preparations containing these agents *must not be given* immediately prior to or during administration of Tomudex, since they may interfere with its action." *See* Ex. 2021 at 1544 (emphasis added); Ex. 2120 ¶ 65.

DHFR. But pemetrexed works primarily by inhibiting TS, a different enzyme that is not needed to convert folic acid into a usable form. Ex. 2120 ¶¶ 46, 164, 181; Ex. 2054 at 110 (LY231514 listed as a TS inhibitor). At a therapeutically effective dose for treating cancer, the POSA would have no reason to believe that pemetrexed would inhibit DHFR sufficiently to block the conversion of folic acid to other folates and thus to stop it from reversing the pemetrexed's efficacy. Ex. 2120 ¶ 179.

Source: Paper 33 at 26; Paper 48 at 16.

Patent Owner's Response

Patent Owner's Response

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To do so, he statistically analyzed more than sixty variables describing patients participating in pemetrexed clinical trials. Dr. Niyikiza published the results from this analysis in two abstracts in 1998. Ex. 1008 (Niyikiza I) at 609P, Ex. 2015 (Niyikiza II) at 2139. The abstracts explained that there was a correlation between pemetrexed toxicity and the level of homocysteine in the patients' blood prior to

participating in pemetrexed clinical trials. Dr. Niyikiza published the results from this analysis in two abstracts in 1998. Ex. 1008 (Niyikiza I) at 609P, Ex. 2015 (Niyikiza II) at 2139. The abstracts explained that there was a correlation between pemetrexed toxicity and the level of homocysteine in the patients' blood prior to pemetrexed treatment. *Id.* Critically, however, he found no such correlation

pemetrexed treatment. *Id.* Critically, however, he found no such correlation between pemetrexed toxicity and MMA levels. Ex. 2015; *see* Ex. 2120 ¶ 33d, 106;

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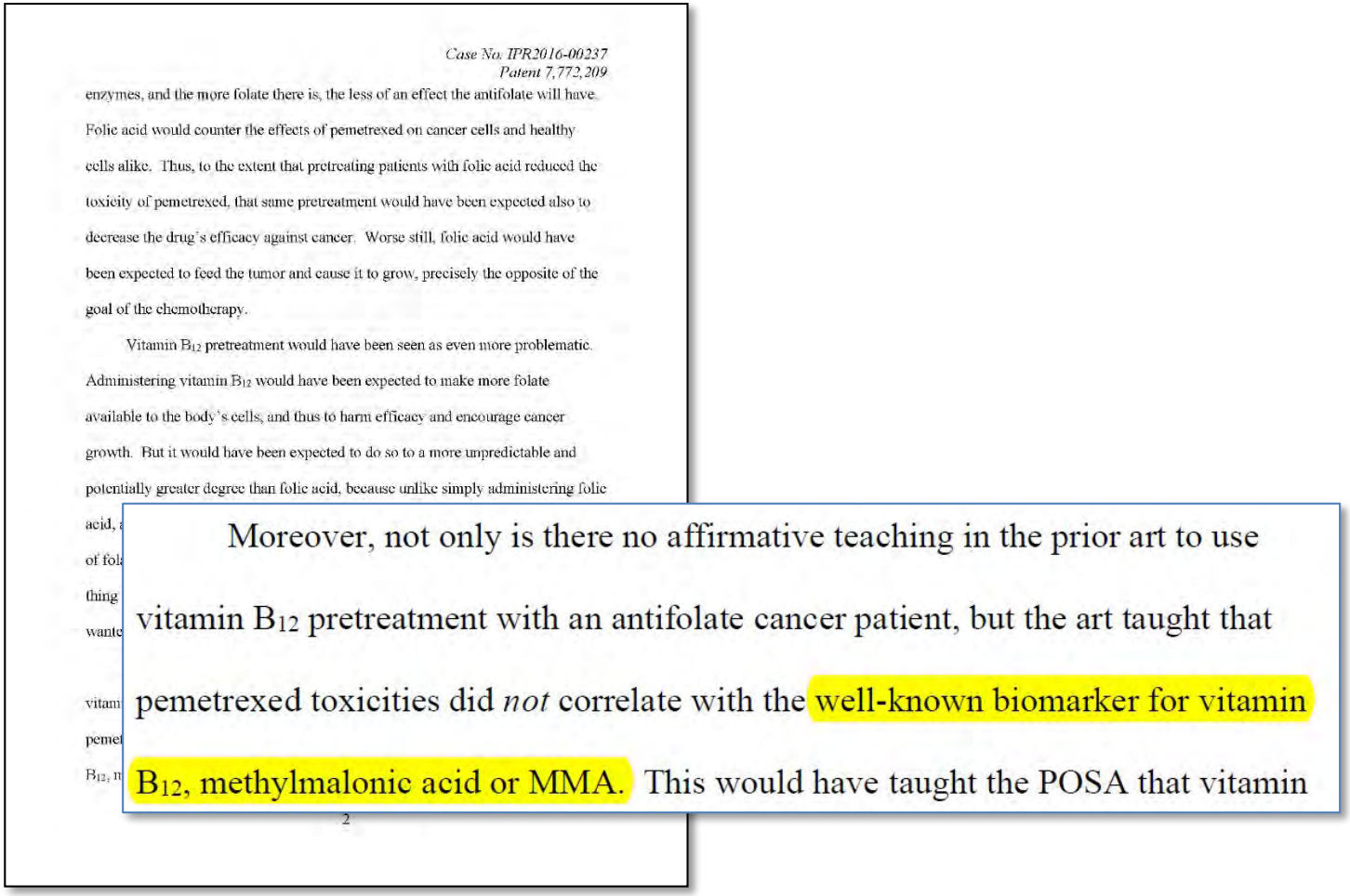
In late 1999, after the critical date for the '209 patent, the calculus changed. Until that point, pemetrexed's toxicities appeared manageable and tolerable. But then, in an ongoing phase III pemetrexed trial, an alarming 7% of patients died, apparently due to severe pemetrexed toxicities. Ex. 2103 at 2. This threatened to halt development of pemetrexed altogether. Ex. 2107 at 16.

Patent Owner's Response



Case No. IPR2016-00237
Patent 7,772,209

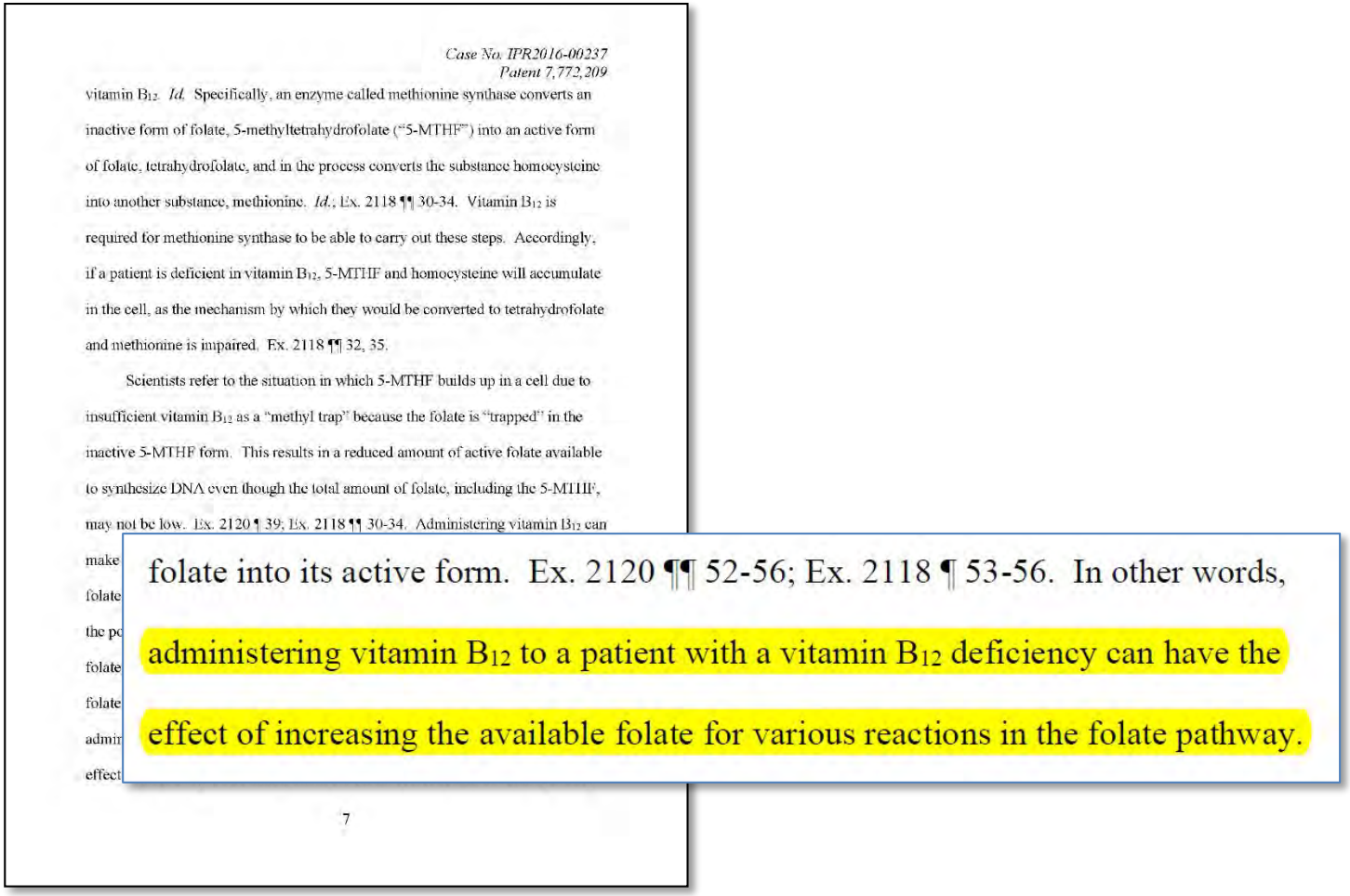
enzymes, and the more folate there is, the less of an effect the antifolate will have. Folic acid would counter the effects of pemetrexed on cancer cells and healthy cells alike. Thus, to the extent that pretreating patients with folic acid reduced the toxicity of pemetrexed, that same pretreatment would have been expected also to decrease the drug's efficacy against cancer. Worse still, folic acid would have been expected to feed the tumor and cause it to grow, precisely the opposite of the goal of the chemotherapy.

Vitamin B_{12} pretreatment would have been seen as even more problematic. Administering vitamin B_{12} would have been expected to make more folate available to the body's cells, and thus to harm efficacy and encourage cancer growth. But it would have been expected to do so to a more unpredictable and potentially greater degree than folic acid, because unlike simply administering folic

Moreover, not only is there no affirmative teaching in the prior art to use vitamin B_{12} pretreatment with an antifolate cancer patient, but the art taught that pemetrexed toxicities did *not* correlate with the well-known biomarker for vitamin B_{12}, methylmalonic acid or MMA. This would have taught the POSA that vitamin

2

Patent Owner's Response



Case No. IPR2016-00237
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vitamin B_{12}. *Id.* Specifically, an enzyme called methionine synthase converts an inactive form of folate, 5-methyltetrahydrofolate ("5-MTHF") into an active form of folate, tetrahydrofolate, and in the process converts the substance homocysteine into another substance, methionine. *Id.*; Ex. 2118 ¶¶ 30-34. Vitamin B_{12} is required for methionine synthase to be able to carry out these steps. Accordingly, if a patient is deficient in vitamin B_{12}, 5-MTHF and homocysteine will accumulate in the cell, as the mechanism by which they would be converted to tetrahydrofolate and methionine is impaired. Ex. 2118 ¶¶ 32, 35.

Scientists refer to the situation in which 5-MTHF builds up in a cell due to insufficient vitamin B_{12} as a "methyl trap" because the folate is "trapped" in the inactive 5-MTHF form. This results in a reduced amount of active folate available to synthesize DNA even though the total amount of folate, including the 5-MTHF, may not be low. Ex. 2120 ¶ 39; Ex. 2118 ¶¶ 30-34. Administering vitamin B_{12} can make folate the po folate folate admir effect

7

folate into its active form. Ex. 2120 ¶¶ 52-56; Ex. 2118 ¶ 53-56. In other words, administering vitamin B_{12} to a patient with a vitamin B_{12} deficiency can have the effect of increasing the available folate for various reactions in the folate pathway.

Patent Owner's Response

EP 005's references to methotrexate and "cancers" as possible causes of elevated homocysteine are not to the contrary. While it is true that methotrexate and certain cancers can cause elevated homocysteine (unlike pemetrexed, *see* Ex. 2120 ¶¶ 126, 138; Ex. 2027 at 75-76), nowhere does the reference suggest that its homocysteine-lowering cocktail should be administered to patients who are about to receive antifolate cancer chemotherapy, which, for all the reasons previously discussed, the POSA would have viewed as problematic. Ex. 2120 ¶ 136; Ex. 2027 at 184-86, 206-08. It certainly provides no information or data on how folic acid or vitamin B_{12} pretreatment would impact methotrexate's anti-cancer efficacy with an antifolate. Ex. 2120 ¶ 136. At most, EP 005 would be understood as a way to lower homocysteine levels *after* methotrexate chemotherapy or cancer has caused them to rise. Ex. 2120 ¶ 139. That is not a relevant disclosure for the antiproliferative effect on cells (and, therefore, would not be undermined through the use of agents that increase folate concentrations). Ex. 2120 ¶¶ 137, 202-204; Ex. 2020 at 1397 (in cancer, methotrexate has an antiproliferative effect; in RA, its

FEDERAL CIRCUIT DECISION

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

IPR Evidence Not Before Federal Circuit:

Niyikiza's ideas. Long before there ever was a '209 patent or his retention as an expert by Lilly, Dr. Chabner was interviewed by the *Wall Street Journal* about what he thought of Dr. Niyikiza's vitamin pretreatment regimen for pemetrexed;

vs.

1996, I think it was, I was asked to be the visiting professor at the Indiana University. And it was called the Eli Lilly Lectureship. I actually showed a picture there of my two dogs in bed with me. And their names were Eli and Lilly. And I said, you know, I've been accused of being in bed with Eli Lilly. It was a joke. And I am.

Source: Paper 63 at 15; Paper 33 at 55.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

IPR Evidence Not Before Federal Circuit:

Curriculum Vitae

Date Prepared: 11-18-2015
Name: Bruce A. Chabner

2003- Advisory Committee for Forteo Eli Lilly

vs.

4 When did you begin working with
5 Lilly on Forteo?

23 was in the -- I told you earlier. It was
24 in, around 2000.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

IPR Evidence Not Before Federal Circuit:

Curriculum Vitae

Date Prepared: 11-18-2015
Name: Bruce A. Chabner

2003- Advisory Committee for Forteo Eli Lilly

vs.

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

+ + + + +

ENDOCRINOLOGIC AND METABOLIC

DRUGS ADVISORY COMMITTEE

+ + + + +

MEETING

+ + + + +

FRIDAY,

JULY 27, 2001

Today we're going to be discussing NDA 21-13 -- I'm sorry -- 318, Forteo, teriparatide injection or recombinant DNA origin. The presenters will be Eli Lilly and Company and the FDA.

In fact, we wish to thank the following experts for working with us and for being here today to assist with your deliberation: Dr. Adamson, Bellizikan, Chabner, Lindsay, Neer, Potts, and Stewart.

Source: Paper 63 at 15; Ex. 2121 at 1-2; Ex. 1057 at 1, 4, 18.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

IPR Evidence Not Before Federal Circuit:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–22 of the '209 patent on the following ground:

References	Basis	Claims challenged
Niyikiza in view of the '974 Patent and further in view of EP 005	§ 103	1–22

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–22 of the '209 patent on the following ground:

References	Basis	Claims challenged
Rusthoven in view of EP 005	§ 103	1–22

Source: Paper 63 at 15; Paper 13 at 19; Paper 14 at 19 (IPR2016-00240).

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

Federal Circuit Ruling:

Given the toxicity correlations that Dr. Niyikiza observed with homocysteine levels but not with MMA levels, Eli Lilly's experts testified that the Niyikiza abstracts "present[ed] no evidence for a relationship of vitamin B12 and pemetrexed toxicity" and would not have motivated a skilled artisan to administer vitamin B12 to patients to address pemetrexed toxicity. J.A. 1466–67; *see also* J.A. 1475, 1942. Defendants' expert, Dr. Ratain, confirmed that if a patient exhibits elevated homocysteine but normal MMA levels, a skilled artisan "would conclude that that patient was folate deficient" but "not [vitamin] B12 deficient." J.A. 622–23.

IPR Evidence Not Before Federal Circuit:

piece, I have said that there are numbers of reasons that homocysteine could be elevated, B12 or low B12 being one of them.

However, in the presence of normal MMA, I believe that Niyakiza does not support the conclusion that B12 is -- B12 deficiency is the cause. It just says that, at least in this group of patients, I can't say it is and I can't rule out it isn't.

Source: Paper 63 at 15; Fed. Cir. Slip Op. at 26; Ex. 1076 at 116:12-20; Paper 48 at 24.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

Federal Circuit Ruling:

But the parties' experts agreed that nothing in the literature as of the critical date described "cancer patients being provided with vitamin B12 supplementation prior to receiving any antifolate," with or without folic acid. J.A.

IPR Evidence Not Before Fed. Cir.: EP 005:

In accordance with the invention there is provided the use in the manufacture of a pharmaceutical preparation for lowering levels of homocysteine or for the prophylaxis or treatment of elevated levels of homocysteine in a patient of a combination which comprises

a) vitamin B6;

b) folate or a suitable active metabolite of folate or a substance which releases folate in vivo;

c) vitamin B12, with or without intrinsic factor.

The pharmaceutical compositions are not only to be used in the treatment of raised homocysteine levels induced nutritionally, genetically or as a result of a variety of diseases, but also in those cases where the elevated homocysteine levels are drug induced or in combination with a B6 or folate antagonistic drug, which has a tendency to raise homocysteine levels. Examples of other situations in which blood homocysteine levels may be elevated are the following: post-menopausal women, liver failure, leukemia, other cancers, chronic renal failure. Slow-release formulation of PL prevents excessive liver oxidation to the biologically inactive pyridoxic acid.

Source: Paper 63 at 15; Fed. Cir. Slip Op. at 26-27; Ex. 1010 at 4, 9; Paper 48 at 21-22.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

Federal Circuit Ruling:

597–98; *see also* J.A. 1957. Defendants fail to point to evidence that, even if folic acid supplementation were known to improve effects of pemetrexed treatment, a skilled artisan would have thought the same of vitamin B12. Indeed, Eli Lilly offered expert testimony that a

IPR Evidence Not Before Fed. Cir.: EP 005:

Furthermore, applicant has surprisingly found that for purposes of controlling blood homocysteine levels, the combination in accordance with the invention of PL, folate and vitamin B12 produces advantageous effects which go substantially beyond what might be expected from a simple additive effect of the action of these drugs. Thus, an unexpected synergism exists when vitamin B12, folate and PL are given concurrently and this effect can be even greater when the vitamins are given in conjunction with a biological

The composition according to the invention is nearly twice as effective as folate alone. This indicates a significantly more than a purely additive effect of the three component combination (synergism).

The tests show that (in contrast to prior art reports teaching the use of folate alone at levels 5 to 20 times higher than in the present trials), nearly 50% of patients do not respond sufficiently to folate alone and 10-20% do not respond to folate alone at all, (not even if the folate dosage rate is greatly increased). By way of contrast, the combination in accordance with the invention, using very low folate concentrations, achieved close on 100% success.

Source: Paper 63 at 15; Fed. Cir. Slip Op. at 27; Ex. 1010 at 4, 9; Paper 48 at 21-22.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

Federal Circuit Ruling:

597–98; *see also* J.A. 1957. Defendants fail to point to evidence that, even if folic acid supplementation were known to improve effects of pemetrexed treatment, a skilled artisan would have thought the same of vitamin B12. Indeed, Eli Lilly offered expert testimony that a

IPR Evidence Not Before Federal Circuit:

Hyperhomocysteinemia due to vitamin B-12 deficiency does not respond to folic acid therapy (Allen et al. 1990). It is likely, that even in subjects with low normal vitamin B-12 concentrations full response to folic acid cannot be achieved unless vitamin B-12 is given concomitantly (Landgren et al. 1995). This view

What doses and what combination of vitamins should be recommended for long-term homocysteine lowering? For several reasons, it seems wise to combine folic acid and cyanocobalamin. First, folic acid seems to reduce almost all but low homocysteine levels. Second, cyanocobalamin will probably secure full folic acid responsiveness. Third, in vitamin B-12 deficiency, erroneous treatment with folic acid may correct the hematological abnormalities but elicit and deteroriate vitamin B-12 neuropathy (Chanarin 1994). Therefore, before start of therapy, vitamin B-12 deficiency must be excluded, and the combination must contain a dose

Source: Paper 63 at 15; Fed. Cir. Slip Op. at 27; Ex. 1063 at 1277S-78S; Paper 48 at 21-22.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

Federal Circuit Ruling:

597–98; *see also* J.A. 1957. Defendants fail to point to evidence that, even if folic acid supplementation were known to improve effects of pemetrexed treatment, a skilled artisan would have thought the same of vitamin B12. Indeed, Eli Lilly offered expert testimony that a

IPR Evidence Not Before Federal Circuit:

In this study, vitamin B-12 supplementation increased the tHcy-lowering potential of folic acid; this was especially obvious

nmol/L. Because folate and vitamin B-12 have a synergistic function as cofactors of methionine synthase, sufficiency of both seems to be important to increase enzyme activity, whereas a higher availability of only one cofactor, especially in subjects with an already good supply of this cofactor, might lead to only a limited increase in enzyme activity.

no apparent chronic or acute illness. Upon B-vitamin supplementation, a significant reduction in tHcy concentration was observed during the first 2 weeks of treatment. Thereafter, tHcy decreased further only slightly and non-significantly. Parallel but opposite changes were seen for

this strong influence, combined administration of B-vitamins to normo-homocysteinemic subjects or to those with mild/moderate hyper-homocysteinemia may still exhibit synergistic effects. In women of childbearing age, the tHcy-lowering effects of folic acid in different combinations with vitamins B_6 and B_{12} were stronger than with folic acid alone [21, 22].

Source: Paper 63 at 15; Fed. Cir. Slip Op. at 27; Ex. 1063 at 1277S-78S; Ex. 1099 at 190 Paper 48 at 21-22.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

Federal Circuit Ruling:

Regarding the dose and schedule of vitamin B12, the district court reiterated that "there are no prior art references where *any amount* of vitamin B_{12} pretreatment had been used with an antifolate in the treatment of cancer."

IPR Evidence Not Before Federal Circuit: EP 005

Formulation type	PL		Folate		B12	
	Range mg	Preferred mg	Range mg	Preferred mg	Range mg	Preferred mg
Normal (no absorption problem)	2-5	5	0,2-15	1,0	0.1-2	0.5
Special (to overcome absorption problems)	2-50	5	2-15	5	0.2-5	1,0

Source: Paper 63 at 15; Fed. Cir. Slip Op. at 27; Ex. 1010 at 8; Paper 48 at 35.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

Federal Circuit Ruling:

instance. Defendants only cite evidence of vitamin B12 doses and schedules that are "routine" in other medical contexts. *See, e.g.*, J.A. 8150, 8169, 756–57. There is no evidence that, considering the context of pemetrexed treatment and associated toxicity problems, a person of ordinary skill would have applied such doses and schedules wholesale.

IPR Evidence Not Before Federal Circuit: EP 005:

The pharmaceutical compositions are not only to be used in the treatment of raised homocysteine levels induced nutritionally, genetically or as a result of a variety of diseases, but also in those cases where the elevated homocysteine levels are drug induced or in combination with a B6 or folate antagonistic drug, which has a tendency to raise homocysteine levels. Examples of other situations in which blood homocysteine levels may be elevated are the following: post-menopausal women, liver failure, leukemia, other cancers, chronic renal failure. Slow-release formulation of PL prevents excessive liver oxidation to the biologically inactive pyridoxic acid.

Folate		B12	
Range mg	Preferred mg	Range mg	Preferred mg
0,2-15	1,0	0.1-2	0.5
2-15	5	0.2-5	1,0

Source: Paper 63 at 15; Fed. Cir. Slip Op. at 27; Ex. 1010 at 4, 8-9; Paper 48 at 21-22, 35.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

Federal Circuit Ruling:

instance. Defendants only cite evidence of vitamin B12 doses and schedules that are "routine" in other medical contexts. *See, e.g.*, J.A. 8150, 8169, 756–57. There is no evidence that, considering the context of pemetrexed treatment and associated toxicity problems, a person of ordinary skill would have applied such doses and schedules wholesale.

IPR Evidence Not Before Federal Circuit:

Q. And would the '97 -- would a POSA consider the '974 teachings to be applicable to pemetrexed?

* * *

A. Actually, it was in the context of an antifolate related -- the predecessor, lometrexol.

Q. Would a POSA have considered the EP '005 teachings to be applicable to the antifolate context?

* * *

A. Yes, I do. I would because the application itself refers to using this approach, the synergism of B12 folic acid in patients with cancer, leukemia, and those receiving folate antagonists.

Source: Paper 63 at 15; Fed. Cir. Slip Op. at 27; Ex. 2135 at 333:6-16; 336:25-337:11; Paper 64 at 12.

Federal Circuit Decision

Lilly's Sur-Reply Argument:

The Board Should Take Notice of the Federal Circuit's Related Decision

Federal Circuit Ruling:

instance. Defendants only cite evidence of vitamin B12 doses and schedules that are "routine" in other medical contexts. *See, e.g.*, J.A. 8150, 8169, 756–57. There is no evidence that, considering the context of pemetrexed treatment and associated toxicity problems, a person of ordinary skill would have applied such doses and schedules wholesale.

IPR Evidence Not Before Federal Circuit:

Q. Would a POSA have applied the Bronstrup reference to the antifolate context?

A. A POSA in the oncology world would use that as evidence that it can be deducted to be useful in their patients on antifolates.

Would a POSA take that information to the oncology patient? There is no reason not to believe that if it worked in the healthy woman between 20 and 34 years of age, that it could also work in a patient about to receive antifolates.

Source: Paper 63 at 15; Fed. Cir. Slip Op. at 27; Ex. 2135 at 331:11-15, 332:8-13; Paper 64 at 12.

OPPOSITION TO MOTIONS FOR OBSERVATION

Dr. Bleyer

Dr. Bleyer's Testimony

Q. -- so now having confirmed the two premises in your sentence, the question is what is the relevance to the person of ordinary skill of the fact that this is in vitro studies

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outside of the antifolate context to the question of whether vitamin B12 pretreatment would cause a tumor to progress?

Now, the answer to your question, this is not strong evidence against vitamin B12 affecting tumor growth. It is in vitro, so it's hard to measure tumor growth in a body, whether it's a rodent or an animal in vitro in the test tube.

So I think the POSA would have a

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healthy degree of skepticism about how to extend this or extrapolate this to the clinical problem, does vitamin B12 cause tumor progression in people.

Q. Is that a general problem with taking in vitro data and applying it to the clinical setting or is that specific to this context?

MS. SPIRES: Objection, incomplete hypothetical.

A. Because there is so many interplay of in vitro, in vivo and human observations, I would want to limit that more to this than to the general world that you asked about. Let me give you another example, at the risk of expressing a new opinion.

What we learn in vitro in cells is highly applicable to understanding what happens in the animal or in a human -- animal includes humans, of course.

The entire understanding of the folate biochemistry came from in vitro studies. So for me to say in answering your question that in vitro studies aren't important would be

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very wrong. They tell us what we need to know in so many cases. So I don't want to eliminate or diminish the value of in vitro studies. They're essential.

Q. Okay. But in this particular circumstance, you think it is less powerful evidence; is that a fair way to put it?

A. I'll agree that this is less powerful than many other in vitro studies with respect to the question you have asked, or Dr. Chabner asserted.

Source: Ex. 2135 at 42:22-43:4, 43:19-45:12; Paper 64 at 2.

Dr. Bleyer's Testimony

Q. It says, it rescues the cell in the presence of pemetrexed by replacing the tetrahydrofolates and its metabolite -- replacing the tetrahydrofolate and its metabolites, methylenetetrahydrofolate and methyltetrahydrofolate that are depleted by pemetrexed. Do you see that?

A. I do.

Source: Ex. 2135 at 51:4-11; Paper 64 at 3.

Dr. Bleyer's Testimony

Q. And I'm going to focus you on your opinion on page 34 of your reply declaration. In A you say, "A POSA would have known that cancer growth has never been reported to be caused by folic acid supplementation in conjunction with an antifolate," correct?

A. That's correct.

Q. Am I correct that Dr. Farber's conclusion that it was the folate that caused the acceleration phenomenon is what gave him the idea for antifolates in the first place?

A. That's right. That's what I understand. That's what he's known for.

Source: Ex. 2135 at 54:4-10, 59:19-24; Paper 64 at 5.

Dr. Bleyer

Dr. Bleyer's Testimony

What is the purpose of giving leucovorin every six hours for five, six, or seven days from the start?

A. The duration of benefit of the leucovorin dose is in the range of six hours, and if you wait much longer, methotrexate's working again because now the reduced folates have been depleted, and so it consumes them, uses them up.

So to maintain the reduced folate pool and bypass the inhibition of the antifolate, it is necessary to give it every six hours because the kinetics of leucovorin are in the range of four to six hours' duration of benefit.

Q. So if you were to only give a patient a single dose of leucovorin, would that re-expose the patient's normal cells to a

BLEYER - 1/31/17

deficiency of reduced folates and cause more toxicity?

A. In all the years that I've used -- used titers of methotrexate, including industrial strength, I don't think there is a single example of a patient getting one dose unless they died before I could give them more.

Q. Why is that?

A. Because for methotrexate, it takes several days for it to be cleared from tissue in normal cells.

With pemetrexed, to get back to the agent of concern here, it would probably take less because the pharmacokinetics of pemetrexed that we know about, and even in '99 know, appear to be considerably shorter in duration than methotrexate. So it may only take a couple of days, would have to look at the kinetic curves, the area on the curve, in which would -- it would undoubtedly take more than a dose.

Source: Ex. 2135 at 344:11-25, 345:23-346:22; Paper 64 at 4.

Dr. Bleyer

Dr. Bleyer's Testimony

A. The muddle, which probably could be described with a better verb, the confusion with regard to whether these patients in Boston had worsening of their cancer was due just to folic acid, which is what was concluded by Dr. Farber and his colleagues, is not absolute because the extract could have had other nutrients of cancer cells.

So when I say that there are a variety of other nutrients and now we think there are more than 50, I will take your advice or suggestion on that, that among those 50 could have been other elements that cause cancer progression in these children and patients.

Source: Ex. 2135 at 59:4-18; Paper 64 at 4.

Dr. Bleyer

Dr. Bleyer's Testimony

Q. In 1999, how frequent was it for a patient to present in your personal practice with a clinical vitamin B12 deficiency?
A. Not speaking for the POSA --
Q. Correct.
A. -- or the other person?
Q. Yes.
A. I think it was fairly routine. Our nutritionists routinely evaluated patient's nourishment status. We're responsible for the patient's diet and often wrote orders that included hyperalimentation, whether it was intravenously or orally or by nasogastric or nasojejunal feeding. And in 1999, B12 would have been in that set of orders, along with a variety of other nutrients. Yes, I think --
Q. Well --
A. -- frequently that was what the nutritionist helped us do.

Q. And in patients who have a B12 deficiency, when you give them B12, you increase the amount of tetrahydrofolate that is created through the homocysteine-to-methionine conversion; correct?
A. Not necessarily. Again, if the patient is vitamin B deficient, and I will repeat, I don't know if they have to have zero vitamin to make that conversion from tetrahydrofolate converting homocysteine to methionine, but if they're deficient, that would happen.
If they're not deficient, I'm not sure that the reduced folates, which are highly regulated in homeostatic balance by the body and by individual cells would cause what you described as increasing the reduced folates

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when vitamin B deficiency wasn't a problem.
Q. Okay. But when --
A. I'm not sure of all that, because I can't cite studies where that's proven, but so many other studies of homeostasis would suggest that the body knows how to keep it, and would have excreted the extra amount if the patient is not B12 deficient.
Q. Okay. Well, let's focus on the ones that are B12 deficient.
A. Yes.

Source: Ex. 2135 at 65:5-23, 67:9-68:12; Paper 64 at 4.

Dr. Bleyer's Testimony

Q. Okay. And so at least in your experience, you would expect that to occur in a significant percentage of the cancer patients you saw because you thought a significant percentage had a vitamin B12 deficiency?

MS. SPIRES: Objection, mischaracterizes.

Q. Correct?

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A. Correct, in general. When you say "significant number," the absolute proportion or even the general proportions is not known to me. I don't remember to what degree that was a problem, but there were patients who were vitamin deficient or suspected -- I'm sorry, vitamin B12 deficient or who were suspected of being B12 deficient.

Source: Ex. 2135 at 68:18-69:9; Paper 64 at 6.

Dr. Bleyer

Dr. Bleyer's Testimony

Q. Okay. And I believe that one point that you make in here is that if you can reduce the toxicity associated with a chemotherapy drug, you may be able to give more cycles of the drug. Is that a point you make?

A. That's a separate point from the therapeutic index.

Q. I understand.

BLEYER - 1/31/17

A. Got it.

Q. But have I understood that point?

A. Yes.

Source: Ex. 2135 at 149:19-150:4; Paper 64 at 7.

Dr. Bleyer's Testimony

Q. Okay. What is that?
A. And this has to emphasize the normal versus tumor cell difference. After methotrexate is cleared, whether it is

deglutamated and then removed from the cell, and it is no longer present to inhibit these enzymes, the amount of reduced folate at that time makes a difference in terms of recovery of the cell.

If there is no reduced folate, folic acid wasn't given, so there is -- and the patient was folate deficient, and there it's less reduced folates after methotrexate has been cleared from the cell, that cell is more likely not to recover.

If there is more reduced folate available after, because the patient wasn't folate depleted to start with and, therefore, there is more in the cell, including glutamates that can be used, there would be less toxicity.

And we take advantage of that principle with the therapeutic index by -- recognizes that some cancer cells, those that are effectively treated with methotrexate or an antifol, are less likely to recover under the same circumstances.

Source: Ex. 2135 at 216:22-217:23; Paper 64 at 7.

Dr. Bleyer's Testimony

> "Folate therapy will reliably reduce plasma homocysteine levels; however, this would also

Source: Ex. 2135 at 121:23-24; Paper 64 at 7.

Dr. Bleyer

Dr. Bleyer's Testimony

Q. Did you testify earlier that Niyikiza's abstract showed an association between pretreatment levels of homocysteine and pemetrexed-related toxicities?

MR. PERLMAN: Objection, leading.

A. Yes.

Q. Given those testimonies, would a POSA in June of 1999 have believed there was an association between lowering homocysteine levels with folic acid and lowering pemetrexed-related toxicities?

A. A POSA would deduct with almost certainty that if -- since it has been well-known for many years that reducing homocysteine can be accomplished with folic acid, all those years we tried to prevent neural tube defects in children born of pregnant women who were folate-deficient, that Niyikiza's observation that there is a correlation between high homocysteine levels prior to treatment and the toxicity that occurred naturally, obviously, logically, a POSA would deduct that reducing homocysteine would reduce toxicity, and using folate before the antifolate would accomplish that.

In other words, Niyikiza taught not just that there was a correlation, but you could do something about it with folic acid.

Source: Ex. 2135 at 338:13-18, 339:2-23; Paper 64 at 7-8.

Dr. Bleyer

Dr. Bleyer's Testimony

Q. And the concept of the therapeutic index is you are looking at the -- essentially the relationship between the benefit that the patient receives and the toxicity that the patient suffers, and all else equal, a wider window is better than a narrower window --

A. It is.

Q. -- is that a fair summary?

A. It is.

MS. SPIRES: Objection, vague.

A. Yes.

Q. And the question about whether -- let me back up.

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A. By "wider window," the less toxic an agent is given the same efficacy makes it wider, and vice versa, the more effective for the same toxicity also makes it wider, and that's what we mean by "wider window."

Q. Okay. At the bottom of page 24 you introduce your graphic where you say, "The following graphic demonstration."

A. Yes.

Q. Okay. You say, "There will be a greater cancer cell kill by an antifolate when the reduction in efficacy is less than the reduction in toxicity," correct?

A. Yes.

A. For efficacy, the goal of all antifolate therapy and cancer therapy is to eliminate the cancer more than the normal cells, and folate is used as it had been with methotrexate both as pretreatment folic acid and especially with leucovorin to improve the

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therapeutic index.

Q. Right. And my question for you is, what is the mechanism by which the person of ordinary skill would have understood folic acid reduced toxicity?

MS. SPIRES: Objection, calls for speculation.

A. There are multiple answers, but the primary one is that the folate rescues the normal cell, the critical tissues that cause the limiting toxicity more than it rescues the tumor cell.

Source: Ex. 2135 at 147:13-148:15, 155:20-156:2, 157:7-17; Paper 64 at 8.

Dr. Bleyer's Testimony

Q. And how would the person of ordinary skill have understood that Hammond's regimen had reduced the toxicity associated with pemetrexed?

A. So folic acid supplementation appears to permit MTA dose escalation by ameliorating toxicity.

Source: Ex. 2135 at 156:17-23; Paper 64 at 8.

Dr. Bleyer

Dr. Bleyer's Testimony

Q. Do you agree with me that the person of ordinary skill would have not been able to conclude from the data in Hammond that the addition of folic acid increased the therapeutic index of pemetrexed relative to that in Rinaldi?

MS. SPIRES: Object to form.

A. I'll agree to that, for the following reason -- reasons as I believe are in the declaration. The attempt was not to document response rates. The primary purpose was to assess toxicity. So the effort was not to assess response rates. Yes, there was an attempt to try to keep the patient on the trial, but that wasn't the goal.

Q. Okay. And just to be clear, Hammond used higher doses of pemetrexed than Rinaldi did; correct?

A. Yes, correct.

Q. Okay. But the person of ordinary skill could not have concluded from the data available in June '99 that those higher doses had led to an increased therapeutic index for pemetrexed?

A. Well, I don't agree with that. I think the person of ordinary skill would more likely assume that because more drug could be

given safely and the optimism that that provides in terms of more treatment doses, because that had been a problem in prior studies, that the therapeutic index would be increased as a result of what was presented in the Hammond reports, yes.

Q. Okay. But there is no data in Hammond that examines that question. Do you agree with me?

MS. SPIRES: Objection, mischaracterizes.

A. No, I don't really agree with that, I'm sorry, because if dose response curves are important in cancer and the more you can give, which is a fundamental premise based on a myriad of both in vitro, in vivo, and in human studies, if the more you can give is more effective, then the fact that that allowed you to escalate the Hammond approach, allowed one to escalate the dose almost twofold, the therapeutic index would have been considered by that reviewer, a POSA, to have more likely increased the therapeutic index than to have decreased it.

Source: Ex. 2135 at 152:23-154:25; Paper 64 at 10.

Dr. Bleyer

Dr. Bleyer's Testimony

Q. And, in fact, in the next sentence they say, "One cause for concern is that the administration of folic acid prior to

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lometrexol and during treatment could potentially supplement the folate requirement of the tumor and thereby circumvent the activity of lometrexol, or worse still, a tumor progression; correct? That's one concern they expressed?

A. It's the reference that we addressed a moment ago. Yes, and then they go on to say, "Such a phenomenon would be difficult to examine unequivocally."

Q. Sure.

A. And that's why we're here because all of this has some equivocation, all right --

Q. You agreed.

A. -- sure, as you just said, but the relationship between the patient's folate status and the rate of disease progression might allow this question to be addressed, so they're hopeful that they have increased the therapeutic index.

Q. Well, how are you getting that? It says, "The relationship between a patient's folate status and the rate of disease progression might allow this question to be

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addressed."

So one, the question hasn't been addressed yet, and they're not even sure whether it will allow it to be addressed. So how are you getting that they're confident they've increased the therapeutic scope?

A. Yeah, I didn't say "confident." I said that there was hope that raising the MTD as they say elsewhere in this document, that they can -- and, in fact, even higher than they stopped at for this report, which I described as 170 milligrams per square meter every three weeks, that they had hoped that it would continue to increase the therapeutic index if they achieved this here.

But there is concern, and with lometrexol there is concern that you can do some harm with folic acid because it's a single enzyme inhibitor and more dependent on the folate pathways as a result.

Q. So what do you mean by that?

A. Well, lometrexol as opposed to pemetrexed, since we want to address pemetrexed, inhibits one of the three target

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enzymes instead of all three that pemetrexed does. So the issue of folic acid given less inhibition of the total multiple pathways from the multitargeted antifolate could be more concerning, and they raised that concern. They used the word "concern."

Source: Ex. 2135 at 164:23-167:7; Paper 64 at 11.

Dr. Bleyer's Testimony

Q. Then the authors say: "Taken together this data would suggest that 2 milligrams folic acid per day is not adequate but that 5 milligram folic acid given orally does ameliorate toxicity." Do you see that?

A. I do.

Q. And would the person of ordinary skill in 1999 have accepted that statement as it related to lometrexol?

MS. SPIRES: Objection, calls for speculation.

A. I don't know, in that I have to study, since I didn't do this adequately beforehand, what that statement is based on, that taken together, these data would suggest that the 2 milligrams is not adequate when 5 is. And I don't really know that that was covered here, but it's got to be --

Q. It's --

A. -- if they say that statement.

Q. It is in the first part of -- the key question paragraph, I think you will find a

reference to the 2 milligram.

A. "An initial report suggested less toxicity at the 2 milligram folic acid dose, but" -- and it looks like "but" is italicized -- "data from only two patients was reported, compared to six and four patients treated at the first two dose levels."

Well, I may be overstating this, but if there are only two patients and then just the four more --

Q. Well, let me ask you a different question, doctor.

A. I don't -- I -- if that is what they're basing the 5 versus 2 on just two patients in one case and four or five in the other, I'm surprised that they came to that conclusion.

Q. Okay. If that is what they were doing, would that cause you to question --

A. That statement?

Q. Well, no, the validity of the entire chapter.

A. No.

Q. Just that statement?

Source: Ex. 2135 at 238:4-239:25; Paper 64 at 12.

Dr. Bleyer

Dr. Bleyer's Testimony

A. No, no. I actually wish I had studied this more because there is other data in here that sounds -- seems very valuable.
Q. That's great. And the next time maybe you will get the opportunity to do that.
A. Yeah.
Q. Let's look back at page 275. Do you agree with me that the authors of this article concluded that their data suggested that the 2 milligrams of folic acid per day is not adequate? That was their conclusion; correct?
A. Yes. They --
MS. SPIRES: Objection.
A. You read the sentence.
Q. Okay. And whether or not you have reviewed enough to be able to evaluate whether you agree with that, we can agree that the person of ordinary skill would have understood that that was at least the conclusion these authors were presenting?
A. Can I say as a suggestion?
Q. Okay.
A. Because that is the word they used as -- as opposed to a --

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Q. Okay.
A. -- conclusion, definitive or otherwise.
Q. And --
A. They suggest from whatever basis.
Q. And if the person of ordinary skill thought that the experience with lometrexol was transferable to pemetrexed, would they understand that at least these authors would suggest that a 2 milligram dose of folic acid per day would not be adequate?
MS. SPIRES: Objection, incomplete hypothetical, mischaracterizes.
A. It is quite a hypothesis to go from a regimen for one antifolate 14 days in a row, 2 milligrams or 5 milligrams a day, to the other one when we don't actually know how they came to the 2 milligram or 5 milligram judgment in the first place.

Source: Ex. 2135 at 240:2-241:20; Paper 64 at 12.

Dr. Bleyer's Testimony

Q. Well, let me -- let me ask you this, doctor: Do you think that the Laohavinij study of 5 milligrams a day for 14 days is relevant to how much folic acid one should give with pemetrexed?

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MS. SPIRES: Objection, vague.

A. I, I would agree it is relevant because if you had nothing else to base the next study with the successor antifolate, you would start with where you left off.

Source: Ex. 2135 at 241:21-242:6; Paper 64 at 12.

Dr. Bleyer

Dr. Bleyer's Testimony

Q. Would a POSA have applied the Bronstrup reference to the antifolate context?
A. A POSA in the oncology world would use that as evidence that it can be deducted to be useful in their patients on antifolates.
Q. What about the doses of folic acid given, and folic acid in B12 given in Bronstrup, would those be applicable in the antifolate context?
MR. PERLMAN: Objection, outside the scope. I didn't ask him about this reference or about this subject, so it is outside the scope of the cross.
A. The dose was low of folic acid, 400 micrograms per day. It was daily for several

weeks. The dose of B12 in the Bronstrup study was 6 micrograms in one regimen and maybe 400 or 500 micrograms in the other regimen, so it was much higher. But even the 6 micrograms had the benefit in reducing homocysteine, which implies with that small dose, some synergism.
Would a POSA take that information to the oncology patient? There is no reason not to believe that if it worked in the healthy woman between 20 and 34 years of age, that it could also work in a patient about to receive antifolates.
Q. And going back to the doses, I believe you testified earlier that Hammond taught a dose of 5 milligrams of folic acid a day; is that correct?
A. Yes, that's correct.
Q. Are you -- I know you just talked about the Bronstrup reference. Are you aware of any other prior art references teaching a POSA that they could effectively lower homocysteine using doses of folic acid lower than 5 milligrams a day?

Dr. Bleyer's Testimony

A. I am. The '974 application stated a range as low as .5, 500 micrograms of folic acid.

Q. And would the '97 -- would a POSA consider the '974 teachings to be applicable to pemetrexed?

MR. PERLMAN: Objection, leading. Objection, outside the scope of the cross.

A. Actually, it was in the context of an antifolate related -- the predecessor, lometrexol.

Q. Are there any other references that would have taught a POSA that they could effectively lower homocysteine using folic acid doses of lower than 5 milligrams a day?

MR. PERLMAN: Objection, outside the scope.

A. Bronstrup in Sweden and the '974 out of the United States are the ones I'm remembering currently. Lometrexol was studied by the Laohavinij group, but I'm having trouble recalling the dose. I think it was higher than the range of micrograms that we were just

discussing. So I'm not sure about that. Again, that was with the different -- with lometrexol, not with pemetrexed.

Q. Were there any teachings to explain to a POSA why a dose of folic acid lower than 5 milligrams a day might be effective at lowering homocysteine?

MR. PERLMAN: Objection, outside the scope of the cross. Objection, leading.

A. Please repeat the question, then.

Q. Were there any teachings to explain to a POSA prior to 1999 why a dose of folic acid lower than 5 milligrams a day might be effective at lowering homocysteine?

MR. PERLMAN: Same objections.

A. I mentioned two articles published before 1999 that would have led a POSA to believe that a lower dose could be effective in lowering homocysteine, the dose of 400 micrograms in the Bronstrup review and doses as low as 500 micrograms in the '974 application so. Why wouldn't a POSA include that in their application to pemetrexed?

Q. Did the addition of B12 affect the

Dr. Bleyer

Dr. Bleyer's Testimony

dose of folic acid that a POSA would want to give to lower homocysteine?

MR. PERLMAN: Objection, leading. Objection, foundation.

A. If B12 is as synergistic as the -- as the European patent association data suggested, and Bronstrup supports, and one wanted to cover the possibility the patient needed B12 for other reasons, that combination of a low dose -- lower dose of folic acid with vitamin B12 would make sense to a POSA, and he or she would deduce it would be worth doing.

Q. You mentioned the European patent association data. What are you referring to there?

A. European patent application '005 or '05 looked at the benefit of reducing folic -- homocysteine with combinations of vitamins. They included folic acid, vitamin B12, vitamin B6, and betaine, I think, but I know for sure about the first three I mentioned.

Q. Do you recall the doses of folic acid used in the European patent application?

MR. PERLMAN: Objection, outside the

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scope.

A. If I can ask to look at that document.

Q. Sure. I will give you what has been previously marked as Exhibit 1010. That is the EP '005 patent application, I believe.

A. One of the reasons to ask for it is because there were multiple regimens, and depending on which set of patients were being tested for this effective combination vitamin therapy, it probably differed.

So I'm looking at example 3 on page 15, where the dose was 650 micrograms of folic acid in each table -- each tablet administered.

And example 8, which is another trial of 100 patients, the random is -- the folate dose was the same as before, 0.65 milligrams or 650 micrograms.

In example 7, that is not one with -- oh, yes -- 1,000 micrograms; and example 6, 1,100 micrograms.

So I think the range is from 650 to 1,100 micrograms of folic acid.

Q. Would a POSA have considered the EP

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'005 teachings to be applicable to the antifolate context?

MR. PERLMAN: Objection, outside the scope and outside of his reply declaration also.

A. Yes, I do. I would because the application itself refers to using this approach, the synergism of B12 folic acid in patients with cancer, leukemia, and those receiving folate antagonists.

Q. And pemetrexed is a folate antagonist?

A. Right. A folate antagonist and an antifol are one and the same.

Dr. Bleyer

Dr. Bleyer's Testimony

Q. So by 1973, it was known in the art

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what the Ki of methotrexate was for DHFR; is that your best understanding?

A. It, it had to be generally known because we considered it an almost irreversible inhibitor.

Source: Ex. 2135 at 300:25-301:6; Paper 64 at 13.

Dr. Bleyer's Testimony

A. Yes. Looking at the diagram which this serves as a legend, and knowing the constants for DHFR and for the other two enzymes that pemetrexed inhibits, point --

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first, first deduction is that it would take a massive amount, and in Dr. Chabner's terms, impossible to deliver it to a person to overcome the inhibition.

Source: Ex. 2135 at 257:22-258:5; Paper 64 at 13.

Dr. Bleyer's Testimony

12 A. And if the patient is deficient in
13 B12, it is obvious that that would generate
14 more tetrahydrofolate.

Source: Ex. 2135 at 259:12-14; Paper 64 at 13.

Dr. Bleyer's Testimony

Q. And then on -- let's go back to 61 then you talk about, in the next sentence, that a POSA would have known that supplementing a patient with B12 would have a synergistic effect in lowering homocysteine levels; right?
A. Yes.

Q. Did the addition of B12 affect the

dose of folic acid that a POSA would want to give to lower homocysteine?
MR. PERLMAN: Objection, leading. Objection, foundation.
A. If B12 is as synergistic as the -- as the European patent association data suggested, and Bronstrup supports, and one wanted to cover the possibility the patient needed B12 for other reasons, that combination of a low dose -- lower dose of folic acid with vitamin B12 would make sense to a POSA, and he or she would deduce it would be worth doing.

Q. And I believe you testified -- let's just go -- if a patient had normal B12 levels, but had a homocysteine level greater than 10, would the POSA expect that administering known standard doses of folic acid in B12 would reduce homocysteine levels more than administering folic acid alone?
MR. PERLMAN: Objection, leading. Objection, compound.
A. Yes.
Q. Why is that?
A. There are several lines of evidence the POSA would have been aware of in 1999. In the European patent application of 1993, '4, the data represented -- and we went over this in my original declaration -- that was very impressive in terms of the synergy of the potency of vitamin B12 to assist in lowering the homocysteine by folic acid.

Source: Ex. 2135 at 258:14-19, 329:5-23, 334:25-335:13; Paper 64 at 14.

Dr. Bleyer's Testimony

Q. That they -- no. Let's back up. I want you to assume that Dr. Chabner is referring to Lilly's Phase III trial of mesothelioma with pemetrexed, okay, and that there were deaths in that study. I will represent to you that that that is the context that he's referring to. Okay? There were deaths in that study.

A. Okay. I accept that.

Source: Ex. 2135 at 272:10-18; Paper 64 at 14.

Dr. Bleyer's Testimony

5	if they were deaths that were a concern, they
6	would have been known to the POSA, because,
7	yes, in our world, we learn about them before
8	we learn about the non-death patients.

Source: Ex. 2135 at 273:5-8; Paper 64 at 14.

Dr. Bleyer's Testimony

A. And they also would be less likely to die, except for death from their disease. They are more likely to die of cancer than the Phase III patient. But deaths in a Phase I trial due to the agent are very concerning. They kill the patient earlier.

Source: Ex. 2135 at 278:7-12; Paper 64 at 15.

Dr. Bleyer's Testimony

Q. Okay. And then next, in "b," you talk about Rinaldi and colleagues publishing a report that three patients expired due to drug-related complications on a Phase I trial?
A. Uh-huh.
Q. Do you see that?
A. Yes.

Source: Ex. 2135 at 274:2-8; Paper 64 at 15.

Dr. Mason's Testimony

Q. Well, let me ask you this: If you had a patient -- I think we discussed this this morning -- but if you had a patient who was replete with vitamin B12, you wouldn't expect administering vitamin B12 to lower their homocysteine, would you?

MS. MALMBERG: Objection, incomplete hypothetical.

A. As far as I can recollect, if you have a patient who's convincingly B12 replete and you give them additional B12, you're probably not going to further lower homocysteine levels.

Q. I mean, I guess you don't know for sure because none of these tests are perfect.

A. Right.

Source: Ex. 2134 at 146:7-20; Paper 66 at 2-3.

Dr. Mason's Testimony

11	all that information together collectively, I think
12	the POSA would have been treating a lot, many, most
13	of his patients about to embark on pemetrexed with
14	vitamin B12.

Source: Ex. 2134 at 182:11-14; Paper 66 at 3.

Dr. Mason's Testimony

Q. Okay. And I actually didn't intend to focus here on pemetrexed. Paragraph 60 says that the POSA -- to paraphrase, the POSA would have had a motivation to administer vitamin B12 to replete

MASON

some or all patients before administering an antifolate therapy. That's what you say here.

A. Correct.

Q. So the POSA as of June 1999 would have, in your view, been motivated to administer B12 before administering any antifolate therapy.

A. The POSA would have likely been particularly attune to certain patient groups that might be at higher risk of B12 depletion and, therefore, treated them with B12.

Q. The POSA would likely have been particularly attune to certain patient groups that might be at higher risk of B12 depletion and, therefore, treated them with B12 before those patients received any antifolate therapy; is that fair?

A. Correct.

Q. Including before they received methotrexate therapy.

MS. MALMBERG: Objection, outside the scope, incomplete hypothetical.

A. Yeah, I think -- I mean, I guess I'm not prepared to provide insight into people about to embark on methotrexate therapy because the focus

MASON

here is on embarking on pemetrexed therapy.

Q. Well, the focus of this paragraph doesn't really seem to be -- I mean, I'm just trying to understand what your opinions are, Doctor, and you seem to be making a general statement about antifolate therapy.

A. No. Because I think this whole document is largely focused on making decisions about people who are about to embark on pemetrexed therapy. Okay. Now, there are some aspects of it where methotrexate has some relevance, but I think I would have to have time to go back and get a sense of what POSAs might do in terms of embarking on methotrexate therapy.

Q. So is paragraph 60 incorrectly worded, in your view?

A. The only limitation I think that one could argue in terms of the way I worded it is that I generalized a little bit and said "before administering antifolate therapy, including pemetrexed," and one could argue that I should have said before administering pemetrexed. But, you know, let me say that POSAs aside, B12 depletion is common enough in vegetarians and in vegans that a

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lot of doctors just go ahead and treat such patients with B12 regardless of whether they're embarking on antifolate therapy or not.

Q. And so for that matter, a person of ordinary skill in June 1999 by the same reasoning would have had a motivation to administer vitamin B12 to vegans and vegetarians who were receiving some other kind of cancer therapy that's not even an antifolate; is that fair?

A. I think that's fair to say.

Source: Ex. 2134 at 126:22-129:11; Paper 66 at 3.

Dr. Mason's Testimony

Q. Okay. And I actually didn't intend to focus here on pemetrexed. Paragraph 60 says that the POSA -- to paraphrase, the POSA would have had a motivation to administer vitamin B12 to replete

MASON

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A. Correct.

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MASON

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Q. And so for that matter, a person of ordinary skill in June 1999 by the same reasoning would have had a motivation to administer vitamin B12 to vegans and vegetarians who were receiving some other kind of cancer therapy that's not even an antifolate; is that fair?

A. I think that's fair to say.

Source: Ex. 2134 at 126:22-129:11; Paper 66 at 3.

Dr. Mason's Testimony

Q. Let's talk about some of these other groups that you identify. I think in this paragraph you're talking about vegetarians and vegans. But then you go on to talk about elderly individuals. It's your view that as of June 1999, the person of ordinary skill in the art would have had a motivation to administer vitamin B12 to elderly patients as a class?

A. Yeah. I think what I'm trying to do in these various paragraphs around this section is to point out the fact that there are several groups, several segments of the patient population that are at higher risk of B12 depletion that would compel a POSA to go ahead and either check their B12 status

or just go ahead and empirically administer B12. And in fact, some POSAs might actually take the position that there's enough patient segment -- there's enough segments of the patient population that are at highest risk, maybe I ought to just administer B12 to everyone.

Q. Regardless of what other therapies they might be on, you're saying?

A. Well, again, we're talking about a POSA who's about to embark on pemetrexed therapy. And I believe that the POSA is going to be especially sensitive to this issue because the POSA already knows that elevated homocysteine predicts toxicity, and the POSA also knows that the most readily available means of decreasing homocysteine is the use of coadministration of folate and B12.

Source: Ex. 2134 at 129:12-130:17; Paper 66 at 3.

Dr. Mason's Testimony

Q. Are there populations in which administering vitamin B12 along with folic acid would be inadvisable?

A. Since B12 has little or no side effects, I cannot think of a population of individuals where it would be inappropriate to coadminister B12 with folic acid.

Q. The person of ordinary skill in the art

MASON

wouldn't have been aware of such a population either; is that fair?

A. I don't think the POSA would have a population of individuals in mind where it would be inappropriate or inadvisable to coadminister vitamin B12 with folate.

Source: Ex. 2134 at 140:18-141:7; Paper 66 at 3.

Dr. Mason's Testimony

Q. You express the opinion in paragraph 60 that the person of ordinary skill in the art in June 1999 would have likely checked vitamin B12 status in vegan and vegetarian patients.

A. Correct.

Q. And a person of ordinary skill would have pretreated those who were found to have a low vitamin B12 status as a result of that test?

A. I believe that the POSA would.

Source: Ex. 2134 at 122:7-15; Paper 66 at 3.

Dr. Mason's Testimony

Q. So as you're using the term, if a patient is experiencing a methyl trap because of a low level of B12, that would be B12 deficiency?
MS. MALMBERG: Objection, mischaracterizes.
A. I'm sorry. Rephrase the question.
Q. As you're using the term in your prior answer, if a patient is experiencing a methyl trap because they don't have sufficient vitamin B12 for methionine synthase to proceed normally that would constitute a vitamin B12 deficiency?
A. I believe so.

Source: Ex. 2134 at 21:10-21; Paper 66 at 4.

Dr. Mason's Testimony

12	Q. And on a theoretical basis, if vitamin B12
13	was administered to a B12 replete patient, it might
14	make more tetrahydrofolate available.

Source: Ex. 2134 at 32:12-14; Paper 66 at 4.

Dr. Mason's Testimony

Q. What was the common practice in terms of whether vitamin B12 pretreatment was used with methotrexate as of 1999?

A. I believe the common practice was pretreatment with folic acid and B12.

Source: Ex. 2134 at 186:17-21; Paper 66 at 5.

Dr. Mason's Testimony

What's the connection between the fact that pemetrexed blocks DHFR, in your opinion, and

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your opinion that folic acid won't reverse pemetrexed's efficacy?

MS. MALMBERG: Objection, calls for speculation, lack of foundation, mischaracterizes.

A. Let me just take a minute here.

Q. Please.

A. The point I'm trying to make is that since pemetrexed inhibits DHFR, it's not going to make folic acid available in a form that is going to negate pemetrexed's efficacy.

Source: Ex. 2134 at 47:24-48:11; Paper 66 at 6.

Dr. Mason's Testimony

Q. Would the POSA have expected pemetrexed not to interfere with efficacy because pemetrexed blocks --

A. Reword that, please.

Q. Sorry.

Would the POSA have expected folic acid not to interfere with efficacy because pemetrexed blocks DHFR and that would be one of the reasons?

A. It would be one of the -- yes, I believe it would be one of the reasons that the POSA would believe that it would not interfere with efficacy.

Source: Ex. 2134 at 65:12-22; Paper 66 at 6.

Dr. Mason's Testimony

25 therapy. It is clear that folate can help promote
1 MASON
2 the proliferation of rapidly dividing cells. Okay?
3 But administering it to the general population, the
4 vast majority of whom do not harbor any precancer
5 or cancerous lesions, is different than
6 administering folic acid to a population of people
7 who are about to embark on antifolate therapy.

Source: Ex. 2134 at 165:20-166:7; Paper 66 at 9.

Dr. Mason's Testimony

Q. There wasn't a differentiation made in the
MASON
literature between folic acid's effect on solid tumors and, for example, leukemia?
MS. MALMBERG: Incomplete hypothetical, outside the scope, calls for speculation, mischaracterizes.
A. I don't think I'm going to answer that because when you say "distinction," I mean, people didn't try to -- there was little attempt to distinguish effects of the different types of tumors.
Q. There wasn't a sense in the field, for example, that folic acid would encourage the growth of leukemia but would not have a similar effect on solid tumors?
MS. MALMBERG: Objection, relevance, outside the scope, calls for speculation.
A. There was so little known about this potential effect that I think it's fair to say that the scientists probing this phenomena didn't know what to expect in terms of which tumors it might affect, which tumors it might not affect.

Source: Ex. 2134 at 170:25-171:22; Paper 66 at 10.

Dr. Feigal's Testimony

Q I think you testified a little while ago you are not opining about obviousness. Are you?

A Not in the -- not in the -- not in the patent sense but in the everyday meaning of that language there has been a role in vitamins in the evaluation of most of the antifolate drugs so in that sense developing a new one, it is an obvious aspect of developing this class of drugs.

Source: Ex. 2133 at 16:13-20; Paper 69 at 2.

Dr. Feigal's Testimony

THE WITNESS: Well, if I understand your question, I think what you are asking is what is the evidence in the -- in the FDA documents that suggests -- that suggests it is obvious.

I think what the FDA documents reflect is the fact that the FDA recognized that with antifolate drugs that folate is sometimes part of the regimen in order to have drugs that are safer and more effective. So most of the discussions were not about whether this was -- this was something which made sense, but how exactly to study it and how to meet the statutory requirements for approval.

Source: Ex. 2133 at 18:3-14; Paper 69 at 2-3.

Dr. Feigal's Testimony

Q So to be very clear, in your declaration you are not pointing to any particular interactions between Lilly and the FDA and saying that those interactions support a conclusion that vitamin supplementation was obvious?

MS. MALMBERG: Objection; mischaracterizes.

THE WITNESS: Well, in the report I don't think I actually stated it that way but I think that it was -- you know, I think that as the issues were discussed even before the, you know, this trial where there was the change in the trial, the option of including vitamins was discussed as you know before this trial even began and some options for different -- different trial designs. So my interpretation of those interactions was that FDA was very used to seeing these kinds of -- these kinds of additions for this, this kind of drug, and there were different study designs that could be used to tease out exactly what the contribution of vitamins would be but it wasn't whether vitamins wouldn't have a role in the safety and effectiveness of this type of a product, it is just a question of how to study it.

Source: Ex. 2133 at 21:23-22:20; Paper 69 at 3.

Dr. Feigal's Testimony

Q And then you conclude 39a with a statement, "This has nothing to do with obviousness."

A Yes. I mean, what I'm talking about in 39a was why was FDA insisting on having a statistical plan before agreeing to make a change to include vitamins in the clinical trials and having a statistical plan doesn't bear on the issue of whether -- whether vitamins were obvious or not.

Source: Ex. 2133 at 18:22-19:4; Paper 69 at 3.

Dr. Feigal's Testimony

And in 39b you speak about some of the difficulties that are involved in modifying a clinical protocol in the midst of a trial, correct?

A Yes.

Q And, again, you say, "This has nothing to do with obviousness."

A Yes. This is a very generic issue that has to do with what happens with trials that are split and trials that are modified in the course that may become difficult to interpret so it doesn't directly relate to the issue of obviousness.

Q Right. And 39c you talk about again some issues for -- relating to changing a treatment midstream relating to randomization and again you comment, "This has nothing to do with obviousness."

A Yes. It is the issue that because the first half of the study and the second half, that's not a randomized comparison that -- that such studies are difficult to interpret no matter what the topic of the study is so, again, that's why I felt that in my opinion the FDA was raising these issues as issues that would undermine the quality of the evidence necessary for approval of the product and didn't relate to the obviousness issue with respect to the vitamins.

Q And 39d is about FDA policies on combination drug regulations and again you say that has nothing to do with obviousness.

A That's correct. I mean, there's a regulation that actually specifies what combination products need to do for approval and that's what FDA was discussing and how the trials would -- would, could or might not accomplish that.

Source: Ex. 2133 at 19:6-20:13; Paper 69 at 3-4.

Dr. Feigal

Dr. Feigal's Testimony

14	Q What you are saying is after the trial began
15	FDA was not expressing skepticism as to the benefits
16	of vitamin supplementation but raising concerns with
17	altering the trial midstream?
18	A Yes.

Source: Ex. 2133 at 93:14-18; Paper 69 at 4.

Dr. Feigal

Dr. Feigal's Testimony

THE WITNESS: Close. I think what they're saying is each drug has its own fingerprint, if you will, of safety and effectiveness and particular adverse reactions and there are statutory requirements that evidence of effectiveness come from adequate and well-controlled trials so that's usually where the sticking point is. There's no flexibility on how you document safety and what the standard is for safety. So every product that is approved has to, you know, has to meet that standard and FDA has the responsibility to decide how to apply that standard and be flexible in how it does that so it is not just a cookie-cutter box-checking exercise. But as I said earlier, I think the majority of the documents I looked at looked at their concerns that the studies themselves would provide an adequate basis and they wouldn't find themselves after a year or two or three with a study that turned out to be too small or hard to interpret and have to start over.

Source: Ex. 2133 at 94:10-95:4; Paper 69 at 4.

Dr. Feigal's Testimony

Q Is it your understanding that in deciding how a trial should be formulated, a clinical trial should be formulated, is it common practice for the FDA to cite efficacy as a concern?

MR. KRINSKY: Objection; vague, leading, outside the scope of the direct or it is outside the scope of the cross.

THE WITNESS: The FDA's concerns about successful clinical trials would almost always -- almost always involve that the trials are adequate to establish efficacy. There are many different ways to establish safety, but -- so as we talked about earlier, if the trial is under powered that would be an efficacy issue. If the study needs to have pooled results but they can't be pooled because the groups are very different, that would be an efficacy issue. So efficacy is almost always involved.

Source: Ex. 2133 at 96:3-20; Paper 69 at 4.

Dr. Feigal's Testimony

THE WITNESS: The regulation that I cited of fixed combination prescription drugs lays out the requirements for evaluation of combination drugs as opposed to a single drug and the shorthand version of it is that if you have a combination of drugs you have to show that the combination adds something to using the drugs individually and so in some settings that would mean comparing the combination to each of the drugs singly and perhaps even a placebo. In cancer where a placebo isn't ethical and vitamins alone wouldn't be an ethical treatment, it usually means studying an existing regimen with -- such as cisplatin versus cisplatin with one drug and then cisplatin with two drugs. So you will see this design actually being discussed by Dr. White, this suggestion that there should be a comparison of vitamins plus pemetrexed versus pemetrexed alone, both in combination, of course, with cisplatin, background of cisplatin. And this is -- this is my experience of times I was at FDA and consulting practice since that time and this is the way FDA approaches when you combine products.

Q BY MR. KRINSKY: So in your opinion this case is about a combination product as is the subject of this regulation?

MS. MALMBERG: Mischaracterizes.

THE WITNESS: This is a combination product. It is -- it is not a fixed combination product which means when the two molecules, the two drugs are combined together in a single form such as, you know, such as Bactrim, there you have two drugs together. So part of the regulation addresses the issue when you fix the combination you don't have the flexibility of the increasing one and decreasing the other but the combination, FDA's approach to combination policies is the same whether -- even when the drugs are administered separately and can be adjusted separately which is the need to actually show what the contribution is of the additional drugs.

Source: Ex. 2133 at 26:7-27:21; Paper 69 at 6.

Dr. Feigal's Testimony

Q Could you take a moment to review Exhibit 2100 and see if there's any such suggestion in it.

A Well, now that I have the document I think I'm remembering Dr. White's comments from his later documents. I think as I stated in my report, my comment about this document was simply that the addition of vitamins was discussed, the fact that it might reduce efficacy was raised as a possibility, and that the FDA left it up to Lilly to decide whether to use the -- use the vitamins in the study or not.

Source: Ex. 2133 at 69:10-20; Paper 69 at 6.

Dr. Feigal's Testimony

Q And have you ever treated patients with cancer?

A Yes. As a general internist with the university practice I often provided the primary care for cancer patients, particularly because at the time my practice was in Sacramento at the University of California Davis and many of the patients were going to the Bay Area to see their oncologists maybe once every three months and I would manage their care between the visits and their general medical care and their palliative care.

Q Have you ever prescribed antifolates?

A Well, there's some antifolate that I have prescribe in --

Q Bactrim.

A Bactrim is the great success story there. But not -- not the oncology agents.

Q Okay. Have you ever prescribed methotrexate?

A I would not have made a decision to prescribe methotrexate but I've had patients who were taking methotrexate for immunologic conditions or -- and, again, I would be managing them with the specialist who would make the decision. Often I would be monitoring toxicity, refilling prescriptions, troubleshooting if there were problems and referring those back to the specialist who was making the decisions about using those drugs.

Source: Ex. 2133 at 9:13-23, 11:10-12:2; Paper 69 at 7-8.

Dr. Feigal's Testimony

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Source: Ex. 2133 at 26:7-27:21; Paper 69 at 8.

Dr. Feigal's Testimony

variety of reasons that studies can be put on hold. And holds are actually pretty common where FDA actually disagrees with the study, study design wants to discuss it further, they reach an agreement, the trial proceeds.

Q So before a Phase 3 clinical trial begins a study design is submitted to the FDA?

A Yes, that's right.

Q And then the FDA reviews that study design as a matter of course before the trial begins?

A Yes. And, you know, there are many trials but the Phase 3 trials get particular attention.

The way the regulations are written is actually the study may be initiated at the date that the study protocol is filed with FDA without waiting for an FDA review. In practice, because these are the studies that the companies want to be sure the FDA agrees would be adequate for an approval decision, the Phase 3 trials, there's customarily a review, sometimes a very detailed discussion of statistical issues, study design issues and points, how to measure them, and then the study proceeds. So what's required and what's done are slightly different but this is -- what happened here appears to be fairly typical that there was a discussion before the study began and the interaction reflected FDA's comments and concerns and then the company made a decision because and the study was allowed to proceed, FDA I can infer did not feel that it warranted a clinical hold for any of the reasons they could have put it on hold.

Q And FDA did consider whether the Phase 3 study design would have been safe?

MS. MALMBERG: Objection; calls for speculation.

THE WITNESS: Well, yes. In -- safety is always in the context of the benefits of the drug so oncology products always, sadly almost always have significant side effects and so it is with the knowledge that that's going to be part of the program. So -- but in the context of this disease and what they knew about this drug, because the study proceeded I think it is fair to say FDA felt that the study was not unsafe. Sometimes FDA does with a double negative. It was safe to proceed.

Q BY MR. KRINSKY: Is the level of safety that's demanded of a Phase 3 candidate oncology drug at the beginning of a clinical trial the same or different from the level of safety the FDA will ultimately insist on before it approves the drug?

MS. MALMBERG: It calls for speculation, outside the scope, compound.

THE WITNESS: That's an interesting question. I think -- I think that the history of oncology drugs is that they are often tested at a high dose. Not so much for biologic agents but for agents like this often there's an attempt find

Source: Ex. 2133 at 41:19-43:25; Paper 69 at 9.

Dr. Feigal

Dr. Feigal's Testimony

what's the highest tolerated dose because very few agents give you a complete response for the tumor so you want to get as much drug to the tumor as you can that the patient can tolerate. Often during the Phase 2 trials you may learn that the dose studied was higher than it needed to be or that the side effects were problematic so it wouldn't unusual to have a Phase 3 trial of one design but the approval to actually learn from that Phase 3 trial and modify the instructions for use and the dose and the regimen based on what was learned in that trial. But, generally speaking, you try to have your pivotal trials, your Phase 3 trials, match what you are going to recommend in the labeling because the labeling is going to contain the side effects from the trial as to what you might expect if you treat a patient the way they're treated in the trial.

Q BY MR. KRINSKY: So to simplify that, sometimes you learn more in the Phase 3 trial that it alters the recommendation regarding what the regimen should be but typically the Phase 3 regimen, the goal is that it will be the same as the approved regimen?

MS. MALMBERG: Objection; mischaracterizes, asked and answered.

THE WITNESS: Yes, I think that's pretty close.

Q BY MR. KRINSKY: And my question was I think related to that but not exactly the same as that which is in terms of safety is the FDA more tolerant of side effects or more tolerant of safety problems at the beginning of the Phase 3 trial than it is at approval or is the standard of what's safe enough for this class of drugs essentially the same at those two points?

MS. MALMBERG: Objection; outside the scope, vague, mischaracterizes.

THE WITNESS: Yeah. It is a hard question to answer but in general the standard is pretty much the same; that they expect by the time you get to the Phase 3 the safety in the Phase 3 should be the safety you would anticipate when the product is used in the market.

Q BY MR. KRINSKY: And the goal -- obviously in Phase 3 one is, you know, always on the lookout for side effects and toxicity problems but is it fair to say the goal of the Phase 3 study is to establish efficacy?

A Well, and safety. It is both, it is both. You can't really evaluate one without the other.

Q But at the beginning of a Phase 3 trial you typically have a sense of the maximum tolerated dose in the case of an oncology drug?

MS. MALMBERG: Objection; mischaracterizes.

THE WITNESS: That's right. Although you may not be going into Phase 3 with a maximally-tolerated dose. Sometimes the efficacy plateaus, it doesn't get better and better as the dose goes up but the side effects keep going up, so that's part of the purpose of dose finding in the earlier phases is to find that right balance between effectiveness and side effects.

Source: Ex. 2133 at 44:1-46:12; Paper 69 at 9.

Dr. Feigal's Testimony

Q BY MR. KRINSKY: What was your involvement with trimetrexate?
A I signed the approval for that, I was the division director. Those drugs for pneumocystis were in the Antiviral Drug Division. I was the division director at the time. I might have also been the office director at the same time. But I was involved in the design of the studies for the -- probably given that I went to FDA in '92, probably not the early studies, but I think, as I recall, I was involved in the design of some of the Phase 3 studies and the approval of the product and the labeling.
Q In your capacity at FDA.
A Yes. Right.

Source: Ex. 2133 at 52:21-53:10; Paper 69 at 9.

Dr. Feigal

Dr. Feigal's Testimony

THE WITNESS: I think the document we are looking for may have been the minutes of the End-Of-Phase 2 meeting or the continuation of the End-Of-Phase 2 meeting.

As I recall there were not specific drugs cited so I'm just offering this as my general experience with FDA that FDA has the advantage compared to the companies of seeing all the drugs and knowing lots of different drugs in the -- in the class and they take advantage of that, of that knowledge in the designing of clinical trials.

Q BY MR. KRINSKY: Okay. Do you know to what extent the FDA took advantage of knowledge of prior drugs in its interactions with Lilly related to pemetrexed?

MS. MALMBERG: Objection; calls for speculation, outside the scope.

THE WITNESS: I don't think there's anything directly in the record that cites specific drugs but I think it is part of what FDA always does is use its entire knowledge of the drug development process when it is going forward with -- going forward with products. One of the challenges for FDA is some of the knowledge it has is confidential with other companies but they still use that information to inform them of developing products with a different -- different company which sometimes leads companies to wonder why did the FDA suggest that but in the written record it may not reflect information that FDA has that has come from other confidential interactions with other companies.

Source: Ex. 2133 at 57:16-58:21; Paper 69 at 8-9.

Dr. Feigal

Dr. Feigal's Testimony

Q BY MR. KRINSKY: I want to delve a little bit more into your history with FDA.
A Sure.
Q You mentioned you were in clinical practice outside of FDA until 1992.
A That's right.
Q Can you just describe the sequence of roles you held at the FDA?
A Sure.
Before I went to FDA I was actually a member of the Antiviral Advisory Committee as a special government employee which is how you are put on those committees, you have to be vetted for conflict of interest and so forth, and you pay for your time at the government rate, so I was on that committee for several years before. And then I had been involved in development of drugs for HIV and some of the studies that I was involved with and designed and I ran data coordinating centers for studies resulted in the approval of an old product that didn't have a usual pharma sponsor, it was a very unusual study, but because that study led to a drug approval I actually had the experience, kind of unusual for an academic, but actually putting together a new drug application and getting that drug approved, the fourth AIDS drug approved.
That was a remarkable study because the patients ran the study, it was a community-based study, they filled out their own case report forms,

Source: Ex. 2133 at 78:22-79:25; Paper 69 at 8-9.

Dr. Feigal's Testimony

the paid for their own medications, but it passed muster with FDA.

But in 1991 I applied -- the position as director of antiviral drugs opened up and at the time I was an associate professor of medicine at the University of California at San Diego but applied for the position, went to FDA. So I initially started as a division director and within about 18 months I also asked if I would concurrently be willing to serve in the role as an office director for the two divisions that took care of all the drugs for infections, all different kinds. And so -- so my C.V. is a little confusing because I was concurrently the division director and an office director and the office directors have the authority to sign off on drugs the very first time they're approved and the division directors approve all of the new indications, new formulations, new safety warnings, all that type of stuff. So I was in the Center for Drugs for about five and a half years.

I then went to the Center for Biologics where I was the medical deputy director and worked particularly closely on blood policy issues, but I was the most senior clinical person in the center because the center director was a chemist and so I

had -- I had a lot of, you know, opportunity to interact with products across, across the whole center. And I supervised the biostatistics and epidemiology group and the advisory committee process and had some direct reports.

And then for the last five years I was at FDA, five and a half years I was the director for the Center For Devices and Radiological Health which is all the equipment and surgical implants. And then on the radiological health side everything from cell phones to theft detectors, a very wide range of products. So in the 12 years I was there I actually worked in all three of the centers that had medical products and had increasing leadership responsibilities over time as the center director and for devices I was a direct report to the commissioner and so it was -- I had a lot of opportunity to do some very interesting things.

Q And then you left. When did you leave FDA?

A In May of 2004.

Q And what encouraged you to leave?

A Well, my wife was at the National Cancer Institute and she was actually the director of, acting director of one of the largest divisions there. And she got an offer in Phoenix, Arizona, to

Source: Ex. 2133 at 80:1-81:25; Paper 69 at 8-9.

Dr. Feigal's Testimony

head up the research side of a new genomics institute. And so we were almost empty nesters so she took off for Arizona and I got my daughter through the prom and off to college and then I moved out to Phoenix, Arizona, and at that time I started teaching at Arizona State University and a consulting practice.

Q I see.

Skipping backwards in time to your work at FDA, you mentioned that you worked with all three centers. The three centers are what?

A The Center For Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center For Devices and Radiological Health.

Q And of those, the one that does small molecule pharmaceuticals is the first?

A Yes.

Q Correct?

A Yes.

Q And your only involvement with -- did you have any involvement with small molecule approvals after you moved on to the biologics division?

A No, I did not.

Q And during your period with the Center For Drug Evaluation and Research you alluded to your dual roles as division director and office director.

A Yes.

Q And I think you touched on what they have authority to approve but can you just describe generally what those two roles are and how they differ from one another?

A Sure.

Well, when I went to FDA there were nine divisions, nine new drug divisions. They later expanded and split some of the groups and now there's I think 16 or 17. And so as a division director I led a group that was initially about 60 people, soon expanded to about 120, that came from a variety of different disciplines; pharmaceutical chemists, biostatisticians, animal toxicologists, animal pharmacologists, human pharmacologists, microbiologists, because they were effective. We had project managers who were usually pharmacists. And the division, we were responsible for improving INDs and changes to the investigational new drug applications and we were responsible for doing the primary review of new NDAs and any -- any changes to new drug applications; new indications, new dosage forms, safety -- safety labeling, safety labeling changes.

Source: Ex. 2133 at 82:1-83:25; Paper 69 at 8-9.

Dr. Feigal

Dr. Feigal's Testimony

So when I was Office Director I supervised two divisions, later split them into three because they were very large, but I supervised the divisions that had anti-infective products and as an office director if there was a product that had not previously been approved in the United States then I would have to have the review and signoff by an office director. So there were five office directors so we were the five people that had the authority to introduce a new drug into the -- into the -- into the U.S., U.S. market.

The work was very hands on, we had a lot -- we had a lot of company meetings every week, a lot of new documents to review, a lot of reviews to write, decisions to be made, and I had, you know, responsibility for the groups.

Q Did any of these groups deal with oncology drugs?

A Indirectly. We had responsibility for the immunosuppressant drugs and they had many of the same adverse reactions that oncology drugs do which is often to cause infections and sometimes to cause tumors like Kaposi sarcoma and some of the things that occur with the immunosuppression. So we often had products that were concurrently being evaluated in multiple divisions, and then of course both as a division director and office director the group of the nine of us, division directors and the five office directors, formed a group that worked on policy documents together, reviewed practice documents, harmonization documents, things like that, so I had a lot of interaction. Nearly all of the directors of, all the leadership in oncology I knew quite well.

Source: Ex. 2133 at 84:1-85:9; Paper 69 at 8-9.

LEGAL AUTHORITY

Legal Authority

Hoffman-LaRoche Inc. v. Apotex, Inc.

748 F.3d 1326, *1331; 2014 U.S. App. LEXIS 6673, **12; 110 U.S.P.Q.2D (BNA) 1494, ***1498

Postmenopausal Osteoporosis ("Riis"). Riis for which antifracture efficacy had been demonstrated. demonstrated that "intermittent iban effective as the continuous treatmer significantly increasing BMD at the spin hip and suppressing markers of bone showed that increases in BMD equiv obtained with a 2.5 mg per day treatmer obtained with a regimen of 20 mg of iba other day for the first 24 days of eve period. Those results, Riis conclude preclinical data showing that it is the to predefined period and not the dosing r the determining factor for effect on b architecture after ibandronate treatment." that a dose-free interval of more than not impact the BMD efficacy of ibandron contrary to Schnitzer's speculation that regimen would not be effective. The Schnitzer's interpretation of the Reck [**13] viewed as teaching away from Riis's contrary findings substantially u interpretation.

Roche argues that Riis did not overc interpretation because Riis was not an Roche argues that prior art focusing on bone-turnover improvements, instead of efficacy, does not bear on the obviousness analysis in this case because such prior art does not establish a reasonable expectation of success in reducing fracture risk.

While it is true that BMD improvements do not perfectly correlate with antifracture efficacy, it was well established in the art that BMD is a powerful surrogate for measuring fracture risk. For example, Roche's own expert explained:

> Bone mineral density is directly related to fracture risk. It is one of the most powerful surrogate markers in the field of medicine. It is as powerful an indicator of osteoporosis as blood pressure is a predictor of stroke. For every standard deviation reduction in bone mineral density, fracture risk is doubled.

Roche's patents do not themselves present data demonstrating antifracture efficacy for a once monthly 150 mg dose. In fact, antifracture efficacy for [**14] Boniva® was demonstrated to the FDA through a "bridging study" that used BMD and bone turnover results—not antifracture testing—to establish the therapeutic noninferiority of the 150 mg monthly dose relative to the previously approved 2.5 mg daily dose, total dose, within a given time period, that would produce effective results. A 1996 article by Ravn et al. ("Ravn") reported the results of a study that measured BMD improvements and bone-turnover markers for daily ibandronate doses of 0.25 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 5 mg. The authors concluded that the "average change in bone mass showed positive outcome in all regions in the groups receiving ibandronate 2.5 and 5.0 mg." The 2.5 mg dose exhibited a response that was "virtually equal" to the 5 mg dose, even though it contained only half the amount of ibandronate. The 2.5 mg dose was thereby deemed the "most effective dose."

A person skilled in the art looking to scale to a monthly dose of oral ibandronate from a known-effective daily dose was thus faced with a very limited set of possibilities: Of the five daily doses tested in Ravn, only the 2.5 and 5 mg doses "showed positive outcome in all regions." Even though the 5 mg dose did not demonstrate greater efficacy than the 2.5 mg dose, it was still deemed an [**16] equivalently effective dose so that someone scaling it to a [***1500] single monthly dose of 150 mg (5 mg/day x 30 days/month) would have anticipated equivalent success in raising BMD and limiting bone turnover, based on Riis.

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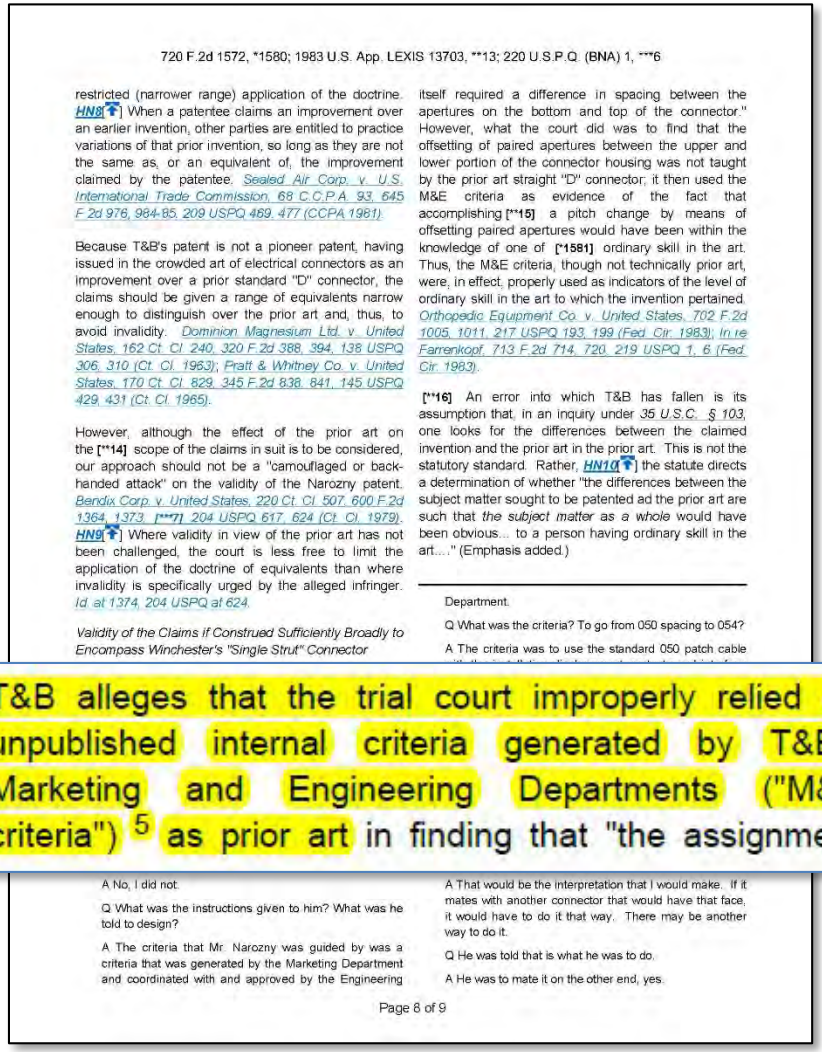
HN1[↑] Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success. See *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Riis—along with other prior art that

Source: *Hoffman-LaRoche Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014); Paper 48 at 3.

Legal Authority

Thomas & Betts Corp. v. Litton Sys., Inc.



720 F.2d 1572, *1580; 1983 U.S. App. LEXIS 13703, **13; 220 U.S.P.Q. (BNA) 1, ***6

restricted (narrower range) application of the doctrine. HN8[↑] When a patentee claims an improvement over an earlier invention, other parties are entitled to practice variations of that prior invention, so long as they are not the same as, or an equivalent of, the improvement claimed by the patentee. *Sealed Air Corp. v. U.S. International Trade Commission, 68 C.C.P.A. 93, 645 F.2d 976, 984-85, 209 USPQ 469, 477 (CCPA 1981).*

Because T&B's patent is not a pioneer patent, having issued in the crowded art of electrical connectors as an improvement over a prior standard "D" connector, the claims should be given a range of equivalents narrow enough to distinguish over the prior art and, thus, to avoid invalidity. *Dominion Magnesium Ltd. v. United States, 162 Ct. Cl. 240, 320 F.2d 388, 394, 138 USPQ 306, 310 (Ct. Cl. 1963); Pratt & Whitney Co. v. United States, 170 Ct. Cl. 829, 345 F.2d 838, 841, 145 USPQ 429, 431 (Ct. Cl. 1965).*

However, although the effect of the prior art on the [**14] scope of the claims in suit is to be considered, our approach should not be a "camouflaged or back-handed attack" on the validity of the Narozny patent. *Bendix Corp. v. United States, 220 Ct. Cl. 507, 600 F.2d 1364, 1373, [***7] 204 USPQ 617, 624 (Ct. Cl. 1979).* HN9[↑] Where validity in view of the prior art has not been challenged, the court is less free to limit the application of the doctrine of equivalents than where invalidity is specifically urged by the alleged infringer. *Id. at 1374, 204 USPQ at 624.*

Validity of the Claims if Construed Sufficiently Broadly to Encompass Winchester's "Single Strut" Connector

itself required a difference in spacing between the apertures on the bottom and top of the connector." However, what the court did was to find that the offsetting of paired apertures between the upper and lower portion of the connector housing was not taught by the prior art straight "D" connector; it then used the M&E criteria as evidence of the fact that accomplishing [**15] a pitch change by means of offsetting paired apertures would have been within the knowledge of one of [*1581] ordinary skill in the art. Thus, the M&E criteria, though not technically prior art, were, in effect, properly used as indicators of the level of ordinary skill in the art to which the invention pertained. *Orthopedic Equipment Co. v. United States, 702 F.2d 1005, 1011, 217 USPQ 193, 199 (Fed. Cir. 1983); In re Farrenkopf, 713 F.2d 714, 720, 219 USPQ 1, 6 (Fed. Cir. 1983).*

[**16] An error into which T&B has fallen is its assumption that, in an inquiry under *35 U.S.C. § 103*, one looks for the differences between the claimed invention and the prior art in the prior art. This is not the statutory standard. Rather, HN10[↑] the statute directs a determination of whether "the differences between the subject matter sought to be patented ad the prior art are such that *the subject matter as a whole* would have been obvious... to a person having ordinary skill in the art...." (Emphasis added.)

Department.

Q What was the criteria? To go from 050 spacing to 054?

A The criteria was to use the standard 050 patch cable

A No, I did not.

Q What was the instructions given to him? What was he told to design?

A The criteria that Mr. Narozny was guided by was a criteria that was generated by the Marketing Department and coordinated with and approved by the Engineering

A That would be the interpretation that I would make. If it mates with another connector that would have that face, it would have to do it that way. There may be another way to do it.

Q He was told that is what he was to do.

A He was to mate it on the other end, yes.

Page 6 of 9

T&B alleges that the trial court improperly relied on unpublished internal criteria generated by T&B's Marketing and Engineering Departments ("M&E criteria") [5] as prior art in finding that "the assignment

However, what the court did was to find that the offsetting of paired apertures between the upper and lower portion of the connector housing was not taught by the prior art straight "D" connector; it then used the M&E criteria as evidence of the fact that accomplishing [**15] a pitch change by means of offsetting paired apertures would have been within the knowledge of one of [*1581] ordinary skill in the art. Thus, the M&E criteria, though not technically prior art, were, in effect, properly used as indicators of the level of ordinary skill in the art to which the invention pertained. *Orthopedic Equipment Co. v. United States, 702 F.2d 1005, 1011, 217 USPQ 193, 199 (Fed. Cir. 1983)*; *In re Farrenkopf, 713 F.2d 714, 720, 219 USPQ 1, 6 (Fed. Cir. 1983)*.

Source: *Thomas & Betts Corp. v. Litton Sys., Inc.*, 720 F.2d 1572, 1580-81 (Fed. Cir.1983); Paper 48 at 6.

Legal Authority

Ex Parte Raychem

1992 Pat. App. LEXIS 21, *7; 25 U.S.P.Q.2D (BNA) 1265, **1267

disclosed in that reference does result [*8] in improved wetting [2] of the electrode by the conductive polymer composition.

Smith-Johannsen is also directed to methods of making electrical devices including self-regulating strip heaters in which the electrically conductive polymer coating exhibits PCT behavior. This reference provides further evidence that at the time of the present invention those of ordinary skill in the art were aware of the need to assure that the electrodes in such devices were adequately wetted by the conductive polymer composition. To this end, Smith-Johannsen discloses that an electrical device, such as a self-regulating heater, which is formed by an otherwise conventional extrusion of a conductive polymer composition around an electrode (s) will have improved electrode wetting when the extruded product is annealed. See column 2, lines 38-54 and column 4, lines 37-43 of Smith-Johannsen.

The examiner has relied upon a definition of "wetting" which appears in the *Metals Handbook*. [3] As seen from this definition, the problem concerning [*9] wetting of the electrodes in the electrical devices of Bedard and Smith-Johannsen would be recognized by those of ordinary skill in the art as involving the degree of adhesion of the conductive polymer composition to the metal electrode as well as the degree of continuity of contact between the conductive polymer composition and the metallic electrode.

definition of "wetting" [**1268] relied upon by the examiner stresses the role that the adhesive force between the metal substrate and the coated material has in this regard and discloses that foreign substances such as grease may prevent wetting.

Gale is further evidence that the problem addressed in Bedard involves a "breakdown in the already poor adhesion between the electrode and the bulk material in the accelerated oxidation and reaction of the PCT material at the electrode interface." See Gale, column 1, lines 43-60 where Bedard is cited as prior art in the reference [*11] and Bedard's attempts to "deal with these problems" are discussed. [4]

Richart is directed to methods for improving the adhesion of thermoplastic coatings to, *inter alia*, metal wire. This reference is relevant to the present inquiry in that the electrical devices of Bedard and Smith-Johannsen are formed using conventional extrusion techniques such as those disclosed in Richart. Richart sets forth at column 1,

Page 4 of 11

Gale is further evidence that the problem addressed in Bedard involves a "breakdown in the already poor adhesion between the electrode and the bulk material in the accelerated oxidation and reaction of the PCT material at the electrode interface." See Gale, column 1, lines 43-60 where Bedard is cited as prior art in the reference [*11] and Bedard's attempts to "deal with these problems" are discussed. [4]

[4] While Gale is not prior art to the claims on appeal, it is proper to consider this reference in determining the patentability of the claims on appeal under ***35 USC § 103.*** Gale is relevant evidence as to (1) characteristics of prior art products, i.e., the electrical devices formed in Bedard, *In re Wilson, 311 F.2d 266, 135 USPQ 442 (CCPA 1962),* and (2) the knowledge possessed by and the level of skill of the ordinary person in this art, *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 308, 227 USPQ 657, 671 (Fed. Cir. 1985); In re Farrenkopf, 713 F.2d 714, 219 USPQ 1 (CCPA 1983).*

Source: *Ex Parte Raychem*, 1992 Pat. App. LEXIS 21, *10-11 & n. 4 (Bd. Pat. App. & Interferences June 30, 1992); Paper 48 at 7.

Legal Authority

Ex Parte Raychem

1992 Pat. App. LEXIS 21, *19; 25 U.S.P.Q.2D (BNA) 1265, **1419

optimize the precise amount of carbon black used in the conductive polymer coating of any individual device would have been *prima facie* obvious to one of ordinary skill in the art. *In re Boesch, supra.*

Raychem argues that Gale is not proper evidence to be relied upon in this reexamination proceeding since it is not prior art. We first point out that Gale can be considered cumulative to the other references relied upon since Gale is

conclusion of obviousness can stand absent reliance upon Gale.

Gale is of interest because it is of a later date than the present invention and in discussing Bedard, states that it

Gale is of interest because it is of a later date than the present invention and in discussing Bedard, states that it was directed to solving problems such as increased resistance at the electrode interface due to breakdown in the already poor adhesion between the electrode and the conductive polymer composition. *In re Wilson, supra.*

USC § 305 as he would be in making a rejection under *35 USC § 103* in any other case.

Raychem's arguments that two of the three inventors named in Gale have stated in declarations that they were unaware of the specific disclosure of Bedard at the time of their work which led to the Gale patent is of little relevance since they signed the original declaration in the U.S. parent application of Gale in which this statement appears. The fact that these two individuals may not have had knowledge of Bedard prior to that time does not detract from the fact that their patent specifically states that Bedard is directed to these problems.

We disagree with the argument on page 24 of the Appeal Brief that Richart "has nothing to do with currenty-carrying devices." Richart discloses that the preheated substrate may be a wire. Wires are certainly current-carrying devices.

Raychem makes much of the fact that Richart prefers annealing the coated substrate in order to achieve improved adhesion of the thermoplastic polymer coating rather than the embodiment in which the wire is preheated prior to contact with the molten coating. The fact that Richart may not prefer the preheating embodiment does not militate against **[*23]** a conclusion of obviousness since all disclosures in a reference must be considered including those which are non-preferred. *In re Mills, 470 F.2d 649, 176 USPQ 196 (CCPA 1972).*

The evidence relied upon from the cited portions of the record does include any objective evidence of nonobviousness which establishesthat the present electrical devices or self-regulating heaters differ in an unexpected manner from those disclosed in Bedard whether they are annealed or non-annealed. While reference is made to the declaration of record of Mr. Clifford Smith on page 27 of the Appeal Brief, we note that Mr. Smith has only stated that the use of the present preheating process results in heaters which are of a "higher quality" than those produced by the prior art annealing process. Mr. **[**1271]** Smith has not substantiated his conclusion with any objective evidence. Thus, it is not clear from this record in what manner the present heaters are considered by Mr. Smith to be of a "higher quality."

Page 7 of 11

Source: *Ex Parte Raychem*, 1992 Pat. App. LEXIS 21, *19-21 (Bd. Pat. App. & Interferences June 30, 1992); Paper 48 at 7.

Legal Authority

Ex Parte McGaughey

types of evidence such as on-sale bars, public use issues or issues relating to fraud. Thus, the implication by the dissent that this decision will result in such issues being authorized is unfounded. For purposes of this appeal, we need not and do not consider whether other facts besides admissions established in the record are authorized under section 305.

[*13]

In the initial examination of patent applications, admissions by the applicant are considered for any purpose including evidence of obviousness under section 103. See *In re Nomiya, 549 F.2d 566, 184 USPQ 607 (CCPA 1975); In re Hellsund, 474 F.2d 1307, 177 USPQ 170 (CCPA 1973);* and *In re Garfinkel, 437 F.2d 1000, 168 USPQ 659 (CCPA 1971).* Those holdings are clearly in accord with sections 132 and 133 and we hold that they are incorporated into section 305. Moreover, in at least one prior decision admissions in the specification of the patent being reexamined were considered as part of the prior art under section 305. See Ex parte Seiko Koko Kabushiki Kaisha Co., 225 USPQ 1260, 1262 (Bd. App. 1984).

An admission is defined as an acknowledged, declared, conceded or recognized fact or truth. [14] Thus, admissions are simply facts. In this case the admission is an uncontroverted fact. Moreover, as pointed out in *Graham v. John*

Rejections based on such a standard would be meaningless. However, as stated in *Strataflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983),* "[i]t is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included." Thus to ignore prior art admissions would handicap any patentability determinations rendering them practically useless. How would such determinations aid the courts or the public by providing a meaningful input as to patentability? Congress certainly did not intend a useless procedure.

Moreover, admissions take different forms. For instance, the preamble of a Jepson claim [15] is an admission usable under *35 USC § 103* when that admission relates to the prior art of another. *Reading & Bates Const. Co. v. Baker Energy, 748 F.2d 645, 223 USPQ 1168 (Fed. Cir. 1984); In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982); In re Ehrreich, 590 F.2d 902, 200 USPQ 504 (CCPA 1979).* Certainly, the preamble of a Jepson claim which relates to prior art of another should not be ignored in a reexamination. As we read section 305 of the statute, any unequivocal admission which would be considered in initial examination under sections 132 and 133 should be

considering section 305 to support a holding that admissions cannot be utilized in a reexamination proceeding. For example, the opinion states:

While the examiner did not cite this rule [*37 CFR 1.106(c)*] in support of his position, we raise the point here because it appears to open reexamination proceedings to any and all issues affecting patentability so long as there is a related admission. However, we are compelled to construe the rule in light of the statute and other implementing rules which, as we discussed hereinabove, specifically restrict reexamination to a consideration of patents and printed publications. Thus, for an admission to form some or all of the basis for a prior art rejection in reexamination proceedings, such admission must necessarily relate to patents or printed publications. Otherwise, patentees or patent owners would be able to circumvent the restrictive nature of the statute by making admissions relating to prior public use, sale, abandonment, etc. issues which, as we have seen were never intended to be resolved by way of reexamination. *(226 USPQ at 702)*

We do not agree. *37 CFR 1.106(c)* is fully supported by section 305 of the statute. There is no basis in the reexamination statute for the narrow interpretation of *37 CFR 1.106(c)* given in Horton.

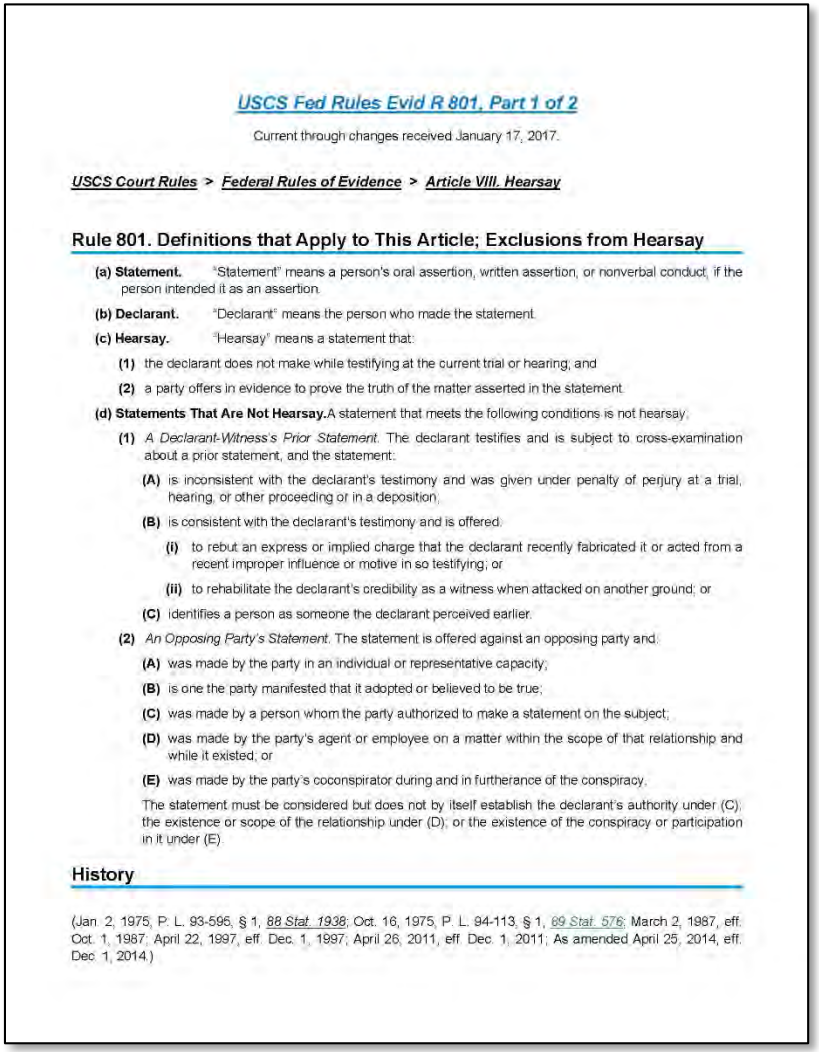
[14] 2 C.J.S. 411.

[15] Ex parte Jepson, 1917 C.D. 62, 243 O.G. 525 (Comm'r. Pats. 1917) and *37 CFR 1.75(e).*

Source: *Ex Parte McGaughey*, 1988 Pat. App. LEXIS 2, 13-15 (Bd. Pat. App. & Interferences Mar. 4, 1988); Paper 48 at 7.

Legal Authority

Fed. R. Evid. 801(d)(2)



USCS Fed Rules Evid R 801, Part 1 of 2

Current through changes received January 17, 2017.

USCS Court Rules > Federal Rules of Evidence > Article VIII. Hearsay

Rule 801. Definitions that Apply to This Article; Exclusions from Hearsay

(a) Statement. "Statement" means a person's oral assertion, written assertion, or nonverbal conduct, if the person intended it as an assertion.

(b) Declarant. "Declarant" means the person who made the statement.

(c) Hearsay. "Hearsay" means a statement that:

(1) the declarant does not make while testifying at the current trial or hearing; and

(2) a party offers in evidence to prove the truth of the matter asserted in the statement.

(d) Statements That Are Not Hearsay. A statement that meets the following conditions is not hearsay:

(1) *A Declarant-Witness's Prior Statement.* The declarant testifies and is subject to cross-examination about a prior statement, and the statement:

(A) is inconsistent with the declarant's testimony and was given under penalty of perjury at a trial, hearing, or other proceeding or in a deposition;

(B) is consistent with the declarant's testimony and is offered:

(i) to rebut an express or implied charge that the declarant recently fabricated it or acted from a recent improper influence or motive in so testifying; or

(ii) to rehabilitate the declarant's credibility as a witness when attacked on another ground; or

(C) identifies a person as someone the declarant perceived earlier.

(2) *An Opposing Party's Statement.* The statement is offered against an opposing party and:

(A) was made by the party in an individual or representative capacity;

(B) is one the party manifested that it adopted or believed to be true;

(C) was made by a person whom the party authorized to make a statement on the subject;

(D) was made by the party's agent or employee on a matter within the scope of that relationship and while it existed; or

(E) was made by the party's coconspirator during and in furtherance of the conspiracy.

The statement must be considered but does not by itself establish the declarant's authority under (C); the existence or scope of the relationship under (D); or the existence of the conspiracy or participation in it under (E).

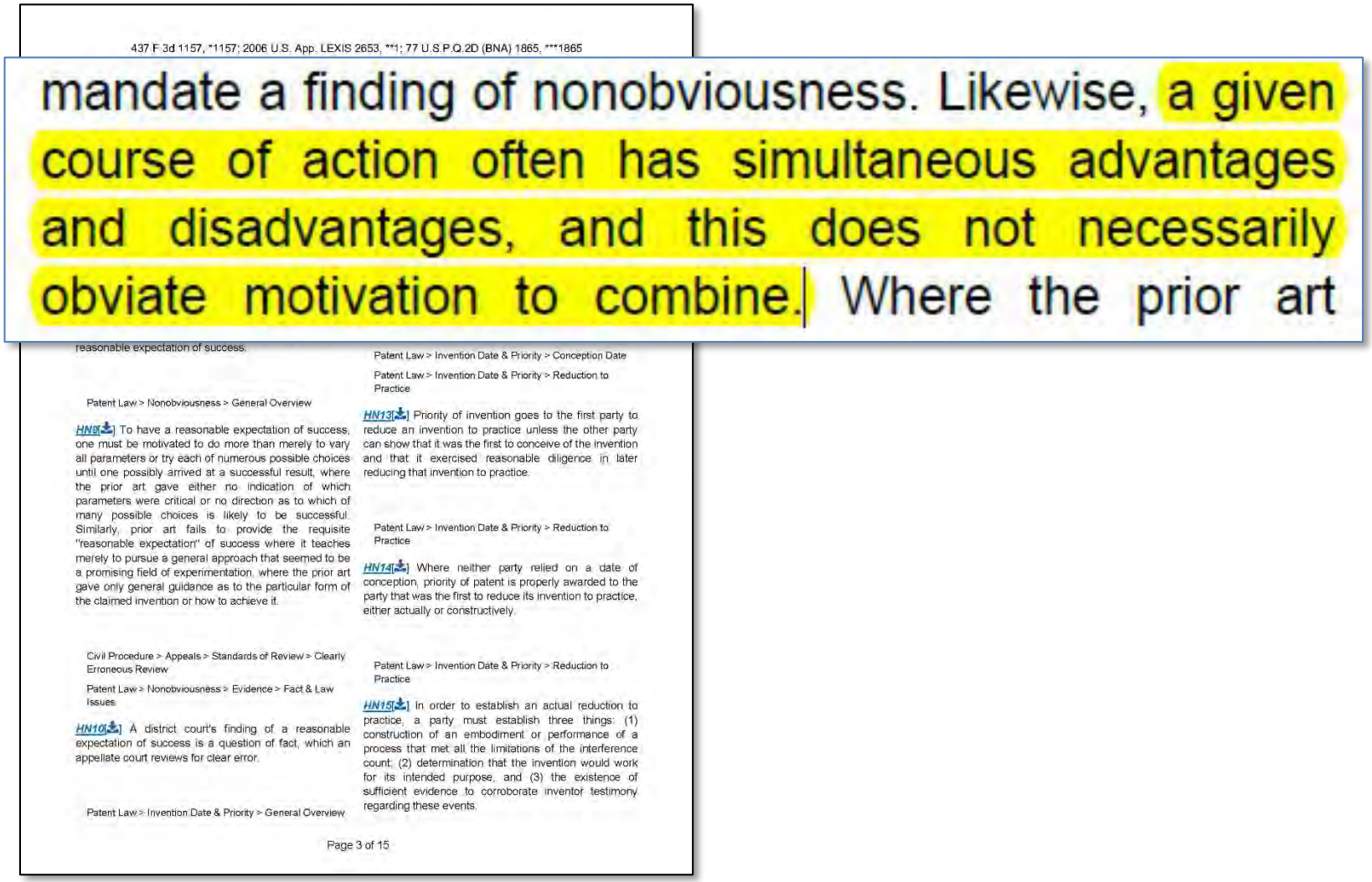
History

(Jan. 2, 1975, P. L. 93-595, § 1, 88 Stat. 1938; Oct. 16, 1975, P. L. 94-113, § 1, 89 Stat. 576; March 2, 1987, eff. Oct. 1, 1987; April 22, 1997, eff. Dec. 1, 1997; April 26, 2011, eff. Dec. 1, 2011; As amended April 25, 2014, eff. Dec. 1, 2014.)

Source: Fed. R. Evid. 801(d)(2); Paper 48 at 7.

Legal Authority

Medichem S.A. v. Rolabo S.I.



437 F.3d 1157, *1157; 2006 U.S. App. LEXIS 2653, **1; 77 U.S.P.Q.2D (BNA) 1865, ***1865

mandate a finding of nonobviousness. Likewise, a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine. Where the prior art

reasonable expectation of success.

Patent Law > Nonobviousness > General Overview

HN9 To have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Similarly, prior art fails to provide the requisite "reasonable expectation" of success where it teaches merely to pursue a general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Civil Procedure > Appeals > Standards of Review > Clearly Erroneous Review

Patent Law > Nonobviousness > Evidence > Fact & Law Issues

HN10 A district court's finding of a reasonable expectation of success is a question of fact, which an appellate court reviews for clear error.

Patent Law > Invention Date & Priority > General Overview

Patent Law > Invention Date & Priority > Conception Date

Patent Law > Invention Date & Priority > Reduction to Practice

HN13 Priority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice.

Patent Law > Invention Date & Priority > Reduction to Practice

HN14 Where neither party relied on a date of conception, priority of patent is properly awarded to the party that was the first to reduce its invention to practice, either actually or constructively.

Patent Law > Invention Date & Priority > Reduction to Practice

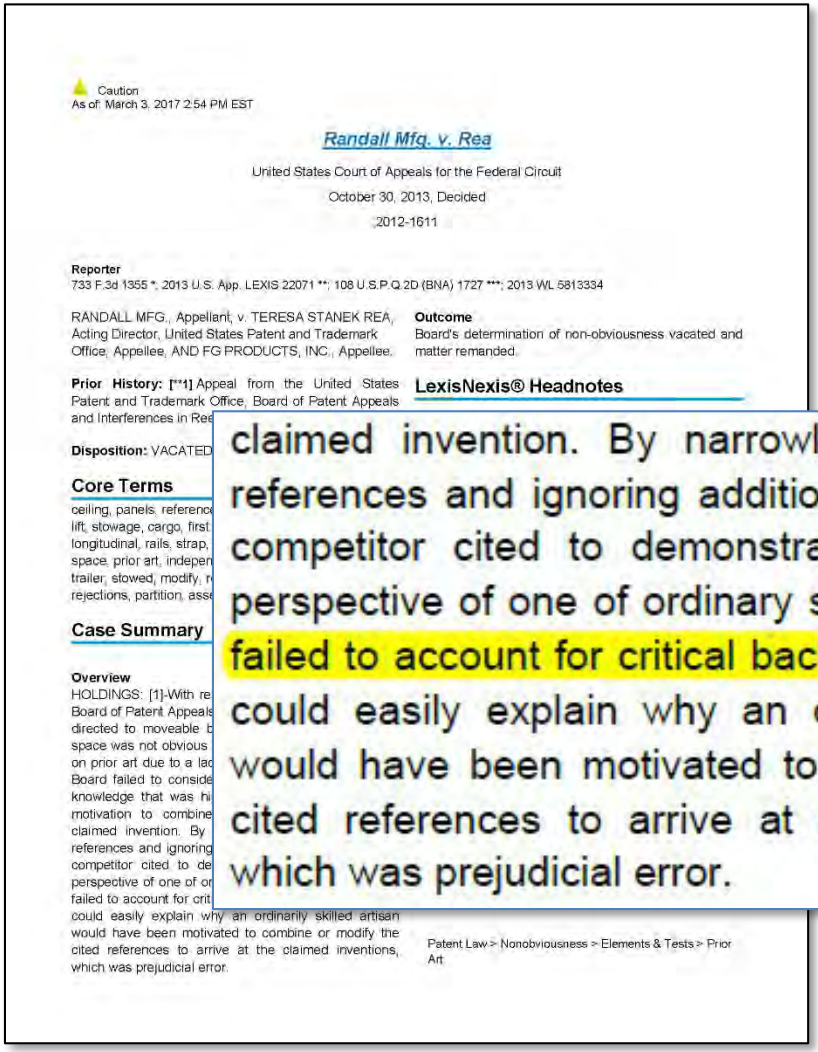
HN15 In order to establish an actual reduction to practice, a party must establish three things: (1) construction of an embodiment or performance of a process that met all the limitations of the interference count, (2) determination that the invention would work for its intended purpose, and (3) the existence of sufficient evidence to corroborate inventor testimony regarding these events.

Page 3 of 15

Source: *Medichem S.A. v. Rolabo S.I.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006); Paper 48 at 15.

Legal Authority

Randall Mfg. v. Rea



Caution
As of: March 3, 2017 2:54 PM EST

Randall Mfg. v. Rea

United States Court of Appeals for the Federal Circuit

October 30, 2013, Decided

2012-1611

Reporter
733 F.3d 1355 *; 2013 U.S. App. LEXIS 22071 **; 108 U.S.P.Q.2D (BNA) 1727 ***; 2013 WL 5813334

RANDALL MFG., Appellant, v. TERESA STANEK REA, Acting Director, United States Patent and Trademark Office, Appellee, AND FG PRODUCTS, INC., Appellee.

Outcome
Board's determination of non-obviousness vacated and matter remanded.

Prior History: [**1] Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences in Ree

Disposition: VACATED

Core Terms

ceiling, panels, referenc
lift, stowage, cargo, first
longitudinal, rails, strap,
space, prior art, indepen
trailer, stowed, modify, r
rejections, partition, ass

Case Summary

Overview
HOLDINGS: [1]-With re
Board of Patent Appeals
directed to moveable b
space was not obvious
on prior art due to a lac
Board failed to conside
knowledge that was hi
motivation to combine
claimed invention. By
references and ignoring
competitor cited to de
perspective of one of or
failed to account for crit
could easily explain why an ordinarily skilled artisan would have been motivated to combine or modify the cited references to arrive at the claimed inventions, which was prejudicial error.

LexisNexis® Headnotes

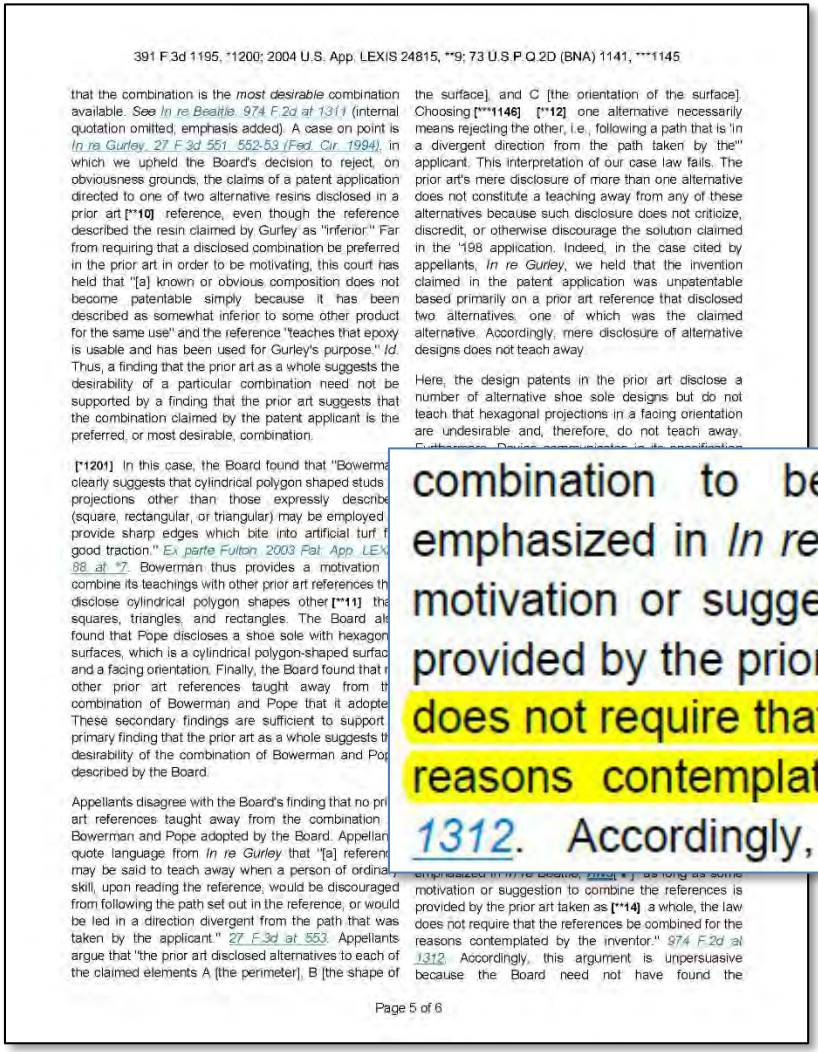
Patent Law > Nonobviousness > Elements & Tests > Prior Art

claimed invention. By narrowly focusing on prior-art references and ignoring additional record evidence the competitor cited to demonstrate the knowledge and perspective of one of ordinary skill in the art, the Board failed to account for critical background information that could easily explain why an ordinarily skilled artisan would have been motivated to combine or modify the cited references to arrive at the claimed inventions, which was prejudicial error.

Source: *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013); Paper 48 at 19.

Legal Authority

In re Fulton



391 F.3d 1195, *1200; 2004 U.S. App. LEXIS 24815, **9; 73 U.S.P.Q.2D (BNA) 1141, ***1145

that the combination is the *most desirable* combination available. *See In re Beattie*, 974 F.2d at 1311 (internal quotation omitted, emphasis added). A case on point is *In re Gurley*, 27 F.3d 551, 552-53 (Fed. Cir. 1994), in which we upheld the Board's decision to reject, on obviousness grounds, the claims of a patent application directed to one of two alternative resins disclosed in a prior art **[**10]** reference, even though the reference described the resin claimed by Gurley as "inferior." Far from requiring that a disclosed combination be preferred in the prior art in order to be motivating, this court has held that "[a] known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use" and the reference "teaches that epoxy is usable and has been used for Gurley's purpose." *Id.* Thus, a finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed by the patent applicant is the preferred, or most desirable, combination.

[*1201] In this case, the Board found that "Bowerma clearly suggests that cylindrical polygon shaped studs projections other than those expressly describe (square, rectangular, or triangular) may be employed provide sharp edges which bite into artificial turf f good traction." *Ex parte Fulton*, 2003 Pat. App. LEX 88 at *7. Bowerman thus provides a motivation combine its teachings with other prior art references th disclose cylindrical polygon shapes other **[**11]** tha squares, triangles, and rectangles. The Board als found that Pope discloses a shoe sole with hexagon surfaces, which is a cylindrical polygon-shaped surfac and a facing orientation. Finally, the Board found that t other prior art references taught away from th combination of Bowerman and Pope that it adopte These secondary findings are sufficient to support primary finding that the prior art as a whole suggests th desirability of the combination of Bowerman and Pop described by the Board.

Appellants disagree with the Board's finding that no pri art references taught away from the combination Bowerman and Pope adopted by the Board. Appellan quote language from *In re Gurley* that "[a] referen may be said to teach away when a person of ordinar skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." 27 F.3d at 553. Appellants argue that "the prior art disclosed alternatives to each of the claimed elements A [the perimeter], B [the shape of the surface], and C [the orientation of the surface]. Choosing **[***1146]** **[**12]** one alternative necessarily means rejecting the other, i.e., following a path that is 'in a divergent direction from the path taken by the'" applicant. This interpretation of our case law fails. The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed in the '198 application. Indeed, in the case cited by appellants, *In re Gurley*, we held that the invention claimed in the patent application was unpatentable based primarily on a prior art reference that disclosed two alternatives, one of which was the claimed alternative. Accordingly, mere disclosure of alternative designs does not teach away.

Here, the design patents in the prior art disclose a number of alternative shoe sole designs but do not teach that hexagonal projections in a facing orientation are undesirable and, therefore, do not teach away.

motivation or suggestion to combine the references is provided by the prior art taken as **[**14]** a whole, the law does not require that the references be combined for the reasons contemplated by the inventor." 974 F.2d at 1312. Accordingly, this argument is unpersuasive because the Board need not have found the

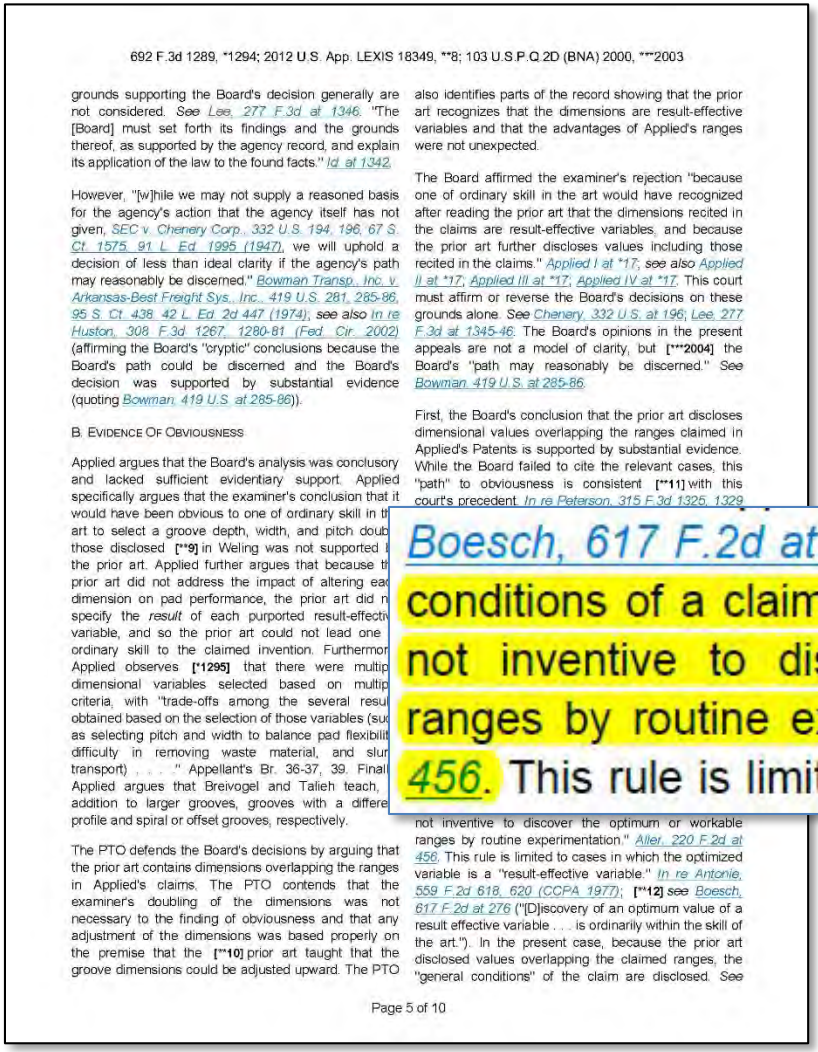
Page 5 of 6

combination to be obvious. Furthermore, as we emphasized in *In re Beattie*, HN5[↑] "as long as some motivation or suggestion to combine the references is provided by the prior art taken as **[**14]** a whole, the law does not require that the references be combined for the reasons contemplated by the inventor." 974 F.2d at 1312. Accordingly, this argument is unpersuasive

Source: *In re Fulton*, 391 F.3d 1195, 1202 (Fed. Cir. 2004); Paper 48 at 25.

Legal Authority

In re Applied Materials, Inc.



692 F.3d 1289, *1294; 2012 U.S. App. LEXIS 18349, **8; 103 U.S.P.Q.2D (BNA) 2000, ***2003

grounds supporting the Board's decision generally are not considered. *See Lee, 277 F.3d at 1346*. "The [Board] must set forth its findings and the grounds thereof, as supported by the agency record, and explain its application of the law to the found facts." *Id. at 1342*.

However, "[w]hile we may not supply a reasoned basis for the agency's action that the agency itself has not given, *SEC v. Chenery Corp., 332 U.S. 194, 196, 67 S. Ct. 1575, 91 L. Ed. 1995 (1947)*, we will uphold a decision of less than ideal clarity if the agency's path may reasonably be discerned." *Bowman Transp., Inc. v. Arkansas-Best Freight Sys., Inc., 419 U.S. 281, 285-86, 95 S. Ct. 438, 42 L. Ed. 2d 447 (1974)*; *see also In re Huston, 308 F.3d 1267, 1280-81 (Fed. Cir. 2002)* (affirming the Board's "cryptic" conclusions because the Board's path could be discerned and the Board's decision was supported by substantial evidence (quoting *Bowman, 419 U.S. at 285-86*)).

B. Evidence Of Obviousness

Applied argues that the Board's analysis was conclusory and lacked sufficient evidentiary support. Applied specifically argues that the examiner's conclusion that it would have been obvious to one of ordinary skill in th art to select a groove depth, width, and pitch doub those disclosed **[**9]** in Weling was not supported b the prior art. Applied further argues that because th prior art did not address the impact of altering eac dimension on pad performance, the prior art did n specify the *result* of each purported result-effecti variable, and so the prior art could not lead one ordinary skill to the claimed invention. Furthermor Applied observes **[*1295]** that there were multip dimensional variables selected based on multip criteria, with "trade-offs among the several resul obtained based on the selection of those variables (su as selecting pitch and width to balance pad flexibilit difficulty in removing waste material, and slur transport) . . . ." Appellant's Br. 36-37, 39. Finall Applied argues that Breivogel and Talieh teach, addition to larger grooves, grooves with a differe profile and spiral or offset grooves, respectively.

The PTO defends the Board's decisions by arguing that the prior art contains dimensions overlapping the ranges in Applied's claims. The PTO contends that the examiner's doubling of the dimensions was not necessary to the finding of obviousness and that any adjustment of the dimensions was based properly on the premise that the **[**10]** prior art taught that the groove dimensions could be adjusted upward. The PTO also identifies parts of the record showing that the prior art recognizes that the dimensions are result-effective variables and that the advantages of Applied's ranges were not unexpected.

The Board affirmed the examiner's rejection "because one of ordinary skill in the art would have recognized after reading the prior art that the dimensions recited in the claims are result-effective variables, and because the prior art further discloses values including those recited in the claims." *Applied I at *17*; *see also Applied II at *17*; *Applied III at *17*; *Applied IV at *17*. This court must affirm or reverse the Board's decisions on these grounds alone. *See Chenery, 332 U.S. at 196*; *Lee, 277 F.3d at 1345-46*. The Board's opinions in the present appeals are not a model of clarity, but **[***2004]** the Board's "path may reasonably be discerned." *See Bowman, 419 U.S. at 285-86*.

First, the Board's conclusion that the prior art discloses dimensional values overlapping the ranges claimed in Applied's Patents is supported by substantial evidence. While the Board failed to cite the relevant cases, this "path" to obviousness is consistent **[**11]** with this court's precedent. *In re Peterson, 315 F.3d 1325, 1329*

Boesch, 617 F.2d at 276. **HN3**[↑] "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *Aller, 220 F.2d at 456*. This rule is limited to cases in which the optimized

not inventive to discover the optimum or workable ranges by routine experimentation." *Aller, 220 F.2d at 456*. This rule is limited to cases in which the optimized variable is a "result-effective variable." *In re Antonie, 559 F.2d 618, 620 (CCPA 1977)*; **[**12]** *see Boesch, 617 F.2d at 276* ("[D]iscovery of an optimum value of a result effective variable . . . is ordinarily within the skill of the art."). In the present case, because the prior art disclosed values overlapping the claimed ranges, the "general conditions" of the claim are disclosed. *See*

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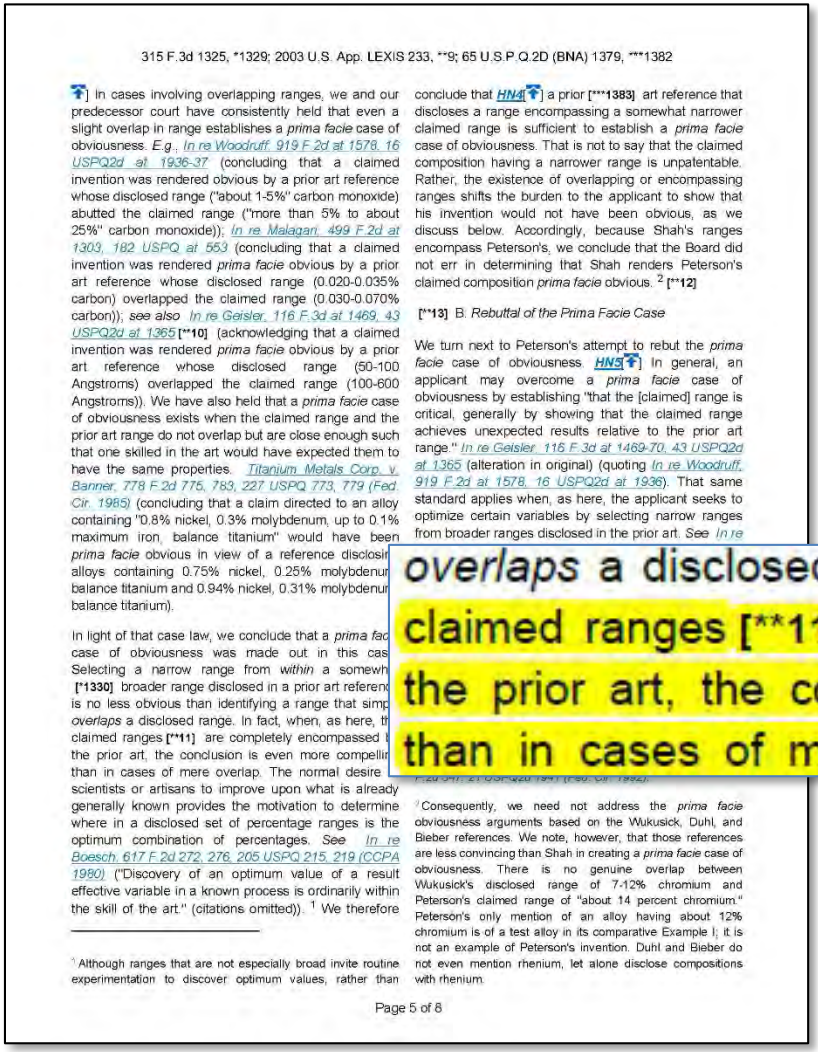
Source: *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012); Paper 1 at 39-40.

Legal Authority

In re Peterson



315 F.3d 1325, *1329; 2003 U.S. App. LEXIS 233, **9; 65 U.S.P.Q.2D (BNA) 1379, ***1382

[1] In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness. *E.g.*, *In re Woodruff*, 919 F.2d at 1578, 16 USPQ2d at 1936-37 (concluding that a claimed invention was rendered obvious by a prior art reference whose disclosed range ("about 1-5%" carbon monoxide) abutted the claimed range ("more than 5% to about 25%" carbon monoxide)); *In re Malagari*, 499 F.2d at 1303, 182 USPQ at 553 (concluding that a claimed invention was rendered *prima facie* obvious by a prior art reference whose disclosed range (0.020-0.035% carbon) overlapped the claimed range (0.030-0.070% carbon)); *see also In re Geisler*, 116 F.3d at 1469, 43 USPQ2d at 1365 [**10] (acknowledging that a claimed invention was rendered *prima facie* obvious by a prior art reference whose disclosed range (50-100 Angstroms) overlapped the claimed range (100-600 Angstroms)). We have also held that a *prima facie* case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 783, 227 USPQ 773, 779 (Fed. Cir. 1985) (concluding that a claim directed to an alloy containing "0.8% nickel, 0.3% molybdenum, up to 0.1% maximum iron, balance titanium" would have been *prima facie* obvious in view of a reference disclosing alloys containing 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium).

In light of that case law, we conclude that a *prima facie* case of obviousness was made out in this case. Selecting a narrow range from *within* a somewhat [*1330] broader range disclosed in a prior art reference is no less obvious than identifying a range that simply *overlaps* a disclosed range. In fact, when, as here, the claimed ranges [**11] are completely encompassed by the prior art, the conclusion is even more compelling than in cases of mere overlap. The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages. *See In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) ("Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." (citations omitted)). [1] We therefore conclude that [HN4] a prior [***1383] art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness. That is not to say that the claimed composition having a narrower range is unpatentable. Rather, the existence of overlapping or encompassing ranges shifts the burden to the applicant to show that his invention would not have been obvious, as we discuss below. Accordingly, because Shah's ranges encompass Peterson's, we conclude that the Board did not err in determining that Shah renders Peterson's claimed composition *prima facie* obvious. [2] [**12]

[**13] B. *Rebuttal of the Prima Facie Case*

We turn next to Peterson's attempt to rebut the *prima facie* case of obviousness. [HN5] In general, an applicant may overcome a *prima facie* case of obviousness by establishing "that the [claimed] range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Geisler*, 116 F.3d at 1469-70, 43 USPQ2d at 1365 (alteration in original) (quoting *In re Woodruff*, 919 F.2d at 1578, 16 USPQ2d at 1936). That same standard applies when, as here, the applicant seeks to optimize certain variables by selecting narrow ranges from broader ranges disclosed in the prior art. *See In re*

[1] Although ranges that are not especially broad invite routine experimentation to discover optimum values, rather than

[2] Consequently, we need not address the *prima facie* obviousness arguments based on the Wukusick, Duhl, and Bieber references. We note, however, that those references are less convincing than Shah in creating a *prima facie* case of obviousness. There is no genuine overlap between Wukusick's disclosed range of 7-12% chromium and Peterson's claimed range of "about 14 percent chromium." Peterson's only mention of an alloy having about 12% chromium is of a test alloy in its comparative Example I; it is not an example of Peterson's invention. Duhl and Bieber do not even mention rhenium, let alone disclose compositions with rhenium.

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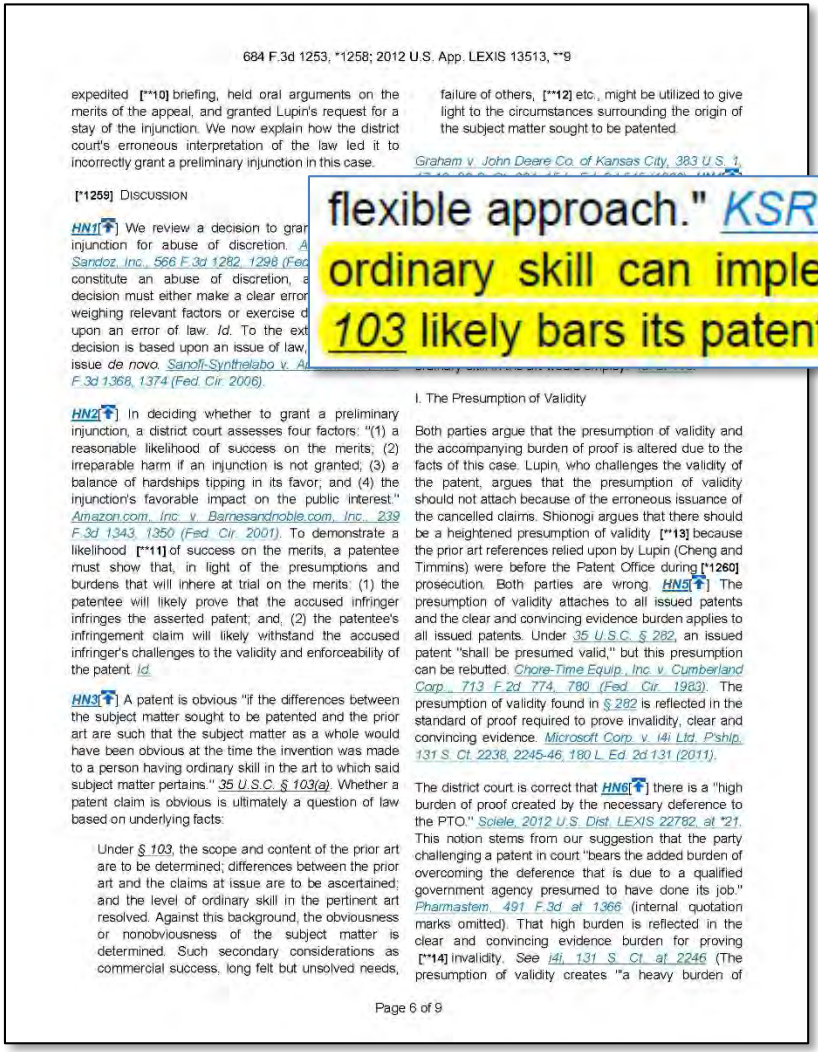
overlaps a disclosed range. In fact, when, as here, the claimed ranges [**11] are completely encompassed by the prior art, the conclusion is even more compelling than in cases of mere overlap. The normal desire of

Source: *In re Peterson*, 315 F.3d 1325, 1329–30 (Fed. Cir. 2003); Paper 1 at 43.

Legal Authority

Sciele Pharma, Inc. v. Lupin Ltd.



684 F.3d 1253, *1258; 2012 U.S. App. LEXIS 13513, **9

expedited [**10] briefing, held oral arguments on the merits of the appeal, and granted Lupin's request for a stay of the injunction. We now explain how the district court's erroneous interpretation of the law led it to incorrectly grant a preliminary injunction in this case.

[*1259] Discussion

HN1[] We review a decision to grar injunction for abuse of discretion. A Sandoz, Inc., 566 F.3d 1282, 1298 (Fed constitute an abuse of discretion, a decision must either make a clear error weighing relevant factors or exercise d upon an error of law. *Id.* To the ext decision is based upon an issue of law, issue *de novo*. Sanofi-Synthelabo v. A F.3d 1368, 1374 (Fed. Cir. 2006).

HN2[] In deciding whether to grant a preliminary injunction, a district court assesses four factors: "(1) a reasonable likelihood of success on the merits; (2) irreparable harm if an injunction is not granted; (3) a balance of hardships tipping in its favor; and (4) the injunction's favorable impact on the public interest." Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1350 (Fed. Cir. 2001). To demonstrate a likelihood [**11] of success on the merits, a patentee must show that, in light of the presumptions and burdens that will inhere at trial on the merits: (1) the patentee will likely prove that the accused infringer infringes the asserted patent; and, (2) the patentee's infringement claim will likely withstand the accused infringer's challenges to the validity and enforceability of the patent. *Id.*

HN3[] A patent is obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Whether a patent claim is obvious is ultimately a question of law based on underlying facts:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, [**12] etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Graham v. John Deere Co. of Kansas City, 383 U.S. 1,

I. The Presumption of Validity

Both parties argue that the presumption of validity and the accompanying burden of proof is altered due to the facts of this case. Lupin, who challenges the validity of the patent, argues that the presumption of validity should not attach because of the erroneous issuance of the cancelled claims. Shionogi argues that there should be a heightened presumption of validity [**13] because the prior art references relied upon by Lupin (Cheng and Timmins) were before the Patent Office during [*1260] prosecution. Both parties are wrong. HN5[] The presumption of validity attaches to all issued patents and the clear and convincing evidence burden applies to all issued patents. Under 35 U.S.C. § 282, an issued patent "shall be presumed valid," but this presumption can be rebutted. Chore-Time Equip., Inc. v. Cumberland Corp., 713 F.2d 774, 780 (Fed. Cir. 1983). The presumption of validity found in § 282 is reflected in the standard of proof required to prove invalidity, clear and convincing evidence. Microsoft Corp. v. i4i Ltd. P'ship, 131 S. Ct. 2238, 2245-46, 180 L. Ed. 2d 131 (2011).

The district court is correct that HN6[] there is a "high burden of proof created by the necessary deference to the PTO." Sciele, 2012 U.S. Dist. LEXIS 22782, at *21. This notion stems from our suggestion that the party challenging a patent in court "bears the added burden of overcoming the deference that is due to a qualified government agency presumed to have done its job." Pharmastem, 491 F.3d at 1366 (internal quotation marks omitted). That high burden is reflected in the clear and convincing evidence burden for proving [**14] invalidity. See i4i, 131 S. Ct. at 2246 (The presumption of validity creates "a heavy burden of

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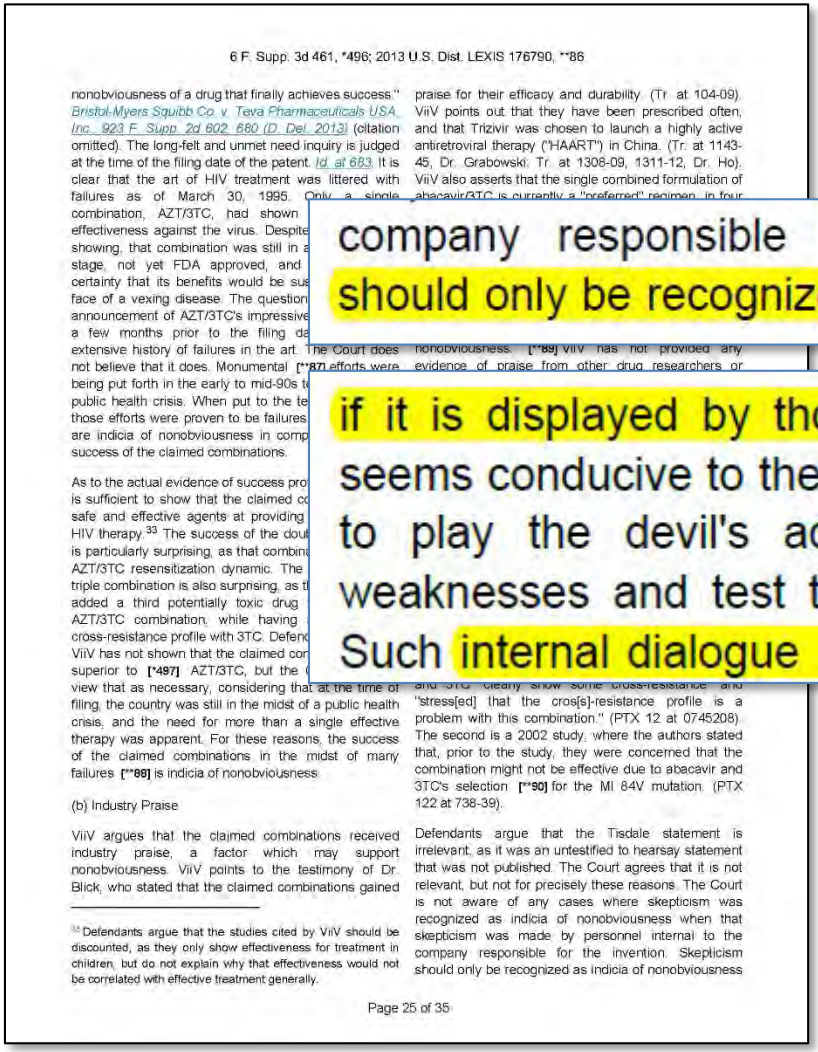
flexible approach." KSR, 550 U.S. at 415. "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." Id. at 417. Ultimately, "a

Source: *Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259 (Fed. Cir. 2012); Paper 1 at 44.

Legal Authority

ViiV Healthcare UK Ltd. v. Lupin Ltd.



6 F. Supp. 3d 461, *496; 2013 U.S. Dist. LEXIS 176790, **86

nonobviousness of a drug that finally achieves success." *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc., 923 F. Supp. 2d 602, 680 (D. Del. 2013)* (citation omitted). The long-felt and unmet need inquiry is judged at the time of the filing date of the patent. *Id. at 683.* It is clear that the art of HIV treatment was littered with failures as of March 30, 1995. Only a single combination, AZT/3TC, had shown effectiveness against the virus. Despite showing, that combination was still in a stage, not yet FDA approved, and certainty that its benefits would be sus face of a vexing disease. The question announcement of AZT/3TC's impressive a few months prior to the filing da extensive history of failures in the art. The Court does not believe that it does. Monumental [**87] efforts were being put forth in the early to mid-90s t public health crisis. When put to the te those efforts were proven to be failures are indicia of nonobviousness in comp success of the claimed combinations.

As to the actual evidence of success pro is sufficient to show that the claimed c safe and effective agents at providing HIV therapy.[33] The success of the dou is particularly surprising, as that combin AZT/3TC resensitization dynamic. The triple combination is also surprising, as t added a third potentially toxic drug AZT/3TC combination, while having cross-resistance profile with 3TC. Defen ViiV has not shown that the claimed cor superior to [*497] AZT/3TC, but the view that as necessary, considering that at the time of filing, the country was still in the midst of a public health crisis, and the need for more than a single effective therapy was apparent. For these reasons, the success of the claimed combinations in the midst of many failures [**88] is indicia of nonobviousness.

(b) Industry Praise

ViiV argues that the claimed combinations received industry praise, a factor which may support nonobviousness. ViiV points to the testimony of Dr. Blick, who stated that the claimed combinations gained praise for their efficacy and durability. (Tr. at 104-09). ViiV points out that they have been prescribed often, and that Trizivir was chosen to launch a highly active antiretroviral therapy ("HAART") in China. (Tr. at 1143-45, Dr. Grabowski; Tr. at 1308-09, 1311-12, Dr. Ho). ViiV also asserts that the single combined formulation of abacavir/3TC is currently a "preferred" regimen in four

[33] Defendants argue that the studies cited by ViiV should be discounted, as they only show effectiveness for treatment in children, but do not explain why that effectiveness would not be correlated with effective treatment generally.

nonobviousness. [**89] ViiV has not provided any evidence of praise from other drug researchers or

and 3TC clearly show some cross-resistance and "stress[ed] that the cros[s]-resistance profile is a problem with this combination." (PTX 12 at 0745208). The second is a 2002 study, where the authors stated that, prior to the study, they were concerned that the combination might not be effective due to abacavir and 3TC's selection [**90] for the M184V mutation. (PTX 122 at 738-39).

Defendants argue that the Tisdale statement is irrelevant, as it was an untestified to hearsay statement that was not published. The Court agrees that it is not relevant, but not for precisely these reasons. The Court is not aware of any cases where skepticism was recognized as indicia of nonobviousness when that skepticism was made by personnel internal to the company responsible for the invention. Skepticism should only be recognized as indicia of nonobviousness

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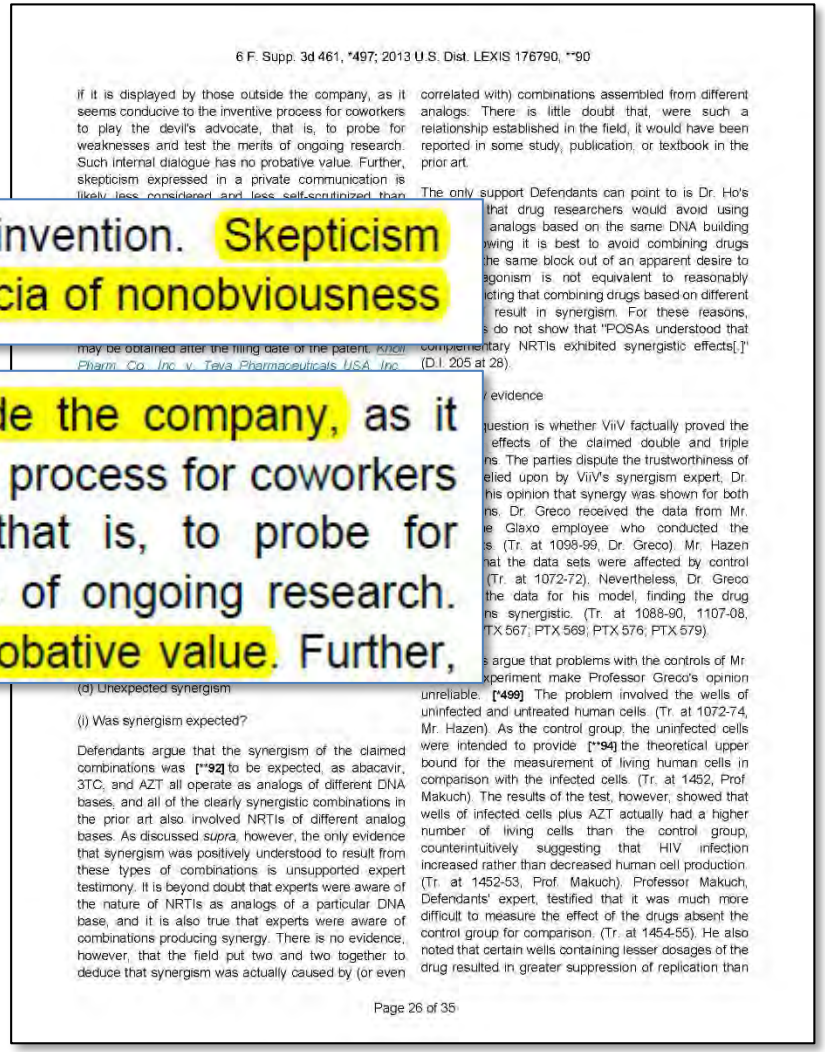
company responsible for the invention. Skepticism should only be recognized as indicia of nonobviousness

if it is displayed by those outside the company, as it seems conducive to the inventive process for coworkers to play the devil's advocate, that is, to probe for weaknesses and test the merits of ongoing research. Such internal dialogue has no probative value. Further,



6 F. Supp. 3d 461, *497; 2013 U.S. Dist. LEXIS 176790, **90

if it is displayed by those outside the company, as it seems conducive to the inventive process for coworkers to play the devil's advocate, that is, to probe for weaknesses and test the merits of ongoing research. Such internal dialogue has no probative value. Further, skepticism expressed in a private communication is likely less considered and less self-scrutinized than

may be obtained after the filing date of the patent. *Knoll Pharm. Co., Inc. v. Teva Pharmaceuticals USA, Inc.*

(d) Unexpected synergism

(i) Was synergism expected?

Defendants argue that the synergism of the claimed combinations was [**92] to be expected, as abacavir, 3TC, and AZT all operate as analogs of different DNA bases, and all of the clearly synergistic combinations in the prior art also involved NRTIs of different analog bases. As discussed *supra*, however, the only evidence that synergism was positively understood to result from these types of combinations is unsupported expert testimony. It is beyond doubt that experts were aware of the nature of NRTIs as analogs of a particular DNA base, and it is also true that experts were aware of combinations producing synergy. There is no evidence, however, that the field put two and two together to deduce that synergism was actually caused by (or even correlated with) combinations assembled from different analogs. There is little doubt that, were such a relationship established in the field, it would have been reported in some study, publication, or textbook in the prior art.

The only support Defendants can point to is Dr. Ho's that drug researchers would avoid using analogs based on the same DNA building owing it is best to avoid combining drugs the same block out of an apparent desire to agonism is not equivalent to reasonably cting that combining drugs based on different result in synergism. For these reasons, s do not show that "POSAs understood that complementary NRTIs exhibited synergistic effects[.]" (D.I. 205 at 28).

evidence

question is whether ViiV factually proved the effects of the claimed double and triple ns. The parties dispute the trustworthiness of elied upon by ViiV's synergism expert, Dr. his opinion that synergy was shown for both ns. Dr. Greco received the data from Mr. e Glaxo employee who conducted the s. (Tr. at 1098-99, Dr. Greco). Mr. Hazen at the data sets were affected by control (Tr. at 1072-72). Nevertheless, Dr. Greco the data for his model, finding the drug ns synergistic. (Tr. at 1088-90, 1107-08, TX 567; PTX 569; PTX 576; PTX 579).

s argue that problems with the controls of Mr. xperiment make Professor Greco's opinion unreliable. [**99] The problem involved the wells of uninfected and untreated human cells. (Tr. at 1072-74, Mr. Hazen). As the control group, the uninfected cells were intended to provide [**94] the theoretical upper bound for the measurement of living human cells in comparison with the infected cells. (Tr. at 1452, Prof. Makuch). The results of the test, however, showed that wells of infected cells plus AZT actually had a higher number of living cells than the control group, counterintuitively suggesting that HIV infection increased rather than decreased human cell production. (Tr. at 1452-53, Prof. Makuch). Professor Makuch, Defendants' expert, testified that it was much more difficult to measure the effect of the drugs absent the control group for comparison. (Tr. at 1454-55). He also noted that certain wells containing lesser dosages of the drug resulted in greater suppression of replication than

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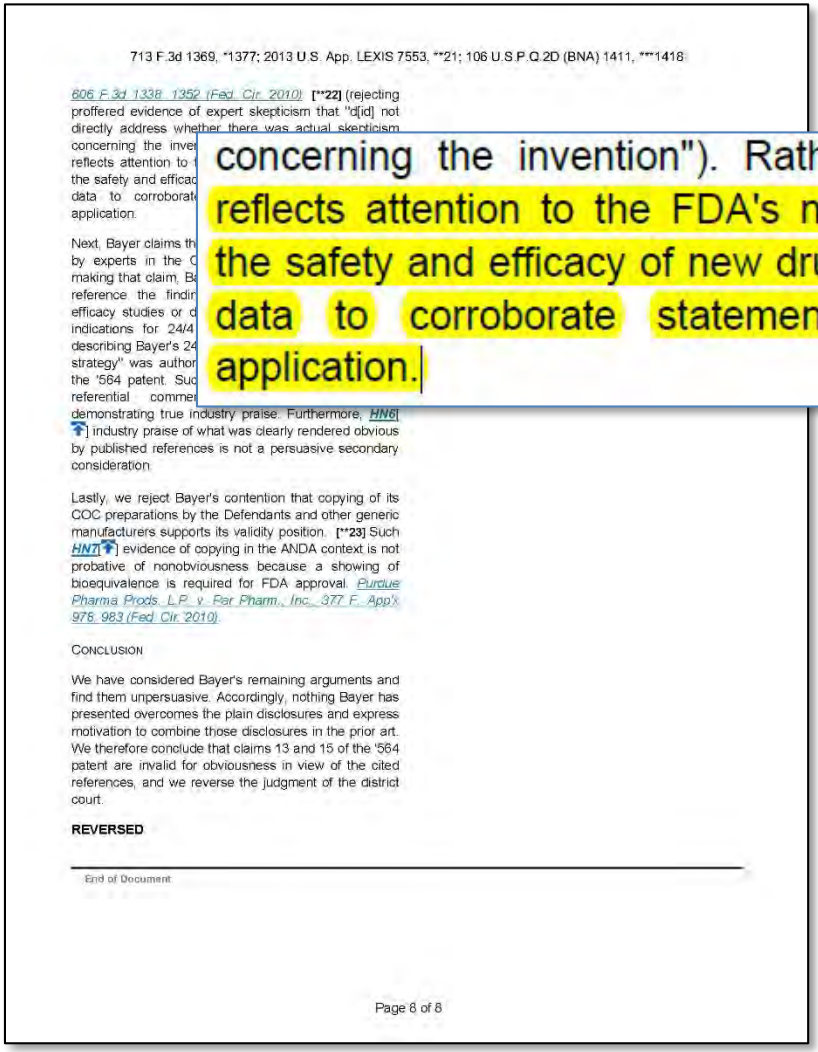
Source: *ViiV Healthcare UK Ltd. v. Lupin Ltd.*, 6 F. Supp. 3d 461, 497 (D. Del. 2013); Paper 48 at 32.

Legal Authority

Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.



713 F.3d 1369, *1377; 2013 U.S. App. LEXIS 7553, **21; 106 U.S.P.Q.2D (BNA) 1411, ***1418

606 F.3d 1338, 1352 (Fed. Cir. 2010). [**22] (rejecting proffered evidence of expert skepticism that "d[id] not directly address whether there was actual skepticism concerning the inve... reflects attention to t... the safety and efficac... data to corroborat... application.

Next, Bayer claims th... by experts in the ... making that claim, Ba... reference the findin... efficacy studies or d... indications for 24/4... describing Bayer's 24... strategy" was author... the '564 patent. Suc... referential comme... demonstrating true industry praise. Furthermore, HN6[ ] industry praise of what was clearly rendered obvious by published references is not a persuasive secondary consideration.

Lastly, we reject Bayer's contention that copying of its COC preparations by the Defendants and other generic manufacturers supports its validity position. [**23] Such HN7[ ] evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval. Purdue Pharma Prods. L.P. v. Par Pharm., Inc., 377 F. App'x 976, 983 (Fed. Cir. 2010).

CONCLUSION

We have considered Bayer's remaining arguments and find them unpersuasive. Accordingly, nothing Bayer has presented overcomes the plain disclosures and express motivation to combine those disclosures in the prior art. We therefore conclude that claims 13 and 15 of the '564 patent are invalid for obviousness in view of the cited references, and we reverse the judgment of the district court.

REVERSED

End of Document

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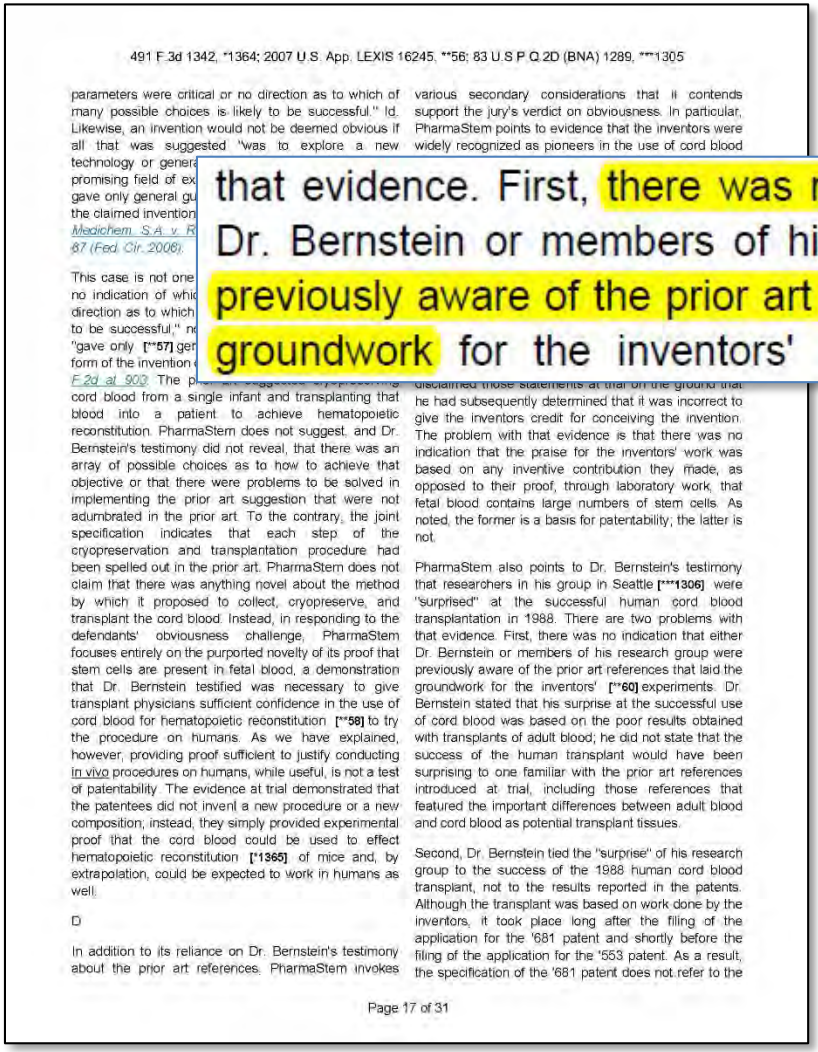
concerning the invention"). Rather, the cited request reflects attention to the FDA's normal duties ensuring the safety and efficacy of new drugs by requiring actual data to corroborate statements in a new drug application.

Source: *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013)*; Paper 48 at 33.

Legal Authority

Pharmastem Therapeutics, Inc. v. Viacell, Inc.



491 F.3d 1342, *1364; 2007 U.S. App. LEXIS 16245, **56; 83 U.S.P.Q.2D (BNA) 1289, ***1305

parameters were critical or no direction as to which of many possible choices is likely to be successful." Id. Likewise, an invention would not be deemed obvious if all that was suggested "was to explore a new technology or genera promising field of ex gave only general gu the claimed invention *Medichem, S.A. v. R 87 (Fed. Cir. 2006).*

This case is not one no indication of whic direction as to which to be successful," n "gave only [**57] ger form of the invention *F.2d at 903.* The p cord blood from a single infant and transplanting that blood into a patient to achieve hematopoietic reconstitution. PharmaStem does not suggest, and Dr. Bernstein's testimony did not reveal, that there was an array of possible choices as to how to achieve that objective or that there were problems to be solved in implementing the prior art suggestion that were not adumbrated in the prior art. To the contrary, the joint specification indicates that each step of the cryopreservation and transplantation procedure had been spelled out in the prior art. PharmaStem does not claim that there was anything novel about the method by which it proposed to collect, cryopreserve, and transplant the cord blood. Instead, in responding to the defendants' obviousness challenge, PharmaStem focuses entirely on the purported novelty of its proof that stem cells are present in fetal blood, a demonstration that Dr. Bernstein testified was necessary to give transplant physicians sufficient confidence in the use of cord blood for hematopoietic reconstitution [**58] to try the procedure on humans. As we have explained, however, providing proof sufficient to justify conducting in vivo procedures on humans, while useful, is not a test of patentability. The evidence at trial demonstrated that the patentees did not invent a new procedure or a new composition; instead, they simply provided experimental proof that the cord blood could be used to effect hematopoietic reconstitution [*1365] of mice and, by extrapolation, could be expected to work in humans as well.

D

In addition to its reliance on Dr. Bernstein's testimony about the prior art references, PharmaStem invokes various secondary considerations that it contends support the jury's verdict on obviousness. In particular, PharmaStem points to evidence that the inventors were widely recognized as pioneers in the use of cord blood

that evidence. First, there was no indication that either Dr. Bernstein or members of his research group were previously aware of the prior art references that laid the groundwork for the inventors' [**60] experiments. Dr.

disclaimed those statements at trial on the ground that he had subsequently determined that it was incorrect to give the inventors credit for conceiving the invention. The problem with that evidence is that there was no indication that the praise for the inventors' work was based on any inventive contribution they made, as opposed to their proof, through laboratory work, that fetal blood contains large numbers of stem cells. As noted, the former is a basis for patentability; the latter is not.

PharmaStem also points to Dr. Bernstein's testimony that researchers in his group in Seattle [***1306] were "surprised" at the successful human cord blood transplantation in 1988. There are two problems with that evidence. First, there was no indication that either Dr. Bernstein or members of his research group were previously aware of the prior art references that laid the groundwork for the inventors' [**60] experiments. Dr. Bernstein stated that his surprise at the successful use of cord blood was based on the poor results obtained with transplants of adult blood; he did not state that the success of the human transplant would have been surprising to one familiar with the prior art references introduced at trial, including those references that featured the important differences between adult blood and cord blood as potential transplant tissues.

Second, Dr. Bernstein tied the "surprise" of his research group to the success of the 1988 human cord blood transplant, not to the results reported in the patents. Although the transplant was based on work done by the inventors, it took place long after the filing of the application for the '681 patent and shortly before the filing of the application for the '553 patent. As a result, the specification of the '681 patent does not refer to the

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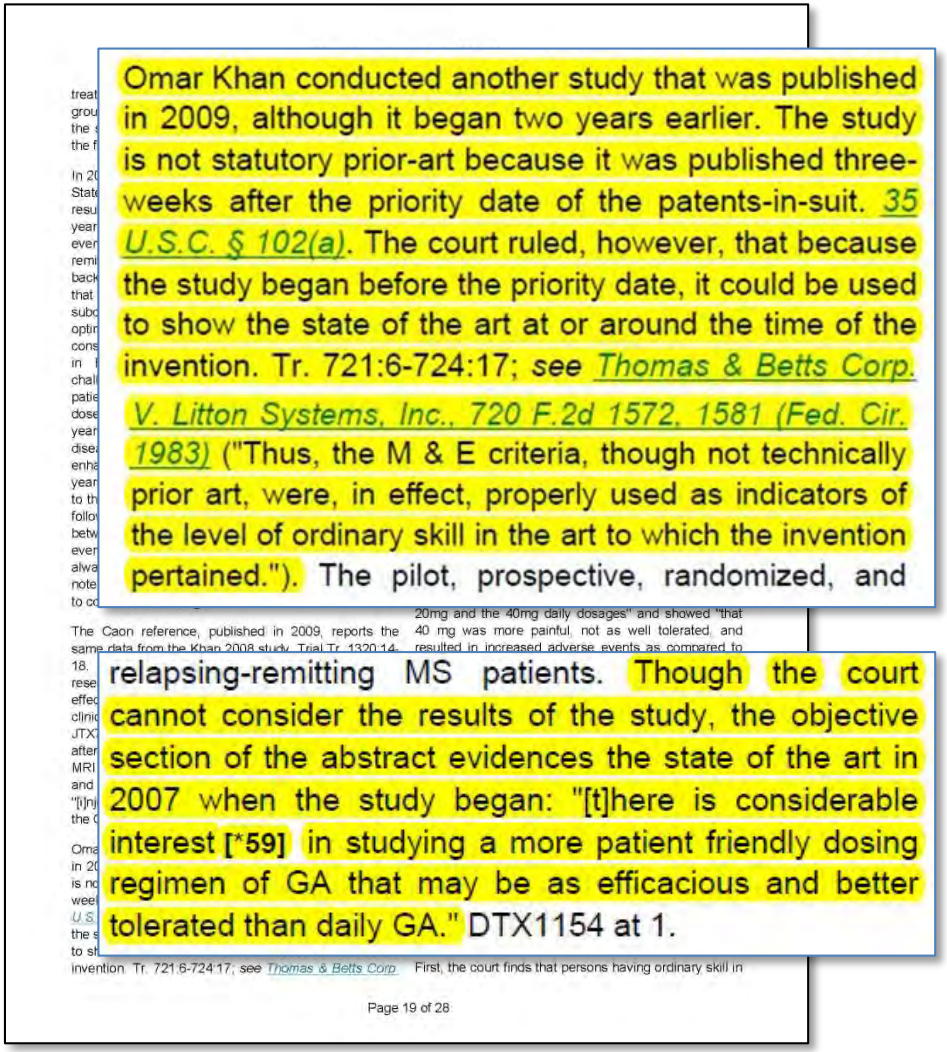
Source: *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342; Paper 48 at 11, 32, 33.

Legal Authority

In re Copaxone Consol. Cases



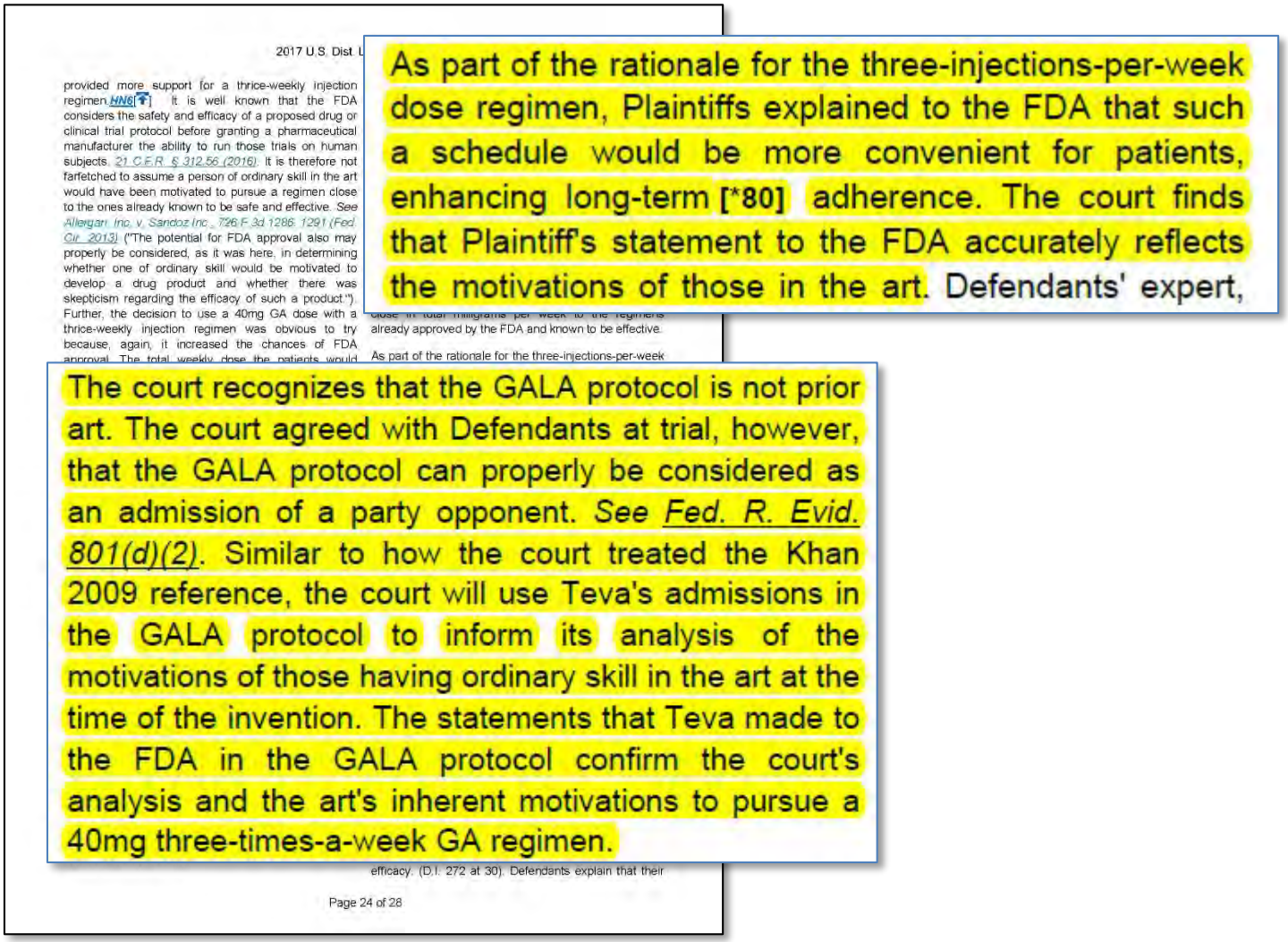
Omar Khan conducted another study that was published in 2009, although it began two years earlier. The study is not statutory prior-art because it was published three-weeks after the priority date of the patents-in-suit. *35 U.S.C. § 102(a)*. The court ruled, however, that because the study began before the priority date, it could be used to show the state of the art at or around the time of the invention. Tr. 721:6-724:17; *see Thomas & Betts Corp. V. Litton Systems, Inc., 720 F.2d 1572, 1581 (Fed. Cir. 1983)* ("Thus, the M & E criteria, though not technically prior art, were, in effect, properly used as indicators of the level of ordinary skill in the art to which the invention pertained."). The pilot, prospective, randomized, and relapsing-remitting MS patients. Though the court cannot consider the results of the study, the objective section of the abstract evidences the state of the art in 2007 when the study began: "[t]here is considerable interest [*59] in studying a more patient friendly dosing regimen of GA that may be as efficacious and better tolerated than daily GA." DTX1154 at 1.

Page 19 of 28

Source: *In re Copaxone Consol. Cases*, 2017 U.S. Dist. LEXIS 12168 at *58-59 (D. Del. Jan. 30, 2017); Paper 57 at 4-5.

Legal Authority

In re Copaxone Consol. Cases



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provided more support for a thrice-weekly injection regimen.HN6[↑] It is well known that the FDA considers the safety and efficacy of a proposed drug or clinical trial protocol before granting a pharmaceutical manufacturer the ability to run those trials on human subjects. 21 C.F.R. § 312.56 (2016). It is therefore not farfetched to assume a person of ordinary skill in the art would have been motivated to pursue a regimen close to the ones already known to be safe and effective. *See Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013) ("The potential for FDA approval also may properly be considered, as it was here, in determining whether one of ordinary skill would be motivated to develop a drug product and whether there was skepticism regarding the efficacy of such a product."). Further, the decision to use a 40mg GA dose with a thrice-weekly injection regimen was obvious to try because, again, it increased the chances of FDA approval. The total weekly dose the patients would

already approved by the FDA and known to be effective.

As part of the rationale for the three-injections-per-week dose regimen, Plaintiffs explained to the FDA that such a schedule would be more convenient for patients, enhancing long-term [*80] adherence. The court finds that Plaintiff's statement to the FDA accurately reflects the motivations of those in the art. Defendants' expert,

The court recognizes that the GALA protocol is not prior art. The court agreed with Defendants at trial, however, that the GALA protocol can properly be considered as an admission of a party opponent. *See Fed. R. Evid. 801(d)(2)*. Similar to how the court treated the Khan 2009 reference, the court will use Teva's admissions in the GALA protocol to inform its analysis of the motivations of those having ordinary skill in the art at the time of the invention. The statements that Teva made to the FDA in the GALA protocol confirm the court's analysis and the art's inherent motivations to pursue a 40mg three-times-a-week GA regimen.

efficacy. (D.I. 272 at 30). Defendants explain that their

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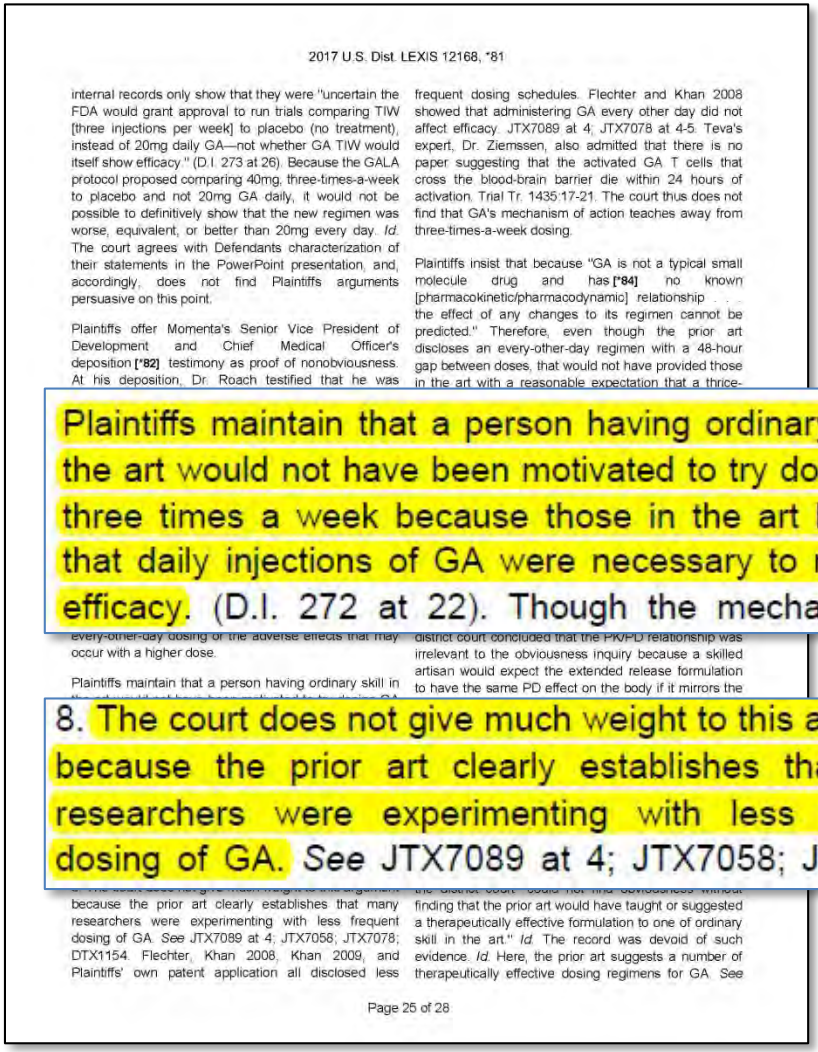
Source: *In re Copaxone Consol. Cases*, 2017 U.S. Dist. LEXIS 12168 at *78 (D. Del. Jan. 30, 2017); Paper 57 at 4-5.

Legal Authority

In re Copaxone Consol. Cases



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internal records only show that they were "uncertain the FDA would grant approval to run trials comparing TIW [three injections per week] to placebo (no treatment), instead of 20mg daily GA—not whether GA TIW would itself show efficacy." (D.I. 273 at 26). Because the GALA protocol proposed comparing 40mg, three-times-a-week to placebo and not 20mg GA daily, it would not be possible to definitively show that the new regimen was worse, equivalent, or better than 20mg every day. *Id.* The court agrees with Defendants characterization of their statements in the PowerPoint presentation, and, accordingly, does not find Plaintiffs arguments persuasive on this point.

Plaintiffs offer Momenta's Senior Vice President of Development and Chief Medical Officer's deposition **[*82]** testimony as proof of nonobviousness. At his deposition, Dr. Roach testified that he was

frequent dosing schedules. Flechter and Khan 2008 showed that administering GA every other day did not affect efficacy. JTX7089 at 4; JTX7078 at 4-5. Teva's expert, Dr. Ziemssen, also admitted that there is no paper suggesting that the activated GA T cells that cross the blood-brain barrier die within 24 hours of activation. Trial Tr. 1435:17-21. The court thus does not find that GA's mechanism of action teaches away from three-times-a-week dosing.

Plaintiffs insist that because "GA is not a typical small molecule drug and has **[*84]** no known [pharmacokinetic/pharmacodynamic] relationship . . . the effect of any changes to its regimen cannot be predicted." Therefore, even though the prior art discloses an every-other-day regimen with a 48-hour gap between doses, that would not have provided those in the art with a reasonable expectation that a thrice-

Plaintiffs maintain that a person having ordinary skill in the art would not have been motivated to try dosing GA three times a week because those in the art believed that daily injections of GA were necessary to maintain efficacy. (D.I. 272 at 22). Though the mechanism of

every-other-day dosing of the adverse effects that may occur with a higher dose.

Plaintiffs maintain that a person having ordinary skill in

8. The court does not give much weight to this argument because the prior art clearly establishes that many researchers were experimenting with less frequent dosing of GA. *See* JTX7089 at 4; JTX7058; JTX7078;

because the prior art clearly establishes that many researchers were experimenting with less frequent dosing of GA. *See* JTX7089 at 4; JTX7058; JTX7078; DTX1154. Flechter, Khan 2008, Khan 2009, and Plaintiffs' own patent application all disclosed less

district court concluded that the PK/PD relationship was irrelevant to the obviousness inquiry because a skilled artisan would expect the extended release formulation to have the same PD effect on the body if it mirrors the

finding that the prior art would have taught or suggested a therapeutically effective formulation to one of ordinary skill in the art." *Id.* The record was devoid of such evidence. *Id.* Here, the prior art suggests a number of therapeutically effective dosing regimens for GA. *See*

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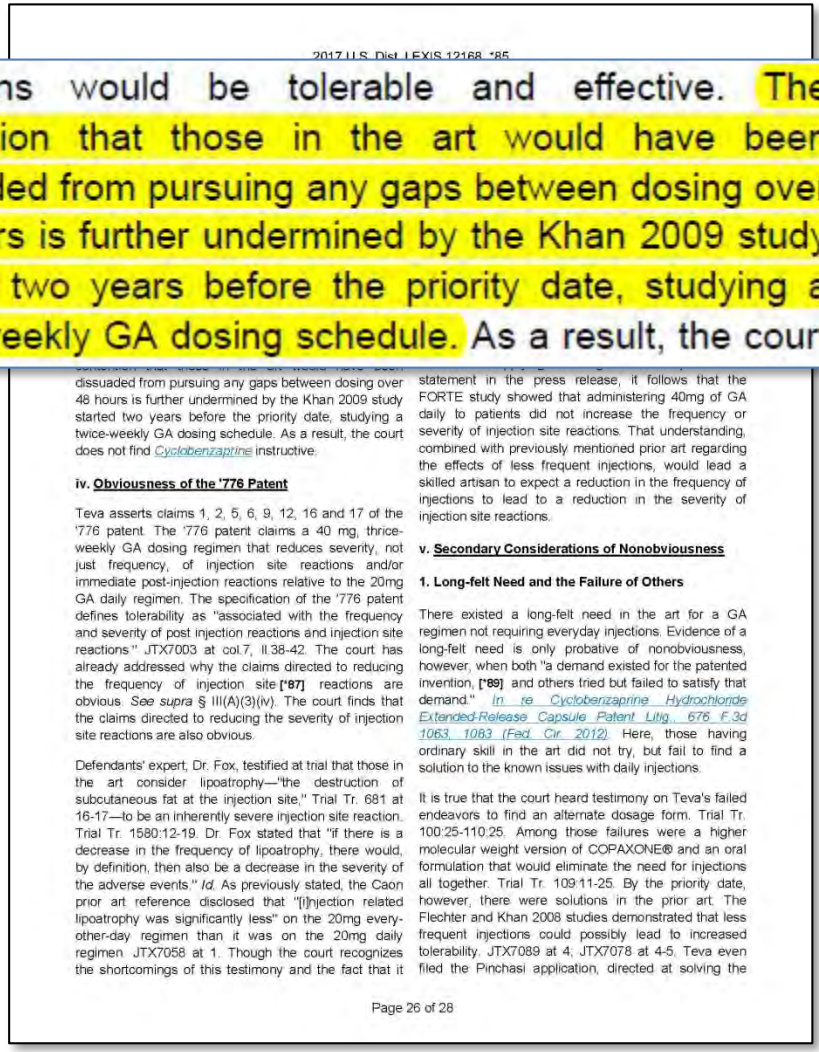

injections would be tolerable and effective. The contention that those in the art would have been dissuaded from pursuing any gaps between dosing over 48 hours is further undermined by the Khan 2009 study started two years before the priority date, studying a twice-weekly GA dosing schedule. As a result, the court

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dissuaded from pursuing any gaps between dosing over 48 hours is further undermined by the Khan 2009 study started two years before the priority date, studying a twice-weekly GA dosing schedule. As a result, the court does not find Cyclobenzaprine instructive.

iv. Obviousness of the '776 Patent

Teva asserts claims 1, 2, 5, 6, 9, 12, 16 and 17 of the '776 patent. The '776 patent claims a 40 mg, thrice-weekly GA dosing regimen that reduces severity, not just frequency, of injection site reactions and/or immediate post-injection reactions relative to the 20mg GA daily regimen. The specification of the '776 patent defines tolerability as "associated with the frequency and severity of post injection reactions and injection site reactions." JTX7003 at col.7, ll.38-42. The court has already addressed why the claims directed to reducing the frequency of injection site **[*87]** reactions are obvious. *See supra* § III(A)(3)(iv). The court finds that the claims directed to reducing the severity of injection site reactions are also obvious.

Defendants' expert, Dr. Fox, testified at trial that those in the art consider lipoatrophy—"the destruction of subcutaneous fat at the injection site," Trial Tr. 681 at 16-17—to be an inherently severe injection site reaction. Trial Tr. 1580:12-19. Dr. Fox stated that "if there is a decrease in the frequency of lipoatrophy, there would, by definition, then also be a decrease in the severity of the adverse events." *Id.* As previously stated, the Caon prior art reference disclosed that "[i]njection related lipoatrophy was significantly less" on the 20mg every-other-day regimen than it was on the 20mg daily regimen. JTX7058 at 1. Though the court recognizes the shortcomings of this testimony and the fact that it

statement in the press release, it follows that the FORTE study showed that administering 40mg of GA daily to patients did not increase the frequency or severity of injection site reactions. That understanding, combined with previously mentioned prior art regarding the effects of less frequent injections, would lead a skilled artisan to expect a reduction in the frequency of injections to lead to a reduction in the severity of injection site reactions.

v. Secondary Considerations of Nonobviousness

1. Long-felt Need and the Failure of Others

There existed a long-felt need in the art for a GA regimen not requiring everyday injections. Evidence of a long-felt need is only probative of nonobviousness, however, when both "a demand existed for the patented invention, **[*89]** and others tried but failed to satisfy that demand." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1083 (Fed. Cir. 2012).* Here, those having ordinary skill in the art did not try, but fail to find a solution to the known issues with daily injections.

It is true that the court heard testimony on Teva's failed endeavors to find an alternate dosage form. Trial Tr. 100:25-110:25. Among those failures were a higher molecular weight version of COPAXONE® and an oral formulation that would eliminate the need for injections all together. Trial Tr. 109:11-25. By the priority date, however, there were solutions in the prior art. The Flechter and Khan 2008 studies demonstrated that less frequent injections could possibly lead to increased tolerability. JTX7089 at 4; JTX7078 at 4-5. Teva even filed the Pinchasi application, directed at solving the

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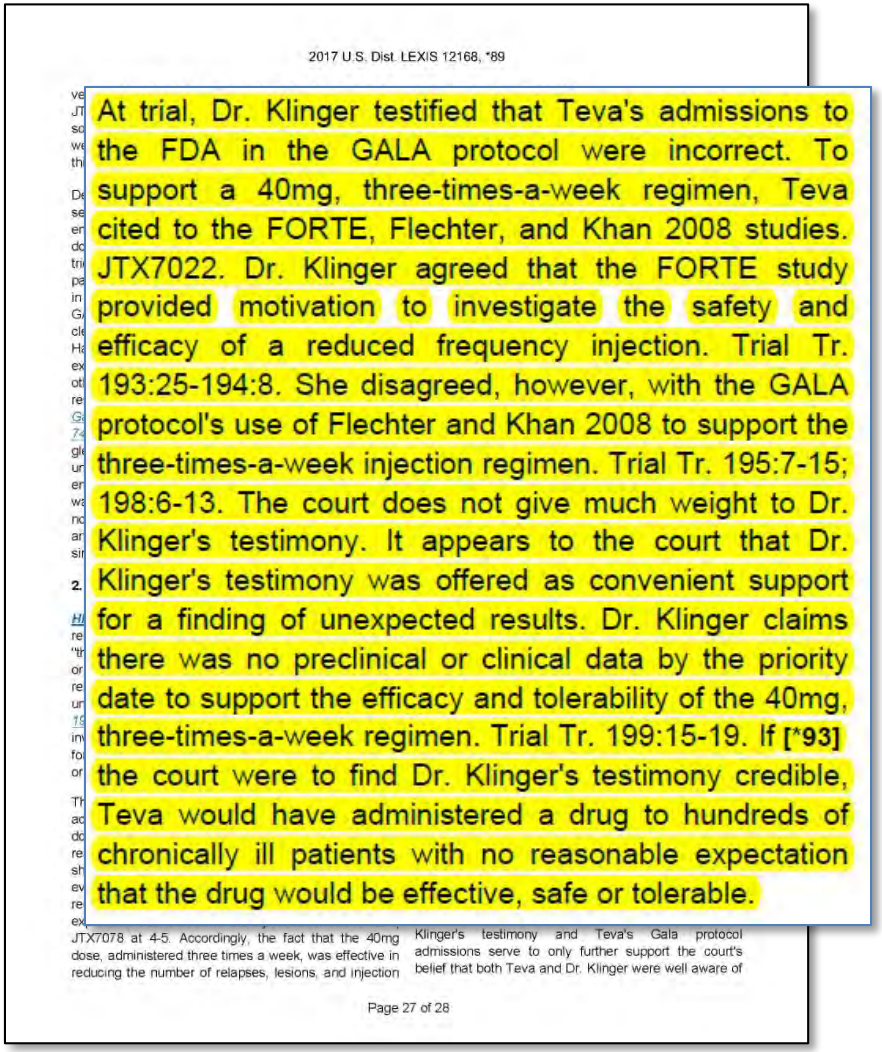
Source: *In re Copaxone Consol. Cases*, 2017 U.S. Dist. LEXIS 12168 at *82-83, 86 (D. Del. Jan. 30, 2017); Paper 57 at 4-5.

Legal Authority

In re Copaxone Consol. Cases



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At trial, Dr. Klinger testified that Teva's admissions to the FDA in the GALA protocol were incorrect. To support a 40mg, three-times-a-week regimen, Teva cited to the FORTE, Flechter, and Khan 2008 studies. JTX7022. Dr. Klinger agreed that the FORTE study provided motivation to investigate the safety and efficacy of a reduced frequency injection. Trial Tr. 193:25-194:8. She disagreed, however, with the GALA protocol's use of Flechter and Khan 2008 to support the three-times-a-week injection regimen. Trial Tr. 195:7-15; 198:6-13. The court does not give much weight to Dr. Klinger's testimony. It appears to the court that Dr. Klinger's testimony was offered as convenient support for a finding of unexpected results. Dr. Klinger claims there was no preclinical or clinical data by the priority date to support the efficacy and tolerability of the 40mg, three-times-a-week regimen. Trial Tr. 199:15-19. If [*93] the court were to find Dr. Klinger's testimony credible, Teva would have administered a drug to hundreds of chronically ill patients with no reasonable expectation that the drug would be effective, safe or tolerable.

JTX7078 at 4-5. Accordingly, the fact that the 40mg dose, administered three times a week, was effective in reducing the number of relapses, lesions, and injection

Klinger's testimony and Teva's Gala protocol admissions serve to only further support the court's belief that both Teva and Dr. Klinger were well aware of

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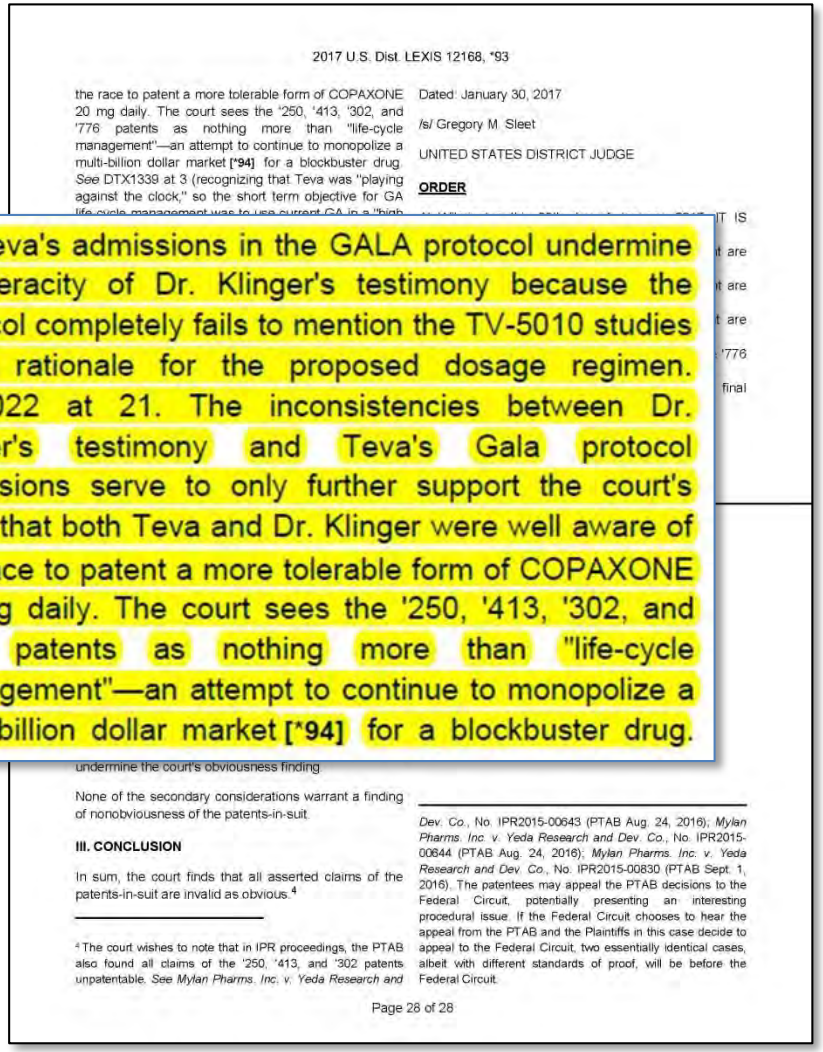

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the race to patent a more tolerable form of COPAXONE 20 mg daily. The court sees the '250, '413, '302, and '776 patents as nothing more than "life-cycle management"—an attempt to continue to monopolize a multi-billion dollar market [*94] for a blockbuster drug. *See* DTX1339 at 3 (recognizing that Teva was "playing against the clock," so the short term objective for GA

Dated: January 30, 2017

/s/ Gregory M. Sleet

UNITED STATES DISTRICT JUDGE

ORDER

18. Teva's admissions in the GALA protocol undermine the veracity of Dr. Klinger's testimony because the protocol completely fails to mention the TV-5010 studies as a rationale for the proposed dosage regimen. JTX7022 at 21. The inconsistencies between Dr. Klinger's testimony and Teva's Gala protocol admissions serve to only further support the court's belief that both Teva and Dr. Klinger were well aware of the race to patent a more tolerable form of COPAXONE 20 mg daily. The court sees the '250, '413, '302, and '776 patents as nothing more than "life-cycle management"—an attempt to continue to monopolize a multi-billion dollar market [*94] for a blockbuster drug.

undermine the court's obviousness finding

None of the secondary considerations warrant a finding of nonobviousness of the patents-in-suit.

III. CONCLUSION

In sum, the court finds that all asserted claims of the patents-in-suit are invalid as obvious.[4]

[4] The court wishes to note that in IPR proceedings, the PTAB also found all claims of the '250, '413, and '302 patents unpatentable. *See Mylan Pharms. Inc. v. Yeda Research and*

Dev. Co., No. IPR2015-00643 (PTAB Aug. 24, 2016); *Mylan Pharms. Inc. v. Yeda Research and Dev. Co.*, No. IPR2015-00644 (PTAB Aug. 24, 2016); *Mylan Pharms. Inc. v. Yeda Research and Dev. Co.*, No. IPR2015-00830 (PTAB Sept. 1, 2016). The patentees may appeal the PTAB decisions to the Federal Circuit, potentially presenting an interesting procedural issue. If the Federal Circuit chooses to hear the appeal from the PTAB and the Plaintiffs in this case decide to appeal to the Federal Circuit, two essentially identical cases, albeit with different standards of proof, will be before the Federal Circuit.

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Source: *In re Copaxone Consol. Cases*, 2017 U.S. Dist. LEXIS 12168 at *92-94 (D. Del. Jan. 30, 2017); Paper 57 at 4-5.

Legal Authority

Noven Pharm., Inc. v. Novartis AG

Federal Circuit's holding in *Watson* that "'susceptibility' to oxidative degradation would not have motivated a person of ordinary skill in the art to add an antioxidant to the transdermal formulation in Enz." *Id.* at 9–10.

We have carefully reviewed Patent Owner's arguments presented in the Request for Rehearing, but do not find them persuasive. In particular, the Decision squarely addresses the Federal Circuit's decision in *Watson* and explains why that decision does not control in this proceeding. Final Dec. 4–5. Specifically, we stated:

> The Federal Circuit's *Watson* decision does not control here because Noven has presented additional prior art and declaratory evidence that was not before the Court in *Watson*. Moreover, in an *inter partes* review, a petitioner's burden of proving unpatentability is by a preponderance of the evidence rather than by clear and convincing evidence, as required in district court litigation. Thus, while we have considered the Federal Circuit's decision, we have independently analyzed patentability of the challenged claims based on the evidence and standards that are applicable to this proceeding.

Id.

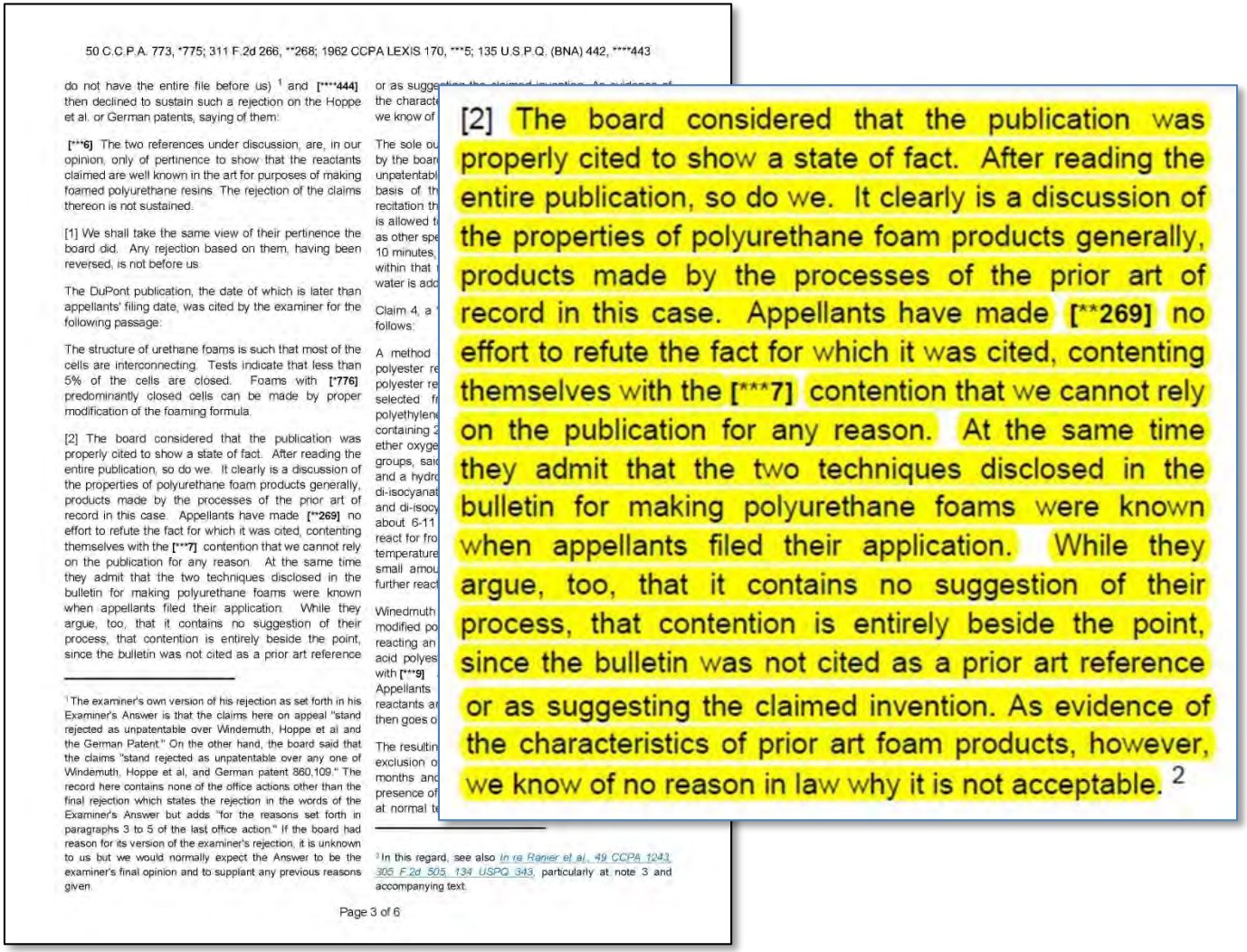
Significantly, the Federal Circuit noted that "[t]he district court admitted that there 'does not appear to be an objectively 'correct' reading [of Elmalem]," rather both arguments regarding whether Elmalem teaches or

However, the deference a district court receives for expert credibility determinations is accorded by the Federal Circuit reviewing an appeal from the district court, not by the Board in an *inter partes* trial proceeding.

Source: *Noven Pharm., Inc. v. Novartis AG*, IPR2014-00550, Paper 77 at 4 n.8; Paper 74 at 1.

Legal Authority

In re Wilson



50 C.C.P.A. 773, *775; 311 F.2d 266, **268; 1962 CCPA LEXIS 170, ***5; 135 U.S.P.Q. (BNA) 442, ****443

do not have the entire file before us) [1] and [****444] then declined to sustain such a rejection on the Hoppe et al. or German patents, saying of them:

[***6] The two references under discussion, are, in our opinion, only of pertinence to show that the reactants claimed are well known in the art for purposes of making foamed polyurethane resins. The rejection of the claims thereon is not sustained.

[1] We shall take the same view of their pertinence the board did. Any rejection based on them, having been reversed, is not before us.

The DuPont publication, the date of which is later than appellants' filing date, was cited by the examiner for the following passage:

The structure of urethane foams is such that most of the cells are interconnecting. Tests indicate that less than 5% of the cells are closed. Foams with [*776] predominantly closed cells can be made by proper modification of the foaming formula.

[2] The board considered that the publication was properly cited to show a state of fact. After reading the entire publication, so do we. It clearly is a discussion of the properties of polyurethane foam products generally, products made by the processes of the prior art of record in this case. Appellants have made [**269] no effort to refute the fact for which it was cited, contenting themselves with the [***7] contention that we cannot rely on the publication for any reason. At the same time they admit that the two techniques disclosed in the bulletin for making polyurethane foams were known when appellants filed their application. While they argue, too, that it contains no suggestion of their process, that contention is entirely beside the point, since the bulletin was not cited as a prior art reference

[1] The examiner's own version of his rejection as set forth in his Examiner's Answer is that the claims here on appeal "stand rejected as unpatentable over Windemuth, Hoppe et al and the German Patent." On the other hand, the board said that the claims "stand rejected as unpatentable over any one of Windemuth, Hoppe et al, and German patent 860,109." The record here contains none of the office actions other than the final rejection which states the rejection in the words of the Examiner's Answer but adds "for the reasons set forth in paragraphs 3 to 5 of the last office action." If the board had reason for its version of the examiner's rejection, it is unknown to us but we would normally expect the Answer to be the examiner's final opinion and to supplant any previous reasons given.

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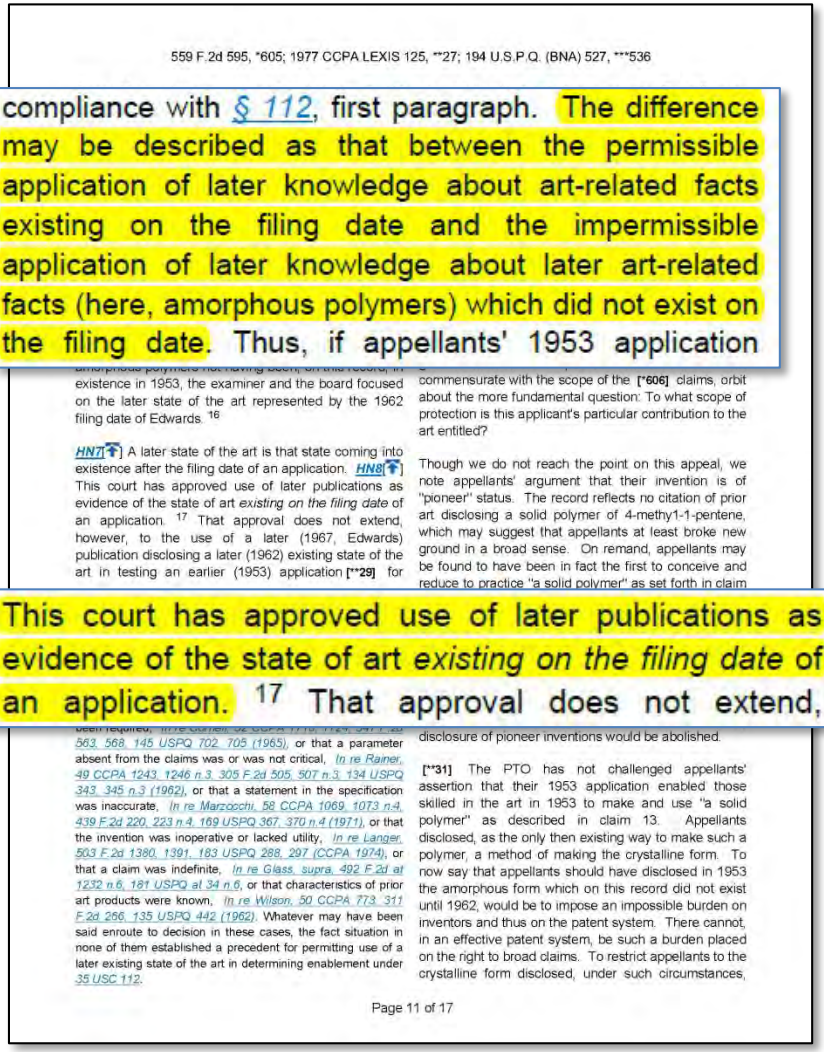
[2] The board considered that the publication was properly cited to show a state of fact. After reading the entire publication, so do we. It clearly is a discussion of the properties of polyurethane foam products generally, products made by the processes of the prior art of record in this case. Appellants have made [**269] no effort to refute the fact for which it was cited, contenting themselves with the [***7] contention that we cannot rely on the publication for any reason. At the same time they admit that the two techniques disclosed in the bulletin for making polyurethane foams were known when appellants filed their application. While they argue, too, that it contains no suggestion of their process, that contention is entirely beside the point, since the bulletin was not cited as a prior art reference or as suggesting the claimed invention. As evidence of the characteristics of prior art foam products, however, we know of no reason in law why it is not acceptable. [2]

Source: *In re Wilson*, 311 F.2d 266, 268-69 (C.C.P.A. 1962); Paper 48 at 6.

Legal Authority

In re Hogan



559 F.2d 595, *605; 1977 CCPA LEXIS 125, **27; 194 U.S.P.Q. (BNA) 527, ***536

compliance with § 112, first paragraph. The difference may be described as that between the permissible application of later knowledge about art-related facts existing on the filing date and the impermissible application of later knowledge about later art-related facts (here, amorphous polymers) which did not exist on the filing date. Thus, if appellants' 1953 application

existence in 1953, the examiner and the board focused on the later state of the art represented by the 1962 filing date of Edwards. [16]

HN7[↑] A later state of the art is that state coming into existence after the filing date of an application. HN8[↑] This court has approved use of later publications as evidence of the state of art *existing on the filing date* of an application. [17] That approval does not extend, however, to the use of a later (1967, Edwards) publication disclosing a later (1962) existing state of the art in testing an earlier (1953) application [**29] for

commensurate with the scope of the [*606] claims, orbit about the more fundamental question: To what scope of protection is this applicant's particular contribution to the art entitled?

Though we do not reach the point on this appeal, we note appellants' argument that their invention is of "pioneer" status. The record reflects no citation of prior art disclosing a solid polymer of 4-methy1-1-pentene, which may suggest that appellants at least broke new ground in a broad sense. On remand, appellants may be found to have been in fact the first to conceive and reduce to practice "a solid polymer" as set forth in claim

This court has approved use of later publications as evidence of the state of art *existing on the filing date* of an application. [17] That approval does not extend,

disclosure of pioneer inventions would be abolished.

[**31] The PTO has not challenged appellants' assertion that their 1953 application enabled those skilled in the art in 1953 to make and use "a solid polymer" as described in claim 13. Appellants disclosed, as the only then existing way to make such a polymer, a method of making the crystalline form. To now say that appellants should have disclosed in 1953 the amorphous form which on this record did not exist until 1962, would be to impose an impossible burden on inventors and thus on the patent system. There cannot, in an effective patent system, be such a burden placed on the right to broad claims. To restrict appellants to the crystalline form disclosed, under such circumstances,

563, 568, 145 USPQ 702, 705 (1965), or that a parameter absent from the claims was or was not critical, In re Rainer, 49 CCPA 1243, 1246 n.3, 305 F.2d 505, 507 n.3, 134 USPQ 343, 345 n.3 (1962), or that a statement in the specification was inaccurate, In re Marzocchi, 58 CCPA 1069, 1073 n.4, 439 F.2d 220, 223 n.4, 169 USPQ 367, 370 n.4 (1971), or that the invention was inoperative or lacked utility, In re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974), or that a claim was indefinite, In re Glass, supra, 492 F.2d at 1232 n.6, 181 USPQ at 34 n.6, or that characteristics of prior art products were known, In re Wilson, 50 CCPA 773, 311 F.2d 266, 135 USPQ 442 (1962). Whatever may have been said enroute to decision in these cases, the fact situation in none of them established a precedent for permitting use of a later existing state of the art in determining enablement under 35 USC 112.

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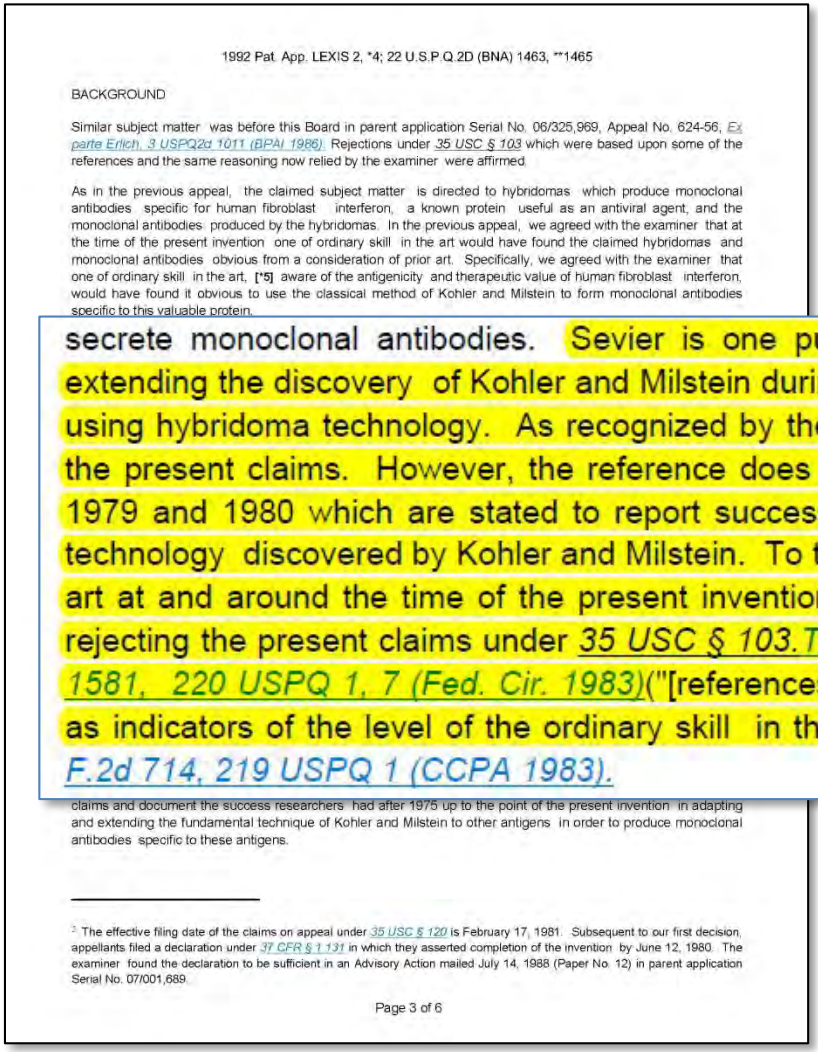
[17] Where, for example, a later publication evidenced that, *as of an application's filing date*, undue experimentation would have been required, *In re Corneil, 52 CCPA 1718, 1724, 347 F.2d 563, 568, 145 USPQ 702, 705 (1965)*, or that a parameter absent from the claims was or was not critical, *In re Rainer, 49 CCPA 1243, 1246 n.3, 305 F.2d 505, 507 n.3, 134 USPQ 343, 345 n.3 (1962)*, or that a statement in the specification was inaccurate, *In re Marzocchi, 58 CCPA 1069, 1073 n.4, 439 F.2d 220, 223 n.4, 169 USPQ 367, 370 n.4 (1971)*, or that the invention was inoperative or lacked utility, *In re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974)*, or that a claim was indefinite, *In re Glass, supra, 492 F.2d at 1232 n.6, 181 USPQ at 34 n.6*, or that characteristics of prior art products were known, *In re Wilson, 50 CCPA 773, 311 F.2d 266, 135 USPQ 442 (1962)*. Whatever may have been

Source: *In re Hogan*, 559 F.2d 595, 605 & n. 17 (C.C.P.A. 1977); Paper 48 at 7.

Legal Authority

Ex Parte Erlich



1992 Pat. App. LEXIS 2, *4; 22 U.S.P.Q.2D (BNA) 1463, **1465

BACKGROUND

Similar subject matter was before this Board in parent application Serial No. 06/325,969, Appeal No. 624-56, *Ex parte Erlich*, 3 USPQ2d 1011 (BPAI 1986). Rejections under 35 USC § 103 which were based upon some of the references and the same reasoning now relied by the examiner were affirmed.

As in the previous appeal, the claimed subject matter is directed to hybridomas which produce monoclonal antibodies specific for human fibroblast interferon, a known protein useful as an antiviral agent, and the monoclonal antibodies produced by the hybridomas. In the previous appeal, we agreed with the examiner that at the time of the present invention one of ordinary skill in the art would have found the claimed hybridomas and monoclonal antibodies obvious from a consideration of prior art. Specifically, we agreed with the examiner that one of ordinary skill in the art, [*5] aware of the antigenicity and therapeutic value of human fibroblast interferon, would have found it obvious to use the classical method of Kohler and Milstein to form monoclonal antibodies specific to this valuable protein.

secrete monoclonal antibodies. Sevier is one publication which documents the success researchers had in extending the discovery of Kohler and Milstein during 1975-1980 to obtain a wide variety of monoclonal antibodies using hybridoma technology. As recognized by the examiner, the Sevier publication itself is not prior art against the present claims. However, the reference does cite a large number of references bearing publication dates of 1979 and 1980 which are stated to report successful obtention of monoclonal antibodies using the hybridoma technology discovered by Kohler and Milstein. To the extentthat Sevier establishes the level of ordinary skill in this art at and around the time of the present invention, i.e., 1980-81, it is properly relied upon by the examiner in rejecting the present claims under 35 USC § 103. *Thomas and Betts Corp., v. Litton Systems, Inc., 720 F.2d 1572, 1581, 220 USPQ 1, 7 (Fed. Cir. 1983)*("[references] though not technically prior art, were, in effect, properly used as indicators of the level of the ordinary skill in the art to which the invention pertained"); *In re Farrenkopf, 713 F.2d 714, 219 USPQ 1 (CCPA 1983).*

claims and document the success researchers had after 1975 up to the point of the present invention in adapting and extending the fundamental technique of Kohler and Milstein to other antigens in order to produce monoclonal antibodies specific to these antigens.

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[2] The effective filing date of the claims on appeal under 35 USC § 120 is February 17, 1981. Subsequent to our first decision, appellants filed a declaration under 37 CFR § 1.131 in which they asserted completion of the invention by June 12, 1980. The examiner found the declaration to be sufficient in an Advisory Action mailed July 14, 1988 (Paper No. 12) in parent application Serial No. 07/001,689.

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Source: *Ex Parte Erlich*, 1992 Pat. App. Lexis 2, *6 (Bd. Pat. App. & Interferences Jan. 16 1992); Paper 48 at 7.