UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC.,	)	
	)	
Plaintiff,	)	
v.	)	Civil Action No.: 05 Civ. 12237 WGY
	)	
F. HOFFMANN-LA ROCHE LTD, ROCHE DIAGNOSTICS GmbH, and HOFFMANN-LA ROCHE INC.,	)	
Defendants.	)	

MEMORANDUM IN SUPPORT OF DEFENDANTS' MOTION TO STRIKE INFRINGEMENT ALLEGATIONS IN AMGEN'S EXPERT REPORTS ON WHICH AMGEN DID NOT PROVIDE DISCOVERY AND TO PRECLUDE TESTIMONY

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I. INTRODUCTION

During fact discovery, Amgen took the position that chemical reactions of polyethylene glycol reagents (hereinafter "pegylation") with any compounds besides EPO was not relevant to any claim or defense in this action. Amgen refused repeated requests for discovery into work that either Amgen or others had performed in the pegylation of non-EPO compounds. Amgen argued that pegylation as applied to other compounds was not relevant to demonstrate how such reactions can create unique new molecules materially changed from the starting material. Amgen expressly argued to this Court that "whether pegylation is simple or difficult or whether pegylation affects the structure, composition or properties of specific molecules that are *not* accused of infringement" is not in issue.[1]

Since Amgen persuaded the Court that the subject matter was not discoverable,[2] Roche received no discovery into Amgen's pegylation involving compounds other than EPO, or their knowledge of such work by others. Amgen not only denied document production and interrogatory responses, but directed witnesses not to answer Roche's deposition questions on this topic. Roche was denied discovery into Amgen's work on applying pegylation to its own molecules GCSF, NESP (Amgen's attempts to pegylate the erythropoetin stimulating agent, Aranesp®), and MGDF.

It is clear now that Amgen intended all along to offer opinions on how routine pegylation was and what material effect that chemical reaction would have on the starting

[1] D.I. 201-1, Amgen Inc.'s Opposition to Defendants' Motion to Compel the Production of Documents at 2.

[2] D.I. 201-1, Amgen Inc.'s Opposition to Defendants' Motion to Compel the Production of Documents, at 7, 9-10 (**"**discovery regarding these proteins is therefore in no way related to the subject matter of Lin's patents - or this litigation).

reagents. Amgen's plan to deny Roche this discovery, in part by arguing to this Court that such information was not relevant, could only be rooted in the attempt to prejudice Roche and impede Roche's ability to rebut effectively -- with Amgen's own information -- these belatedly presented opinions.

Now that fact discovery has closed, Amgen has served expert reports advancing the argument that pegylation is a routine process that does not materially affect the structure, composition, or properties of a molecule. No fewer than three such reports contain detailed opinions in the very area, non-EPO pegylation, as to which Amgen consistently refused discovery. Having denied the relevance of whether pegylation requires significant experimentation and the ways in which pegylation alters a compound--and prevailed before the Court on this argument--Amgen should be estopped from tendering expert opinions on this topic.

It is fundamentally unfair to require Roche to respond to these expert opinions without the benefit of discovery into Amgen's own pegylated compounds, including the characteristics of such compounds and any difficulties or failings Amgen experienced in this work. Amgen has taken one position in order to bar discovery on this topic, and should not be permitted to wield its experts' opinions on the same topic as a sword to attack Roche's non-infringement contentions. Having been denied discovery on this issue, Roche is severely prejudiced, and with rebuttal reports due in less than two weeks, Roche cannot even request additional time for discovery on this topic -- unless the Court would otherwise change the current schedule.

The only meaningful remedy at this late juncture is for the Court to strike the portions of Amgen's expert reports that discuss non-EPO pegylation, to preclude these

experts from discussing or opining on non-EPO pegylation at trial or arguing that pegylation is routine and does not substantially change a molecule. The following chart lists the portions of concern[3]:

Expert Report	Paragraphs that Roche Asks be Stricken
Harvey F. Lodish	62 and 184
Vladimir P. Torchilin	28, 30, 32, 33, 65, 73, 78, 82-89, 91, 95, 96 and 109-111
Nandini Katre	3-5, 16-18, 29-30 and 39-40

II. ARGUMENT

Amgen has argued throughout this case that pegylation with compounds other than EPO was not relevant -- until now. On April 6, Amgen reversed itself, submitting expert reports purporting to describe pegylation as a well-known process that effects an insubstantial change to compounds and citing the pegylation of compounds like G-CSF, MGDF and various types of Interferon as supporting evidence. Roche of course contests these issues. Amgen's own work with pegylation belies these Amgen experts' opinions. Roche repeatedly requested discovery into this subject matter and was rebuffed by Amgen who successfully argued to the Court that this was not part of the case. Amgen should not be permitted to change course given that Roche has been deprived of discovery into Amgen's work in the field of pegylation that forms the context for Amgen's expert reports.

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[3] Roche does not feel it necessary at this time for the Court to review the relevant paragraphs of Amgen's **confidential** expert reports, which also contain Roche confidential and trade secret information, as Roche summarizes the information that is relevant to the present motion. If the Court would like to examine these paragraphs, however, Roche has prepared a document excerpting the relevant paragraphs and is prepared to submit it to the Court for *in camera* review.

A. Amgen Should be Barred from Submitting Opinions Based on Subject Matter that Amgen Excluded from Discovery on Grounds of Relevance

Very early in fact discovery, Roche propounded several requests for documents relating to Amgen's efforts in developing pegylated compounds using G-CSF, MGDF and NESP.[4] Amgen refused to provide this discovery on the grounds that documents related to "'any Pegylated Compound' other than erythropoietin" was "not reasonably calculated to lead to the discovery of admissible evidence".[5] After negotiating with Amgen to no avail,[6] Roche moved the Court to compel production of such documents.[7] In its opposition, Amgen asserted that "documents relating to Amgen's pegylated proteins other than EPO are not relevant" and, specifically with regard to G-CSF and MGDF, that "discovery regarding these proteins is therefore in no way related to the subject matter of Lin's patents - or this litigation."[8] The Court adopted Amgen's position in its January 3 Order, denying discovery into pegylation with non-EPO compounds.

Amgen took a strict view of the Court's Order and refused any discovery into pegylation as it related to other compounds, including instructing its witnesses not to answer questions on this subject. For instance, when Roche asked Amgen witness

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[4] Defendants' First Set of Requests for the Production of Documents and Things to Amgen, Inc. (Nos. 1-123) dated October 30, 2006.

[5] Amgen Inc.'s Objections and Responses to Defendants' First Set of Requests for the Production of Documents and Things (Nos. 1-123) dated December 4, 2006 at Responses to Requests Nos. 20, 31, 34-35, 105. (Exhibit A to accompanying Declaration of Alfred H. Heckel ("Heckel Decl.")); *See also* Responses to Requests Nos. 19, 58-59, 106-112. (Heckel Decl., Exh. A).

[6] *See* Suh Letter to Fishman, 12/7/06 (Heckel Decl., Exh. B); Gaede Letter to Suh, 12/13/06 (Heckel Decl., Exh. C).

[7] D.I. 170-1, Defendants' Motion to Compel the Production of Documents, December 15, 2006.

[8] D.I. 201-1, Amgen Inc.'s Opposition to Defendants' Motion to Compel the Production of Documents at 7, 9-10.

Graham Molineux about a paper which the witness characterized as involving "pegylated GCSF," Amgen's counsel instructed the witness not to answer.[9] Amgen contradicted its prior representations regarding the irrelevance of its attempts to develop a pegylated compound using the active compound in Aranesp® by asserting that Aranesp® was covered by the patents in suit, but withheld discovery into this area,[10] maintaining that it was precluded by the Court's Order.[11]

Roche anticipated that Amgen might argue that pegylation did not result in a materially changed compound with new structural and functional characteristics. Thus, Roche propounded an interrogatory seeking Amgen's contention as to whether MIRCERA™ was materially changed within the meaning of 35 U.S.C. § 271(g).[12] Amgen provided a conclusory one-line statement about pegylation with no information or elaboration.[13] Despite Roche's repeated requests for elaboration, Amgen concealed its contentions on this issue while also withholding document and deposition discovery.[14]

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[9] Molineux Dep. at 24:20 - 25:22. In order to avoid filing confidential documents with the Court, Roche has not attached cited deposition testimony to the motion. However, should the Court require review of any cited deposition testimony, Roche will provide the documents and will not oppose if Amgen seeks to seal them.

[10] See Gaede to Carson and Fleming, 3/6/07 (Heckel Decl., Exh. D); Gaede Letter to Fratangelo, 3/14/07 (Heckel Decl., Exh. E); Plaintiff's Objections to Defendants' First Notice of Deposition Pursuant to Rule 30(b)(6), dated February 23, 2007 (Heckel Decl., Exh. F); Elliott Dep. at 133:22 - 134:25; Boone Dep. at 20:17-23:2.

[11] Roche disagrees that pegylation work with NESP was subject to the Court's Order given Amgen's contention after the Order that Aranesp® is covered by at least one of the patents-in-suit. Roche's argument is set forth in its Motion to Compel Production of Documents and Deposition Testimony Under Rule 30(b)(6) Relating to Pegylation and Aranesp currently pending before the Court. (D.I. 331).

[12] Defendants' First Set of Interrogatories (Nos. 1-13) dated December 6, 2006, at Interrogatory No. 9.

[13] Plaintiff's Responses to First Set of Interrogatories (Nos. 1-12) dated January 9, 2007.

[14] *See* Heckel Letter to Gaede, 1/24/07 (Heckel Decl., Exh. G); Gaede Letter to Heckel, 1/24/07 (Heckel Decl., Exh. H); Heckel Letter to Gaede, 3/1/07 (Heckel Decl., Exh. I); Gaede Letter to Heckel, March 6, 2007 (Heckel Decl., Exh. J).

Roche asserted that Amgen's own experiences with pegylation reactions using various molecules support Roche's view that MIRCERA™ is a new and different molecule from its starting reagents and is materially changed therefrom. Roche also argued that Amgen's work with pegylation is relevant to issues of invalidity. For instance, Amgen's difficulties in its pegylation program for NESP and MGDF, which failed to yield commercial products, belie Amgen's current contention that pegylation is a simple process. Additionally, the structural conformation, biological activity and half-life of such compounds after undergoing pegylation reactions shed light on the degree to which this process effects a substantial change. Amgen itself, in some of the scant documentation Roche has received from Amgen's proceedings against Ortho/J & J, represented that such changes to a molecule could result in major differences and cited its own failed efforts to apply pegylation techniques to MGDF to make a pharmaceutically acceptable composition.[15]

However, before this Court, Amgen prevailed in its argument that pegylation outside the context of EPO was beyond the scope of discovery. Instead of adhering to this argument, Amgen now seeks to rely on evidence that pegylation with other compounds effects no substantial change. As the First Circuit has stated:

> The purpose of discovery is to make a trial less a game of blind man's bluff and more a fair contest with the basic issues and facts disclosed to the fullest practicable extent. Once a proper discovery request has been seasonably propounded, we will not allow a party sentiently to avoid its obligations by filing misleading or evasive responses, or by failing to examine records within its control.

[15] Ortho Biotech, Inc. and Ortho Pharmaceutical Corp. v. Amgen, Inc. and Kirin-Amgen, Inc., Arbitration Hearing, Day 10, October 8, 1998 at 2195-98. As with cited deposition testimony, Roche has not attached this confidential document but if the Court wishes to review the document Roche will submit it and will not oppose Amgen if it seeks to seal the document.

Anderson v. Cryovac, Inc., 862 F.2d 910, 929 (1st Cir. 1988). Courts are empowered to exclude expert opinion that constitutes surprise or a shift in a litigant's previous position. *See Thibeault v. Square D Co.*, 960 F.2d 239, 246-47 (1st Cir. 1992); *Freund v. Fleetwood Enterprises, Inc.*, 956 F.2d 354, 358 (1st Cir. 1992). "The doctrine of judicial estoppel prevents a litigant from pressing a claim that is inconsistent with a position taken by that litigant either in a prior legal proceeding or in an earlier phase of the same legal proceeding." *InterGen N.V. v. Grina*, 344 F.3d 134, 144 (1st Cir.2003). "The doctrine's primary utility is to safeguard the integrity of the courts by preventing parties from improperly manipulating the machinery of the judicial system." *Alternative System Concepts, Inc. v. Synopsys, Inc.*, 374 F.3d 23, 33 (1st Cir. 2004) (citing *New Hampshire v. Maine*, 532 U.S. 742, 750 (2001)). It is widely accepted that two conditions must be satisfied to establish judicial estoppel. *Id.* "First, the estopping position and the estopped position must be directly inconsistent, that is, mutually exclusive." *Id.* "Second, the responsible party must have succeeded in persuading a court to accept its prior position." *Id.* Courts frequently also consider whether the party asserting the inconsistent position would derive an unfair advantage absent estoppel and whether judicial acceptance of that party's initial position conferred a benefit on that party. *Id.*; *see also New Hampshire*, 532 U.S. at 751 (2001); *United States v. Levasseur*, 846 F.2d 786, 793 (1st Cir.1988).

Amgen argued to the Court that pegylation as a general matter, and specifically pegylation reactions with compounds other than EPO, were not relevant to any issue in dispute, and it received the benefit of not having to provide discovery on this subject, discovery which Roche firmly believes would contradict the positions of Amgen's experts. Amgen's reports now take the contrary position that not only is pegylation with

other proteins relevant, but supports Amgen's infringement arguments. All of the elements of judicial estoppel are present. Amgen previously stated, for example, that "Amgen's 'view' of pegylation is simply not relevant to Defendants' infringement of the Lin Patents."[16] However, Amgen's expert reports advance Amgen's "view" that pegylation is routine and insubstantial and does not generally impart materially different characteristics to biological proteins. Amgen cannot have it both ways and should be estopped from advancing these arguments.

B. Amgen's Experts Improperly Offer Opinions on the Very Topics Relating to Pegylation that Roche was Barred from Exploring in Discovery

Amgen's experts' reports, particularly those of Dr. Nandini Katre, Dr. Vladimir Torchilin and Dr. Harvey Lodish, are replete with assertions that pegylation with all manner of molecules was common practice at the time Roche developed MIRCERA™, and would yield expected results. Although Amgen's experts predictably do not weigh in their analysis Amgen's unsuccessful attempts to apply pegylation to recombinant EPO, the experts do consider other molecules to which pegylation has been applied as support for their conclusions.

Amgen's own difficulties in modifying other compounds with pegylation could provide crucial rebuttal evidence, and further evidence going to the invalidity of the asserted patents as previously argued by Roche. However, because Amgen succeeded in excluding the topic of pegylation with non-EPO molecules from the scope of discovery, Roche was denied its opportunity to address the points now introduced by Amgen's experts.

[16] D.I. 201-1, Amgen Inc.'s Opposition to Defendants' Motion to Compel the Production of Documents at 1.

Dr. Lodish--erroneously, Roche contends--labels "pegylation" as a "well-understood" technique, and he cites to the fact that "[a] number of recombinantly produced human proteins have been pegylated, including EPO, G-CSF, interferon-α2b, interferon-γ, and IL-2." Lodish Report ¶ 62. The evidence that Roche had wanted to develop in anticipation of such a statement would likely have shown that Amgen was substantially unsuccessful in chemical reactions with pegylation. Amgen's discovery conduct thwarted Roche's efforts to explore these facts.

Dr. Torchilin, for his part, recites at length the history of pegylation, including efforts to pegylate molecules other than EPO, including Amgen's Neulasta product (G-CSF): "As discussed in paragraphs 9-33, scientists have conjugated therapeutic proteins with water soluble polymers . . . for over thirty years." Paragraph 91 of this expert's report lists Amgen compounds to which pegylation has been applied, the very line of inquiry that Roche was precluded from pursuing in discovery.

The Katre report continues Amgen's heavy reliance on material it denied Roche in discovery. That expert's stated purpose is to "address the issue ... of whether linking chemistries that Roche used to pegylate EPO were known and routine and whether the use in the past of PEG..." has relevance to the biological activity of molecules "in vivo." Katre Report ¶ 29. To support her opinion of MIRCERA™ as "materially changed", Dr. Katre cites publications that deal with pegylation applied to molecules other than EPO, including insulin, lysozyme, and catalase. Dr. Katre later offers opinions on, *inter alia,* whether pegylation affects the biological activity of EPO, an issue on which Roche was denied discovery. *Id.* at ¶ 39. Amgen's discovery tactics have left Roche without essential evidence to refute these analyses. The specific paragraphs in Amgen's expert

reports that unfairly rely on information Roche was denied during discovery are as follows:

Expert Report	Paragraphs that Roche Asks be Stricken
Harvey F. Lodish	62 and 184
Vladimir P. Torchilin	28, 30, 32, 33, 65, 73, 78, 82-89, 91, 95, 96 and 109-111
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C. Roche Is Substantially Prejudiced By Amgen's Reliance on Subject Matter on Which it Withheld Discovery

Amgen's own work in applying pegylation to recombinant proteins would surely provide evidence that relates to, and is likely to contradict, Amgen's experts' opinions on pegylation. Roche is at a serious disadvantage without this information. Amgen knew all along that it intended to use this information, so it devised a plan to ambush Roche by springing these opinions in expert reports long after fact discovery ended. Not only did Amgen obstruct the discovery necessary to challenge its arguments regarding pegylation, but it withheld the arguments themselves, as demonstrated by its refusal to supplement its response to Roche's Interrogatory No. 9 when it clearly had access to prior art regarding pegylation and information regarding its own pegylation work. Amgen has ambushed Roche with new arguments in its expert reports on topics as to which Amgen deprived Roche of discovery. Roche is, in a sense, doubly prejudiced.

Amgen told the Court that the issues of the difficulty of pegylation and of whether pegylation affects the structure, composition or properties of non-EPO molecules were not relevant or discoverable.[17] Amgen's experts now offer opinions on this exact subject matter. Amgen should be held to its original position, its experts' opinions on these

[17] D.I. 201-1, Amgen Inc.'s Opposition to Defendants' Motion to Compel the Production of Documents at 2.

issues should be stricken, and Amgen should be barred from offering such opinions on any related topic at trial.

III. CONCLUSION

For all the foregoing reasons, Amgen's expert opinions regarding whether pegylation was a routine procedure or effected a substantial change to compounds other than EPO, should be stricken from their reports, Amgen should be estopped from relying on evidence relating to this subject matter, and its experts should be precluded from offering such or related testimony and opinions.

Dated: April 30, 2007
Boston, Massachusetts

Respectfully submitted,

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