**NOT FOR PUBLICATION**

**UNITED STATES DISTRICT COURT**
**DISTRICT OF NEW JERSEY**

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| HOFFMANN-LA ROCHE INC.,<br><br>Plaintiff,<br><br>v.<br><br>COBALT PHARMACEUTICALS INC., and COBALT LABORATORIES, INC.,<br><br>Defendants. | Civil Action No. 07-4539 (SRC) (MAS)<br>Civil Action No. 07-4540 (SRC) (MAS)<br>Civil Action No. 08-4054 (SRC) (MAS)<br>(consolidated with 07-4539 for all purposes)<br><br>**OPINION** |

**CHESLER, U.S.D.J.**

This matter comes before the Court on the motion for a preliminary injunction by Plaintiff Hoffman-La Roche Inc. ("Roche") against Defendants Cobalt Pharmaceuticals Inc. and Cobalt Laboratories, Inc. (collectively, "Cobalt.") For the reasons stated below, the motion will be granted.

## BACKGROUND

The background to this Hatch-Waxman action for patent infringement has been presented in previous Opinions and will not be repeated here. On November 16, 2010, the 30-month stay on FDA approval of Cobalt's ANDA for a generic ibandronate product will expire. Roche, the owner of two patents which cover its branded ibandronate product, Boniva®, expects that Cobalt will then launch its generic ibandronate product. Roche moves for a preliminary injunction to prevent this product launch.

The parties briefed this motion on an expedited basis, followed quickly by hearings held on November 1 and 3, 2010.

## APPLICABLE LEGAL STANDARDS

### I. Preliminary Injunction

"The grant of a preliminary injunction under 35 U.S.C. § 283 is within the discretion of the district court." Curtiss-Wright Flow Control Corp. v. Velan, Inc., 438 F.3d 1374, 1378 (Fed. Cir. 2006). "A plaintiff seeking a preliminary injunction must establish that he is likely to succeed on the merits, that he is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest." Winter v. NRDC, Inc., 129 S. Ct. 365, 374 (2008).

As to the requirement that the movant establish that he is likely to succeed on the merits, the Federal Circuit has held:

> [T]he patentee seeking a preliminary injunction in a patent infringement suit must show that it will likely prove infringement, and that it will likely withstand challenges, if any, to the validity of the patent. In assessing whether the patentee is entitled to the injunction, the court views the matter in light of the burdens and presumptions that will inhere at trial. . . .

Titan Tire Corp. v. Case New Holland, Inc., 566 F.3d 1372, 1376 (Fed. Cir. 2009) (citation omitted).

"[A]n issued patent comes with a statutory presumption of validity under 35 U.S.C. § 282." Id.

> If [] the alleged infringer responds to the preliminary injunction motion by launching an attack on the validity of the patent, the burden is on the challenger to come forward with evidence of invalidity, just as it would be at trial. The patentee, to avoid a conclusion that it is unable to show a likelihood of success, then has the burden of responding with contrary evidence, which of course may include analysis and argument. . . .
>
> [T]he trial court first must weigh the evidence both for and against validity that is available at this preliminary stage in the proceedings. Then . . . if the trial court

> concludes there is a 'substantial question' concerning the validity of the patent, meaning that the alleged infringer has presented an invalidity defense that the patentee has not shown lacks substantial merit, it necessarily follows that the patentee has not succeeded in showing it is likely to succeed at trial on the merits of the validity issue.

Id. at 1377-79.

The Federal Circuit then stated definitively the standard that the trial court must apply in ruling on a validity challenge in the context of an application for a preliminary injunction:

> [W]hen analyzing the likelihood of success factor, the trial court, after considering all the evidence available at this early stage of the litigation, must determine whether it is more likely than not that the challenger will be able to prove at trial, by clear and convincing evidence, that the patent is invalid.

Id. at 1379.

## II. Patent Invalidity

"A patent is presumed to be valid, 35 U.S.C. § 282, and this presumption can only be overcome by clear and convincing evidence to the contrary." Bristol-Myers Squibb Co. v. Ben Venue Labs., 246 F.3d 1368, 1374 (Fed. Cir. 2001) (citations omitted). The party asserting invalidity bears the burden of establishing it. 35 U.S.C. § 282. "This burden is especially difficult when . . . the infringer attempts to rely on prior art that was before the patent examiner during prosecution." Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1348 (Fed. Cir. 2004) (quotation omitted).

### A. Invalidity due to Anticipation

A patent may be invalidated for anticipation under 35 U.S.C. § 102, which states:

> A person shall be entitled to a patent unless . . .
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

"To anticipate a claim, a single prior art reference must expressly or inherently disclose each claim limitation." Finisar Corp. v. DirecTV Group, Inc., 523 F.3d 1323, 1334 (Fed. Cir. 2008). "Anticipation is a question of fact. However, without genuine factual disputes underlying the anticipation inquiry, the issue is ripe for judgment as a matter of law." SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1343 (Fed. Cir. 2005).

B. Invalidity due to obviousness

To patent an invention, the subject matter must be non-obvious:

> A patent may not be obtained . . . 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. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. § 103(a).

The Federal Circuit has set forth these basic principles to guide the determination of obviousness:

> Obviousness is ultimately a question of law, based on underlying factual determinations. The factual determinations that form the basis of the legal conclusion of obviousness include (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, known as objective indicia of non-obviousness.

Altana Pharma AG v. Teva Pharms. USA, Inc., 566 F.3d 999, 1007 (Fed. Cir. 2009) (citations omitted).

## ANALYSIS

### I. Roche has demonstrated that it is likely to succeed on the merits.

At issue are claim 4 of Roche's U.S. Patent No. 4,927,814 (the "'814 patent") and claims

1 and 6 of Roche's U.S. Patent No. 7,410,957 (the "'957 patent.") This Court has previously granted motions for summary judgment which determined that Cobalt's generic product will infringe these three claims. To show a likelihood of success on the merits, Roche must show that, in light of the burdens and presumptions that will inhere at trial, it will likely withstand Cobalt's challenges to the validity and enforceability of the patents. Roche has met this burden.

A. Cobalt's anticipation challenge to the '814 patent

Cobalt contends that claim 4 of the '814 patent is anticipated by two prior art references: U.S. Patent No. 4,327,039 (the "Blum '039 patent") and U.S. Patent No. 4,504,463 (the "Van Duzee patent.") Claim 1 of the '814 patent claims a disphosphonate compound with a particular formula. '814 Patent col. 13 ll.23 - 29. This formula may be considered to have three parts: a defined base molecule, and two variable elements, $R_1$ and $R_2$, which attach to a nitrogen atom. Claim 4 states: "The diphosphonate compound of claim 1 designated 1-hydroxy-3-(N-methyl-N-pentylamino)-propane-1,1-diphosphonic acid and the physiologically active salt thereof." Id. at col. 13 ll. 36 - 39. There is no dispute that the compound of claim 4 is the compound of claim 1 in which $R_1$ and $R_2$ are methyl and n-pentyl groups; this is ibandronate.

The Blum '039 patent discloses the same defined base molecule as claim 1 and, similarly, there are two variable elements, $R_1$ and $R_2$, which attach to the nitrogen atom. Blum '039 Patent col. 2 ll.11 - 19. In the description of the invention, the patent states that "$R_1$ and $R_2$ are selected from the group consisting of hydrogen and lower alkyl." Id. at col. 2 ll.21 - 22. There is no dispute that a methyl group falls within the scope of the phrase "lower alkyl." The parties dispute whether a pentyl group falls within the scope of "lower alkyl." The question of whether the Blum '039 patent anticipates claim 4 of the '814 patent thus turns on an interpretation of the

scope of the phrase "lower alkyl" in the specification of the Blum '039 patent.

The parties neither briefed nor argued the legal principles this Court should apply to this inquiry, but appeared to agree that this is a factual question of how the skilled artisan would have understood "lower alkyl" in the context of the Blum '039 specification. This seems appropriate, given the relevant legal test:

> The proper test of a publication as a § 102(b) bar is whether one skilled in the art to which the invention pertains could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention on which a patent is sought.

In re Elsner, 381 F.3d 1125, 1128 (Fed. Cir. 2004) (quotation omitted).

In support of its contention that the skilled artisan would understand "lower alkyl" as limited to groups having from one to four carbon atoms, Roche points to the reports of two experts, Drs. Benedict and McKenna. (Benedict Rebuttal Report ¶ 228, PI-APP-689; McKenna Rebuttal Report ¶ 131, PI-APP-2205.) To support their views, both of Roche's experts cite the same two pages in an organic chemistry textbook, the third edition of Morrison & Boyd.

The third chapter of Morrison & Boyd was produced and discussed at length during the hearing. (11/1/10 Hrg. Tr. 115:2-125:6.) This Court finds that neither the cited pages, nor the third chapter, of Morrison & Boyd states any clear definition of the phrase "lower alkyl." The structure of the subsection headings in the third chapter does, however, suggest that the phrase "higher alkanes" refers to pentanes and alkanes with higher numbers of carbon atoms. This provides some support for Roche's contention that the skilled artisan would not understand "lower alkyl" to include pentyl groups.

In support of its contention that "lower alkyl" includes pentyl groups, which have five

carbons, Cobalt offers the declaration of its expert, Dr. Rosini. (Third Rosini Dec. ¶ 279.) In support for his position, Dr. Rosini observes that two of Dr. Benedict's own publications state definitions of "lower alkyl" as including one to five, and one to eight, carbon atoms. Id. This is interesting, but the fact that one expert used two different definitions at different times suggests that "lower alkyl" probably does not have one standard definition in the art. Furthermore, Cobalt points to definitions in two other U.S. Patents: No. 4,208,401 (lower alkyl is 1-6 carbon atoms) and No. 4,558,142 (lower alkyl is 1-7 carbon atoms.)

On the whole, the evidence of record suggests that "lower alkyl" did not have a clearly delimited and commonly understood definition in the art but, rather, that different skilled artisans used the term differently at different times. Cobalt's own evidence shows four differing definitions of lower alkyl as including one through five, six, seven, and eight carbon atoms. Moreover, the four definitions are all in patents or patent applications. This suggests that the patentees in those cases all felt the need to be their own lexicographers and to define "lower alkyl," which further supports the inference that there was no clear and commonly understood definition of the term in the art. Since the evidence of record does not demonstrate that there was any generally accepted definition of "lower alkyl," the question then becomes what definition the patentee (Blum) intended.

The problem is that neither party has pointed to any evidence within the four corners of the Blum '039 Patent that makes clear whether the patentee intended "lower alkyl" to include pentyl groups. Cobalt points to this statement in the specification: "Other .beta.-alanines, which have their hydrogen atoms located on the amino group partially or completely replaced by lower alkyl radicals, such as methyl, ethyl or propyl, also may be used as starting products." Blum '039

patent col.2 ll.31 - 35. Cobalt argues, persuasively, that the use of the phrase "such as" signals that "lower alkyl" is not limited to methyl, ethyl and propyl, but must include at least one more in the series, i.e., butyl. This gets "lower alkyl" to four carbon atoms, but not to five – which is precisely what Roche contends.

This Court has considered the arguments both for and against finding that the Blum '039 patent discloses a bisphosphonate compound with a pentyl group at $R_2$, and thus anticipates claim 4 of the '814 patent. The Court observes that the Blum '039 patent was before the examiner during prosecution of the '814 patent, and so it will be especially difficult for Cobalt to prove invalidity based on anticipation by this reference. On this record, this Court cannot conclude that Cobalt is more likely than not to be able to prove anticipation by clear and convincing evidence. The evidence of record does not appear to clearly and convincingly show that "lower alkyl" includes pentyl groups. Roche has shown a likelihood of success in defending claim 4 of the '814 patent to this validity challenge.

Cobalt also contends that the Van Duzee patent anticipates claim 4 of the '814 patent. There appears to be no dispute that the Van Duzee patent discloses a genus of which ibandronic acid is one species. On this subject, the Federal Circuit has stated:

> It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus. There may be many species encompassed within a genus that are not disclosed by a mere disclosure of the genus. On the other hand, a very small genus can be a disclosure of each species within the genus.

Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006). A genus anticipates a species "when the class of compounds that falls within the genus is so limited that a person of ordinary skill in the art can at once envisage each member of this limited class." In re Gleave,

560 F.3d 1331, 1338 (Fed. Cir. 2009) (quotation omitted). The issue, then, is whether, in this case, the particular genus is so limited that a skilled artisan can at once envisage each species.

Roche argues that the genus disclosed in the Van Duzee patent is not so limited. Cobalt does not dispute that the disclosed genus is numerous, but contends that the patent's statements of preference, in disclosing the preferred embodiments, "drastically reduce" the number of options. (Cobalt's Opp. Br. 33.) Cobalt, however, provides no detailed explanation to substantiate this contention. Cobalt has not persuaded this Court that, based on the statements of preference, a skilled artisan could at once envision the species that is ibandronic acid. On this record, this Court cannot conclude that Cobalt is more likely than not to be able to prove anticipation by the Van Duzee patent by clear and convincing evidence.

B. Cobalt's obviousness challenge to the '814 patent

In its opposition brief, Cobalt points to a number of pieces of prior art which, it contends, render claim 4 of the '814 patent obvious. At oral argument, Cobalt placed greatest emphasis on the Boonekamp reference. The parties do not dispute that, at the First International Workshop on Cells and Cytokines in Bone and Cartilage, held in Davos, Switzerland in December of 1985, Boonekamp presented a talk in which the superior potency of the compound olpadronate, relative to pamidronate, was disclosed, and it was theorized that the modification to chemical structure which transformed pamidronate into olpadronate resulted in the enhanced potency. (PI-APP-6535.) The parties also do not dispute that olpadronate and ibandronate are alkyl homologues, and differ in structure only because olpadronate contains a methyl group where ibandronate contains a pentyl group.

Cobalt further offers the testimony of its experts, Drs. Rosini and Newton, that it was

well-known in the art at that time that the potency of bisphosphonate compounds might be optimized by testing a range of alkyl homologues. Thus, Cobalt contends, it would have been obvious to a skilled artisan to optimize the potency of olpadronate by creating homologues with progressively longer alkyl chains at $R_2$, which would have led to the discovery of ibandronate as an inhibitor of bone resorption. Specifically, Dr. Rosini said that he had varied the length of the alkyl chains when investigating alendronate, and that Dr. Fleisch had done so with etidronate, and that this kind of investigation had produced useful results in both instances. (Third Rosini Dec. ¶ 50; see also Newton Dec. ¶¶ 79-80.) Thus, a skilled artisan would have been motivated to perform this optimization process with olpadronate. Cobalt notes that Roche's expert Benedict stated at his deposition that the skilled artisan, at that time, would have done "a systematic program to vary the parts of the molecule and to determine what, what would make them better and what would make them less good." (Benedict Dep. Tr. 109:13-18.)

At first glance, Cobalt's theory is appealing: the skilled artisan would have been motivated to apply a known strategy for improving a bisphosphonate to olpadronate, recently found to have superior potency, which would lead to ibandronate. Yet this theory has several major difficulties. First, olpadronate was disclosed in the prior art references that were before the examiner during prosecution of the '814 patent. Roche's expert Dr. Benedict stated that the Schmidt-Dunker patents, which were before the examiner, disclosed olpadronate. (Benedict Rebuttal Rpt. ¶¶ 232.) The examiner initially rejected a set of claims as obvious over Schmidt-Dunker. Referring to Schmidt-Dunker, along with two other patents, the examiner stated that "three references disclose lower homologues of the instant compounds having the instant utility. Absent evidence that the instant compounds have greater effectiveness, the instant compounds

are obvious." (Harris Dec. ¶ 133(f).) The applicant overcame the obviousness rejection by submitting evidence of greater effectiveness. Thus, the examiner considered the issue of obviousness over the compounds of Schmidt-Dunker, including olpadronate, and an obviousness rejection was overcome. Because of the greater difficulty of proving invalidity using prior art that was before the patent examiner, this is a red flag that Cobalt's theory may be unsupported.

Second, a key problem is that the underlying evidence does not support Cobalt's claim that the modification which transformed olpadronate into ibandronate was a known optimization strategy. Cobalt points to two areas of research in the prior art.

First, Cobalt points to the research by Fleisch and Shinoda on alkyl homologues of etidronic acid. Etidronic acid, however, differs from olpadronate and ibandronate in that it has no nitrogen atom. Fleisch and Shinoda varied the length of an alkyl chain that was attached directly to the PCP core. None of the investigated compounds had an amino group, which olpadronate and ibandronate have.

Second, Cobalt points to Rosini's research on pamidronate, which showed that the alkyl homologue series produced results conforming to a curve known as the Hansch curve. Yet, while pamidronate has an amino group, this research did not look to vary alkyl chains on the outside of the nitrogen atom. Rather, in this research, the alkyl groups between the nitrogen and the PCP core molecule were varied.

Cobalt's obviousness theory relies on persuading that the skilled artisan, looking at these bodies of research, would have concluded that lengthening alkyl chains – wherever they were – would have been a useful investigative strategy for optimizing bisphosphonate compounds. On this record, however, this Court finds that the differences between the strategy that transformed

olpadronate into ibandronate and the strategies employed in the prior art research overshadow the similarities. The chief difference is the relative location on the molecule: the prior art varied the length of the single alkyl chain that connected directly to the PCP core, whereas transforming olpadronate into ibandronate involves lengthening one of two alkyl chains that connect to the nitrogen atom, but not to the PCP core. Olpadronate and ibandronate have two carbon atoms that connect in series to the PCP core, which then connect to the nitrogen atom. The nitrogen atom then connects to two alkyl groups. It is by lengthening one of these two alkyl chains on the outside of the nitrogen atom that olpadronate becomes ibandronate. The prior art strategies are not the same strategy that transformed olpadronate into ibandronate.

Moreover, the prior art optimization research varied the length of a single alkyl chain. Olpadronate and ibandronate have two alkyl groups on the outside of the nitrogen atom. How is the skilled artisan to apply a single-chain technique to a double-chain situation? Cobalt did not deal with this issue at all. While this Court has no expertise in pharmaceutical chemistry, it would appear that having two alkyl chains raises new questions: should the chains be symmetrical or asymmetrical, for instance? It is difficult to see, on this record, how this does not require innovation.[1]

In KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007), the Supreme Court stated the basic principles of the relevant obviousness inquiry:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this

[1] Furthermore, having two alkyl chains substantially increases the number of potential configurations. Cobalt has not even attempted to suggest that the skilled artisan would have had some reason to select the methyl/pentyl configuration that characterizes ibandronate.

> leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Cobalt's obviousness argument depends on the proposition that the investigative strategy of varying the length of olpadronate's exterior alkyl chains was one of a finite number of identified, predictable solutions. On this record, this Court finds scant evidence that suggests this to be the case. Cobalt's evidence suggests that, if anything was a recognized solution, it was the strategy of varying the single alkyl chain that connected directly to the PCP core.[2] The technique of varying the two alkyl chains that connected only to the nitrogen atom, and not to the PCP core, appears on this record to have been novel. An artisan who applied the investigative strategy suggested by Cobalt's prior art research would have modified olpadronate by lengthening the single alkyl chain between the PCP core and the nitrogen atom.[3] Such a strategy would not have produced ibandronate. Applying KSR, the applicant's use of the strategy of lengthening one of the two alkyl chains connected to the nitrogen atom and not directly connected to the PCP core appears to be innovation – not the application of ordinary skill and common sense.

This conclusion finds support in Dr. Rosini's testimony that neither Boonekamp, who disclosed the superior potency of olpadronate in 1985, nor anyone on his research team, ever attempted to explore homologation of this compound. (Rosini Dep. Tr. 185:12-17.) If it would have been common sense to the skilled artisan in 1986 to optimize olpadronate by varying the

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[2] At the hearing, the experts referred to this alkyl chain as the "spacer" or the "lozenge." (See, e.g., 11/1/10 Hrg. Tr. 98:16.)

[3] Dr. McKenna pointed this out: had the skilled artisan followed the strategy suggested by Dr. Rosini's research, the molecule would have been modified by lengthening the "spacer." (11/1/10 Hrg. Tr. 99:18-25.)

length of the alkyl chains in 1986, why didn't Boonekamp's team do so?[4]

Roche contends that Cobalt's argument must be considered in light of the lead compound inquiry most recently set forth by the Federal Circuit in Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd., 619 F.3d 1346 (Fed. Cir. 2010). In Daiichi, the Federal Circuit stated:

> When a patent claims a chemical compound, a prima facie case of obviousness under the third Graham factor frequently turns on the structural similarities and differences between the compounds claimed and those in the prior art. Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old.

Id. Roche observes that, in the instant case, like in Daiichi, Cobalt advances an argument based on the structural similarity between the claimed compound (ibandronate) and a prior art compound (olpadronate). Applying this analysis leads to two principal questions: 1) would the skilled artisan have been motivated to select olpadronate as the lead compound; and 2) would the skilled artisan have had a reasonable expectation that the new compound would have had similar or improved properties compared with the old? On this record, Cobalt has not persuaded that either question should be answered in the affirmative.

As to the first question, as Roche observes, two important pieces of evidence undercut Cobalt's lead compound case. First, Dr. Rosini testified that, in 1986, he believed alendronate to be the strongest compound in the literature for inhibiting bone resorption. (Rosini Dep. Tr. 149:2-8.) Thus, Dr. Rosini testified that he did not attempt to work with olpadronate until 1991.

[4] Furthermore, since the Schmidt-Dunker '432 patent disclosed olpadronate in 1976, one might wonder why no one had thought to modify olpadronate earlier. Cobalt explains that the 1976 Schmidt-Dunker patent disclosed olpadronate, but that olpadronate's value in inhibiting bone resorption was not recognized until Bijvoet's work in 1985. (Cobalt Opp. Br. 19.)

(11/1/10 Hrg. Tr. 241:17-21.) Furthermore, Dr. Rosini testified that, even though he was aware of olpadronate from Boonekamp's 1985 work at the time, he chose to do his research during that time period on alendronate.[5] (Rosini Dep. Tr. 174:5-23.) This evidence raises serious questions about the assertion that the skilled artisan would have been motivated to select olpadronate as the lead compound in 1986.

It is on the second question that Cobalt's obviousness case really breaks down: the evidence that the skilled artisan would have had a reasonable expectation that ibandronate would have had similar or superior properties to olpadronate. Cobalt's theory is that the skilled artisan would have had a reasonable expectation that varying alkyl chain length would have led to results that conformed to a Hansch curve. Even if true, that means that the skilled artisan would have expected only that the effectiveness of ibandronate would fall somewhere on that curve – and that somewhere could just have easily been under the effectiveness of olpadronate as equal to it or superior.[6] Thus, the Hansch curve theory actually backfires for Cobalt, since it makes clear that the skilled artisan would have had no expectation of where ibandronate would fall on the

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[5] Moreover, Dr. Rosini testified that it was not until "years later" that he considered substituting the amino group with alkyl groups. (Rosini Dep. Tr. 173:18-22.)

[6] Cobalt's expert Dr. Newton summarized the theory as follows: "As you homologate, so you get an increase in activity up to maximum and then a decrease again." (11/1/10 Hrg. Tr. 185:3-5.) The skilled artisan homologating olpadronate, then, would not have been able to predict whether ibandronate would have shown increased or decreased activity. Dr. Newton conceded this in discussing the investigation into lengthening the alkyl chains on olpadronate: "it wasn't predictable that the best compound would be C5." (Id. at 192:2-3.) In discussing homologues with varying chain lengths, Dr. Rosini made the same concession: "We cannot predict which one is the most effective." (Id. at 232:15-16.) These concessions that the properties of ibandronate were unpredictable are devastating to Cobalt's obvious optimization theory, which depends on proving the opposite.

curve.[7] The Hansch curve theory makes clear that, in 1986, the skilled artisan would not have had any particular expectation for the performance of ibandronate relative to that of olpadronate. Absent evidence that a skilled artisan would have had a reasonable expectation that ibandronate would have had similar or improved properties compared with the prior art olpadronate, Cobalt cannot prove obviousness with this theory.

Cobalt's optimization theory does not pass muster under KSR, for at least two reasons. First, the evidence does not show that either the optimization strategy itself or the set of results likely to fall on the Hansch curve qualify as "identified, predictable solutions." KSR, 550 U.S. at 421. Rather, as Drs. Newton and Rosini conceded, the strategy was not predictable, since no one could predict where any particular compound would fall on the Hansch curve. Nor does the evidence demonstrate that the user of the strategy would have anticipated success with any particular compound. What Cobalt did not demonstrate was that the skilled artisan, applying the optimization strategy to olpadronate, would have had reason to anticipate success with ibandronate. Rather, Cobalt's experts conceded that the artisan would have had no prediction of success for any particular compound. To look at the results of the optimization and say that the success of ibandronate was anticipated, when it clearly was not, is a great example of the distorting effect of hindsight: "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." Id. Cobalt's contention that the success of ibandronate would have been anticipated relies upon just such *ex post* reasoning.

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[7] This inference is supported by Dr. Russell's testimony that, before ibandronate was made and tested, the skilled artisan would have had no expectation of what its potency would be. (11/1/10 Hrg. Tr. 172:9-10.)

On this record, it does not appear that it is more likely than not that, at trial, Cobalt will be able to prove the '814 patent invalid as obvious by clear and convincing evidence.

C. Cobalt's inequitable conduct challenge to the '814 patent

Cobalt contends that, even if valid, this Court should refuse to enforce the '814 patent because of inequitable conduct on the part of the applicant. Cobalt's inequitable conduct case is quite complex, but, in brief, the most troubling accusation is that, to overcome the examiner's obviousness rejection, Dr. Bosies submitted a declaration which, in various ways, misrepresented the superiority of the claimed compounds over the prior art.

The Federal Circuit has set forth the fundamental law of an inequitable conduct claim as follows:

> To successfully prove inequitable conduct, the accused infringer must present evidence that the applicant (1) made an affirmative misrepresentation of material fact, failed to disclose material information, or submitted false material information, and (2) intended to deceive the [PTO]. Further, at least a threshold level of each element--i.e., both materiality and intent to deceive--must be proven by clear and convincing evidence. And even if this elevated evidentiary burden is met as to both elements, the district court must still balance the equities to determine whether the applicant's conduct before the PTO was egregious enough to warrant holding the entire patent unenforceable.

Star Sci., Inc. v. R.J. Reynolds Tobacco Co., 537 F.3d 1357, 1365 (Fed. Cir. 2008) (citations omitted).

The factual underpinnings of this claim are extraordinarily complicated, but this Court is not persuaded that Cobalt is likely to be able to prove the requisite scienter. The Court observes that, while there is no dispute that the data in the Bosies Declaration for Example 6 was incorrect, the patent application contained the correct data. While the Bosies Declaration did not contain data for Compound F, data for Compound F was submitted to the PTO in a companion

application, submitted on the same day as the application at issue, and before the same examiner. One of Cobalt's weightiest accusations alleges substantial overstatements of the dosage data for Compounds D and E in the Bosies Declaration. Roche counters that Cobalt is misinterpreting what is a typo in the report received from Dr. Fleisch, and points to testimony from Dr. Bauss, who conducted research with Dr. Fleisch, in support. Roche also notes that use of "mg P/kg" units was a key element of the design protocol that Dr. Fleisch used, that Dr. Fleisch tested large numbers of compounds, reported dosing using the "mg P/kg" units in all other cases, and was unlikely to have used completely different units for these few compounds. Clearly, this is a material factual issue, but, on this record, this Court cannot conclude that Cobalt is likely to be able to prove that Dr. Bosies intended to deceive the PTO as to Compounds D and E.

Viewed as a whole, this evidence weighs against finding the requisite intent to deceive the PTO. Cobalt has not persuaded this Court that it is more likely than not to be able to prove by clear and convincing evidence that Dr. Bosies submitted his declaration with the requisite intent to deceive the PTO. The evidence before the Court at this time is simply not clear and convincing.

Moreover, this Court is not persuaded on this record that, even if Cobalt did prove the elements of inequitable conduct by clear and convincing evidence, the balancing of the equities would lead to a refusal to enforce the patent. The problem for Cobalt is that, even if it succeeded in showing that the Bosies Declaration contains the false statements that Cobalt asserts, the evidence still supports the conclusion that ibandronate is superior to the prior art. Especially persuasive is Dr. Russell's review of the substantial body of research which supports this. (Russell Supp. Rpt. ¶¶ 207-209, 252, 253.) Given this body of evidence that ibandronate, a

claimed compound, was truly superior to the prior art compounds, even if Cobalt succeeded in proving the factual prerequisites to a jury by clear and convincing evidence – no small feat –, this Court has substantial doubts that it would find the misconduct egregious enough to warrant holding the patent unenforceable. Absent that, Cobalt's equitable conduct defense cannot succeed.

D. Cobalt's inventorship challenge to the '814 patent

Cobalt also argues that the '814 patent is invalid for improper inventorship. In response, Roche disagrees, but argues that, even if true, 35 U.S.C. § 256 allows for the correction of inventorship, as long as the error arose in the absence of deceptive intent. Cobalt has not made a persuasive case that the inventors on the '814 patent have been incorrectly identified. More significantly, this Court agrees that Cobalt appears unlikely to be able to prove that any errors in inventorship arose due to deceptive intent, and thus is unlikely to succeed in invalidating the patent with its inventorship challenge.

Having examined the record and considered the arguments on both sides regarding Cobalt's challenges to the validity and enforceability of the '814 patent, this Court does not find it more likely than not that Cobalt will be able to prove by clear and convincing evidence at trial that the '814 patent is invalid or unenforceable. This Court has previously ruled that Cobalt's generic product infringes claim 4 of the '814 patent. Roche has shown that, in light of the burdens and presumptions that will inhere at trial, it will likely withstand Cobalt's challenges to the validity and enforceability of the '814 patent.

Because Roche has shown a likelihood of success on the merits in regard to the '814 patent, this Court need not reach the issues regarding the '957 patent. Even if this Court were to

conclude that Cobalt was more likely than not to prove the '957 patent invalid at trial, this would not negate Roche's entitlement to the rights adhering to the '814 patent.

**II. Roche has demonstrated that it is likely to suffer irreparable harm in the absence of injunctive relief.**

Roche contends that it will suffer irreparable harm if an injunction is not granted, for several reasons. First, the entry of a generic competitor into the marketplace will cause it to lose market share and sales; Roche estimates losses in the range of 50% to 90% of sales. Roche contends that the losses would be irreversible, in that Boniva® would not be able to regain its status in the formularies of third-party payors. Second, Roche would be harmed by significant price erosion, which would be irreparable, because Roche could never increase the price of Boniva® to pre-generic levels. Third, Roche contends that the harm it will suffer will not be susceptible to calculation: the osteoporosis treatment market has been in such flux, and will continue to be so in the near future, that it will not be possible to accurately ascertain and quantify the damage done to Roche's business by Cobalt's entry of its product into the marketplace. Fourth, Roche's goodwill and reputation will be damaged.

At the hearing, Roche offered the testimony of John Lyons, brand director for Boniva®. Lyons testified that Roche expected to have net revenue of $500 million from Boniva® in the current year, and that Boniva® had a market share of 15% of the market for prescription oral bisphosphonates. (11/1/10 Hrg. Tr. 21:7-8, 21.) Lyons stated that Roche expected that a new branded competitor, Atelvia, would enter the market in the next several months. (Id. at 23:1-7.) Sales of Boniva® are also likely to be influenced in the near future by the launch of a new competitor in the marketplace, Prolia. (Id. at 22:16-19.)

Lyons explained the formulary tier structure used by major third-party payors, and its consequences for Roche in this matter. (Id. at 23:11-31:9.) Boniva® currently enjoys a favorable tier placement which was the result of a complex series of negotiated interactions. (Id. at 25:18-24.) Generic competition would likely result in a less favorable tier placement, and Roche would likely never be able to regain the favorable tier placement even if the generic product left the market. (Id. at 28:21-29:13, 29:24-30:13.) Based on Roche's experience with its branded drug Fosamax®, Lyons anticipated that generic competition would likely cause Roche to lose 50% of its market share within weeks, and up to 90% within months. (Id. at 28:2-6.) This severe drop in market share would result in having to cut the Boniva® sales force to zero. (Id. at 34:15-23.)

At the hearing, Roche also presented the testimony of an economist, Dr. Vellturo. Dr. Vellturo explained the erosion of Boniva's® price that is likely to occur with the entry of a generic product into the marketplace. (11/1/10 Hrg. Tr. 68:21-25.) Dr. Vellturo stated that, should Cobalt's generic product enter the marketplace, it will be very difficult to distinguish the damage done to Boniva® sales by generic competition from the effects of the other competitors in the marketplace. (Id. at 72:10-13, 77:1-78:11.)

Roche has persuaded this Court that it is likely to suffer irreparable harm if an injunction does not issue. Clearly, the entry of a generic competitor into the marketplace will hurt Roche's sales of Boniva®. The phenomenon of price erosion in the pharmaceutical industry is well-known.[8] The question is only whether the harm will be irreparable, and Roche has persuaded

[8] For an example of a similar case:

Sanofi would suffer irreversible price erosion in light of a complex pricing

that it will be. This Court finds especially persuasive Roche's contention that third-party payors control a substantial portion of its sales, and that a generic entrant into the marketplace has the potential to irreversibly alter the reimbursement relationship, producing an irreparable impact on Roche's business. Roche has also persuaded that the marketplace is likely to be reshaped by a number of factors in the coming year – including the entry of Prolia and Atelvia into the marketplace – that will make it extremely difficult, if not impossible, to ascertain with certainty the losses attributable to Cobalt's entry of its generic product. Thus, while it is true that Roche's licensing agreement with Genentech for Boniva® specifies the decrease in Roche's royalty due to the start of generic competition, the change in royalty rates is likely not to fully capture Roche's actual damages.[9] Lastly, this Court credit's Roche's prediction that it would have to eliminate much of its sales force. These are irreparable harms.

Cobalt's rebuttal to Roche's claim of likely irreparable harm is unpersuasive. Cobalt points to Roche's size and profitability, and the small impact the likely harms would have on Roche's overall profitability. That says nothing about whether such harms are irreparable. The rest of Cobalt's rebuttal is largely bluster: the fact that businesses routinely make economic

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> scheme that is directly affected by the presence of the generic product in the market. In particular, the court found that since Apotex's generic product entered the market, Sanofi has been forced to offer discounted rates and price concessions to third-party payors, such as health maintenance organizations, in order to keep Plavix® on a favorable pricing tier, which governs what consumers pay for that drug.

Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1382 (Fed. Cir. 2006).

[9] Lyons stated that, under the terms of Roche's licensing agreement with Genentech, Roche's royalty rate would decrease from 15% to 5% if generic ibandronate enters the market. (11/1/10 Hrg. Tr. 40:24-41:2.)

forecasts does not show that all damages are readily quantified with accuracy.

Cobalt argues that, because there is no dispute that Roche does not sell any 2.5mg ibandronate product, Roche cannot be harmed by Cobalt's sale of a generic product at that dose. Roche counters, persuasively, that a daily dose generic product would cannibalize sales of its monthly product because third-party payors would place the daily generic on a tier which gives it a preference over a branded monthly dose, which would discourage sales of Boniva®. (11/1/10 Hrg. Tr. 33:15-34:8.)

Having heard the evidence offered by the parties, this Court finds that Roche has demonstrated that it is likely to suffer irreparable harm in the absence of a grant of injunctive relief. Not granting the injunction will cause Roche substantial, irreversible lost profits, price erosion, loss of market share, lost jobs, and loss of goodwill. The Federal Circuit has recognized that such injuries may constitute irreparable harms. See, e.g., Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1362 (Fed. Cir. 2008).

Price erosion is most likely to occur in cases like this one, in which no generic competitors have yet entered the marketplace, placing the patentee in an exclusive position. This Court rejects Cobalt's contention that money damages could adequately redress any injury to Roche. As the Federal Circuit explained in Polymer Techs. v. Bridwell, 103 F.3d 970, 975 (Fed. Cir. 1996):

> Competitors change the marketplace. Years after infringement has begun, it may be impossible to restore a patentee's (or an exclusive licensee's) exclusive position by an award of damages and a permanent injunction. Customers may have established relationships with infringers. The market is rarely the same when a market of multiple sellers is suddenly converted to one with a single seller by legal fiat. Requiring purchasers to pay higher prices after years of paying lower prices to infringers is not a reliable business option.

Cobalt contends that Roche's asserted injuries are all reducible to calculable money damages. This Court does not agree: Roche has persuaded this Court that allowing a generic competitor to enter the marketplace will damage its position in the bisphosphonate market in a way that cannot be undone, and that such damage will not be readily and accurately quantified, such that it may be fully redressed by money damages. This factor weighs in favor of granting the preliminary injunction.

**III. Roche has demonstrated that the balance of hardships and the public interest weigh in favor of granting the preliminary injunction.**

Cobalt argues that it will be harmed by the grant of an injunction by the loss of the market opportunity it has at this point in time: it can now be the first and only generic in the marketplace. While this is a genuine and significant harm, on balance, the harm to Roche in terms of damage to its existing business appears far more significant. The balance of hardships weighs in favor of granting the injunction.

Lastly, as to the public interest, the parties take the traditional positions of branded and generic pharmaceutical manufacturers. Roche contends that the public interest favors the enforcement of valid patents, while Cobalt argues that the public interest favors the availability of low cost drugs. This Court finds, on this record, that the public interest favors encouraging investment in drug development by protecting and enforcing a valid pharmaceutical patent. Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1384 (Fed. Cir. 2006).

**CONCLUSION**

For the reasons stated above, this Court finds that all four factors in the preliminary injunction analysis weigh in favor of granting Roche's motion for a preliminary injunction.

Roche has shown that it is likely to succeed on the merits at trial, that it is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in its favor, and that an injunction is in the public interest. Because all four factors weigh in favor of granting the injunction, Roche's motion for a preliminary injunction, pursuant to 35 U.S.C. § 283, is granted.

The parties disagree as to the amount of the bond that Roche should provide. Cobalt asks for $557 million; Roche asks for $5 million. In view of the fact that this case is now well into the summary judgment phase, and will be heading for plenary trial in the very near future, this Court does not see any need for the sizable bond that Cobalt seeks. Roche shall provide a bond in the amount of $10 million.

s/ Stanley R. Chesler
Stanley R. Chesler, U.S.D.J.

Dated: November 10, 2010