A REVIEW OF THE MODERN IPR PROCESS

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INTRODUCTION

In the pharmaceutical industry, patents protect a drug-maker's right to exclusively produce a drug or issue a license for its production by another entity. In either instance they have the ability to control distribution and, more importantly, the cost. This exclusivity exists until the time the patent term expires, at which point other manufacturers can begin producing a generic versions of the drug. Production of generic drugs significantly cuts the market share of brand name drug as well as drives down the overall cost of the drug. This makes patent protection a big concern for pharmaceutical companies spending years and billions of dollars in drug development.

Once a patent is issued for a drug there is still a chance that the validity of the patent may be challenged. One such way a purported infringer or competitor can challenge a patent's validity is through an *inter partes* review (IPR) Process allowed by the United States Patent and Trademark Office (USPTO). Until recently the use of this process by generic drug-makers to invalidate patents has had no success. However, a recent decision by the Patent Trial and Appeal Board (PTAB) gave generic drug-makers their first break when they invalidated the patent for the multiple sclerosis drug Gilenya. The following will review the IPR process and examine the decision by the PTAB to invalidate the Gilenya patent under 35 U.S.C §103.

I. THE IPR PROCESS

The IPR process was introduced by the USPTO on September 16th 2012 as part of the America Invents Act (AIA). This act allows a party who is not the owner of the patent to petition

the USPTO to review the validity of a patent, with several limitations. This process is available to review any patents regardless of its filing under AIA or pre-AIA conditions but, may only be filed nine-months after the issuance or reissuance of a patent. If the validity of the patent were to be challenged within the nine month period a post grant review process would be initiated.

It is important to note that a civil action challenging the validity of the same patent is not usually concurrent with an IPR. If the petitioner is part of a civil action that action will be (subject to court discretion) stayed in lieu of the IPR. Along these same lines, if a petitioner is requesting an IPR in response to a claim for patent infringement, then the IPR request must be filed within one year of being served the complaint. This allows the proposed infringer to tackle the infringement claim by using the IPR process to claim the patent is invalid.

A. *Filing and challenging claims under the IPR*

The IPR process only allows the validity of the patent to be challenged under 35 U.S.C §102 or §103. 35 U.S.C §102(a) states that a patent will be valid unless the claimed invention was previously described in a single piece of prior art, such as a prior patent, publication, etc. According to 35 U.S.C §103, a patent will not be granted if in light of prior art the claimed invention would have been obvious to someone skilled in the art. Multiple prior art references can be combined to show that the claimed invention would have been obvious to someone skilled in the art. When filing for an IPR, the petitioner must identify which claims are being challenged, the grounds of challenge for each claim, and most importantly the evidence that supports those challenges. Given the limitation of the IPR rules that the claims must be argued under 35 U.S.C §102 and §103 the evidence used in order to challenge the claims in question will primarily consist of patents, printed publications, and declarations or affidavits from experts

in the art. Upon receipt of the petition the patent owner may review the evidence supplied by the petitioner and issue a response as to why the IPR should be denied.

B. *Burden of proof during the IPR*

If, upon review, the USPTO decides there is a valid issue the request will be granted and the PTAB will conduct the review of the patent. The burden placed upon the petitioners is that they must show the patent is invalid by a preponderance of evidence. If the petitioner is successful, the patent owners may then argue the validity of the patent under the same burden. If the patent owner is unsuccessful in showing the validity by a preponderance of the evidence they may then amend the claims in order to make them valid. The patent owner is limited during the amendment process as they may not increase the scope of the claims or introduce new matter. In order to successfully amend the claims the patent owner must show that the new claims will not be invalid based on the evidence presented to invalidate the other claims. Ultimately, if either the petitioner or patent owner is unsatisfied with the PTAB's decision, then the party may appeal the decision.

II. REVIEW OF THE '283 PATENT

Novartis AG and Mitsubishi Pharma Corporation were owners of the patent for Gileyna, a multiple sclerosis drug in tablet form. This drug was covered under U.S. Patent No. 8,324,283 B2 (the '283 patent), which would have given them exclusive rights to produce the drug until 2026. This status was in jeopardy when a number of drug-makers challenged the validity of the patent by filing an IPR process with the USPTO PTAB. Two separate IPRs were filed: one by

Torrent Pharmaceuticals (Torrent) and the other by Apotex Inc. and Mylan Pharmaceuticals. Torrent filed the first action on December 1, 2014 and the second action was joined with the petition filed by Torrent. Fear of losing the patent is justified as it would mean a significant drop in sales and drive down market share as generics are allowed to enter the market. In 2014 Gilenya generated $2.5 billion in sales for Novartis, and with exclusivity until 2026 would be an extremely valuable drug. Unfortunately for Novartis, this fear has become reality as the PTAB invalidated the '283 patent in the IPR.

While the petitioners challenge claims 1-32, claims 1 and 19 are reproduced below and are representative of all the challenged claims.

> Claim 1: A solid pharmaceutical composition suitable for oral administration, comprising:
> (a) a S1P receptor agonist which is selected from 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propane-diol or 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]propyl-1,3-propane-diol, 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]-2-ethyl-1,3-propane-diol, and its phosphates or a pharmaceutically acceptable salt thereof; and
> (b) a sugar alcohol
>
> Claim 19: A solid pharmaceutical composition suitable for oral administration, comprising mannitol and 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol or a pharmaceutically acceptable salt thereof.

The drug name at use in Gileyna is FTY720, also known as fingolimod. The patent essentially describes pairing FTY720 with mannitol, where mannitol is being used as an excipient. Excipients are components of the drug formulation in addition to the active ingredient and can affect things such as stability and uptake of the drug. One of the primary benefits of Gileyna is that it is a solid composition pharmaceutical for oral administration, which in many cases is considered beneficial to liquid forms that are injected via syringe. The patented make-up of the pharmaceutical allows for its solid form by providing optimum efficacy in a stable

compound and uniform distribution of the active ingredient throughout the tablet during the manufacturing procedure.

A. Prior art used by petitioners

Torrent, Apotex, and Mylan challenged claims 1-32 of '283 patent on the grounds of obviousness under 35 U.S.C §103. In order to support this position the petitioners relied primarily on two pieces of prior art, Chiba and Aulton.[1][2]

The Chiba patent teaches the immunosuppressive mechanism of various compounds. Of particular interest to the present case is the effectiveness of compound FTY720, the effective compound in the '283 patent. The Chiba patent also teaches the potential usefulness of the FTY720 compound for the treatment of autoimmune diseases such as multiple sclerosis.

The Aulton reference used by petitioners primarily teaches methods of using tablets and capsules for final drug formulation so the drug can be administered orally. Excipients are given careful consideration given their overall effect on the final product. They can provide stability for the active compound as well as assist with solubility and uptake by the end user. Aulton teaches which characteristics are desirable in a finished product and the ways in which to achieve those characteristics by recommending certain formulations. Of primary concern in the instant case is that Aulton teaches mannitol is a common used excipient in the pharmaceutical industry.

There are two primary concerns that need to be addressed when making an argument for obviousness under 35 U.S.C §103. One should consider whether it would have been obvious to someone skilled in the art to combine teachings and whether or not someone would have had a

reasonable expectation of success in combining the prior art. If these two requirements are not met then the present invention may not have been obvious to someone skilled in the art. In the instant case the petitioners feel that a person having ordinary skill in the art would have had reason to combine the teachings of Aulton and Chiba as well as have a reasonable expectation of success.

B. Review of Claim 19 under 35 U.S.C §103

The first issue addressed by the board is whether or not it would have been obvious for someone skilled in the art to combine mannitol and fingolimod. As stated, petitioners use the Chiba and Aulton teachings as the basis for their argument of obviousness of the mannitol and fingolimod combination. Specifically, Chiba teaches that fingolimod is compatible with many excipients commonly used in the pharmaceutical industry. Aulton further teaches that mannitol is a common excipient used in the formulation of tablets. These teachings would make it reasonably obvious to one skilled in the art to at least try this combination. As additional evidence the petitioners reference the Sakai patent (US 6,277,888) that specifically teaches the combination of these two ingredients in liquid formulation. These three references, along with numerous others, is used as proof this combination would have been obvious to someone skilled in the art.

The patent owners initial response to these arguments is that prior art offered by the petitioners does not make their claimed invention obvious. The patent owners argue their motivation for combining the two teachings was different than that of the prior art. The patent owners claim low concentration instability of the fingolimod made it necessary for them to use mannitol. They argue that since the prior art references do not mention the ability of mannitol to

fix low-dose instability of fingolimod that their finding would not have been obvious. The court rejects this reasoning by stating "the motivation in the prior art to combine the references does not have to be identical to that of the [patentee] to establish obviousness. *In re Kemps*, 97 F.3d 1427, 1430 (Fed. Cir. 1996). The board also goes on to explain that simply because the patent owner found another benefit of the combination it is not enough to put them into the realm of patentability. Given the failed arguments of the patent owners and in light of the references provided by the petitioners, the court ultimately finds that combining mannitol and fingolimod would have been obvious to someone skilled in the art. Concluding, "[i]t is irrelevant that [p]etitioners have failed to establish that the inventors actual subjective reason for combining mannitol and fingolimod was know in the prior art". *Torrent Pharmaceuticals Ltd. v. Novartis AG*, IPR2014-00784, Paper 112 at 19 (PTAB Sept. 24 2015).

The next issue addressed by the board is whether the prior art would have led the patent owners to have a reasonable expectation of success in combining mannitol and fingolimod. The patent owners primary argument is that because Chiba does not specifically mention the use of mannitol and Aulton does not specifically mention the use of mannitol with fingolimod that there would have been no reasonable expectation of success. The patent owners explain that someone skilled in the art would have had a large number of combinations and parameters to explore before finding the correct combination. In light of the large amount of experimentation still needed the prior art suggested no reasonable expectation of success. The board is not persuaded by this argument and simply relies primarily on the teaching of Sakai. In light of all the prior art teaching the combination of mannitol and fingolimod the board feels it would have been reasonable to expect success.

C. Secondary consideration for non-obviousness

Given the patent owners were unable to defeat the claims of non-obviousness in light of the prior art, they move to secondary considerations for showing the invention was non-obvious. These secondary considerations can be used to show that although the prior art may teach towards the invention it still would not have been obvious to someone skilled in the art. The additional arguments offered by the patent owners include unexpected results, an un-met need in the industry, industry praise, and commercial success.

When claiming unexpected results as evidence of non-obviousness, "[i]t is the established rule that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support" *Allergan Inc. v. Apotex Inc.,* 754 F.3d 952, 965 (Fed. Cir. 2014). Put more simply, the unexpected results need to be reflected in the claims at issue.

The patent owners first argument is that the results they achieved were unexpected and therefore novel. They argue that the low dose of fingolimod, 0.25mg, in combination with mannitol offered stability that was unexpected. In light of the current standard this argument is found unpersuasive as the claim at issue, claim 19, reflects no specific dosing in its limitation. If the patent owners wanted to reflect their unexpected results the claim should have stated the specific dosage requirement that was unexpected, it does not.

The second argument patent owners turn to is a long-felt but unmet need. They argue that there was an unmet need in the marketplace for a solid dosage MS drug. Two issues arise with this argument by the patent owners. First, petitioners offer a response to this argument that the market need was for a solid dose MS drug, not specifically the fingolimod and mannitol combination developed by the patent owners. Since the need was not specifically for the combination expressed by the patent owners it is not within the scope of claim 19. Second, the

petitioners offer evidence of other solid dosage MS drugs on the market, although they were not FDA approved and not formulated using fingolimod as the active ingredient. Due to both the prior treatments in the marketplace and no specific need for fingolimod solid dosage the patent owners argument ultimately fails to be persuasive.

The third argument offered by the patent owners indicating non-obviousness was the industry praise for their drug. As evidence to this they offer statements from participants in the clinical trials and from the MS foundation. In order for this argument to be persuasive the "[i]ndustry praise must be linked to the patent invention" *Power-One, Inc. v. Artesyn Tech. Inc.*, 599 F.3d 1343, 1352 (Fed. Cir. 2010). Additionally, if the praise is "due to an element in the prior art, no nexus exists". *Tokai Corp. v. Easton Enters. Inc.*, 632 F.3d 1358, 1396 (Fed. Cir. 2011). Given the praise was only for a solid dose MS drug and not the specific combination in the claimed invention, this argument fails for lack of nexus between the invention and praise given.

The final argument given by the patent owners for evidence of non-obviousness is the commercial success of Gileyna. "[C]ommercial success is relevant only when it is due to [something] disclosed in the patent…which is not readily available in the prior art." *Richdel, Inc. v. Sunspool Corp.*,714 F.2d 1573, 1580 (Fed. Cir. 1983). To make a persuasive argument patent owners must show "significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent." *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). The board finds that the success of Gileyna was due to it being a solid dosage MS drug and not the specific combination of fingolimod and mannitol. In light of this finding there is not a significant connection between the specific patented invention and the commercial success. The board also found that the patent owners provided no relevant evidence

of sufficient market share. While the patent owners did provide sales numbers there was no reference as to whether Gileyna occupied a 'significant' share of the market.

For the reasons stated above, Claim 19 of the '283 patent is found obvious in light of the prior art and therefore invalid. Since claim 19 was found to be invalid the remaining claims, 1-18 and 20-32, were all easily addressed by the board. Given claim 19 was the narrowest of the challenged claims the others were also found to be obvious in light of the prior art.

D. *Amendment of claims for the '283 patent*

Upon the finding that claims 1-32 of the '283 patent were invalid for obviousness the patent owners moved to amend the claims. Under the IPR process the patent owners are permitted to amend the claims in order to bring them out from under the prior art. Upon doing this "[t]he burden is not on the petitioners to show [the] unpatentability [of the proposed claims], but on the patent owner to show patentable distinction over the prior art of record and also [the] prior art known to the patent owner". *Idle Free Sys., Inc. v. Bergstrom, Inc.,* Case IPR2012-00027, slip op. at 7 (PTAB June 11, 2013)(Paper 26). To comply with the IPR process the patent owners must

> "[S]et forth a prima facie case of patentability of narrower substitute claims over the prior art of record, the burden of production shifts to Petitioner. In its opposition, Petitioner may explain why Patent Owner did not make out a prima facie case of patentability, or attempt to rebut that prima facie case, by addressing Patent Owner's evidence and arguments and/or by identifying and applying additional prior art against proposed substitute claims. Patent Owner has an opportunity to respond in its reply. The ultimate burden of persuasion remains with Patent Owner, the movant, to demonstrate the patentability of the amended claims."

Microsoft Corp. v. Proxyconn, Inc., 789 F.3d 1292, 1306

In the instant the patent owners attempt to amend and add claims 33-64. Claim 51 is the primary focus of the amended claims as it attempts to narrow claim 19. As an amendment the petitioners offered the following in addition to the original claim 19, "wherein the composition is stable, wherein the composition has substantially uniform distribution of the agonist throughout the composition, and wherein the composition is made on automated equipment". Mot. To Amend 38-39. The additional limitations offered attempt to narrow claim 19 and bring it out from under the prior art. The patent owners offer the same arguments discussed under the original claim 19. As they did for the original claim, the board finds these arguments unpersuasive and finds the amended claims do not defeat the finding of obviousness given the prior art. Predictably, all the additionally amended claims are also found obvious and the motion to amend was denied.

In summary the petitioners showed, by a preponderance of the evidence, that the '283 patent would have been obvious in light of the prior art. Since the original claims and the patent owners amended claims failed to defeat the finding obviousness the '283 patent at issue was found to be invalid.

CONCLUSION

The success of the petitioners IPR marked the first win for generic drug-makers in the IPR process. It is doubtful however that this will be the end of the battle over the '283 patent as Novartis can appeal the decision issued by the PTAB, and likely will. If the decision stands however, Gileyna will lose its protection in 2019 as opposed to the 2026 date it previously held. While this is obviously a big loss for Novartis it also means more competition for other brand name MS drugs currently facing limited competition in the marketplace. Invalidation of pharmaceutical patents through the IPR process creates more competition in the marketplace and

ultimately drives down cost for consumers. However, the other consideration is what it may mean for overall drug development. A basic premise for offering patent protection is that it is an incentive for the creation of new inventions. Drug companies spend billions in developing drugs with only a fractionally small number of them ever receiving FDA approval and reaching market. The cost and time invested in development has typically been rewarded with the awarding of a patent and exclusive rights to sell the drug in the market place. This allows companies to recoup some of the costs of development and fund development of new drugs. While ensuring patents are not issued for non-novel inventions is important, use of the IPR process to invalidate drug patents may have the adverse affect of slowing drug development.

ENDNOTES

[1]Chiba et al., US 6,004,565, issued Dec. 21, 1999 (“Chiba”)

[2]Pharmaceuticals: The Science of Dosage Form Design, 223-321 (Michael E. Aulton ed. 1988)