IP NEWS QUARTERLY

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THE NECESSITY OF EFFICACY DATA

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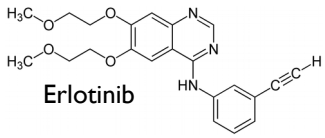
Introduction

On October 4, 2019, the United States Court of Appeals for the Federal Circuit reversed a previous Patent Trial and Appeal Board (PTAB) decision and stated that United States Patent No. 6,900,221 was valid in view of prior art, as none of the prior art showed efficacy data for the treatment of Non-Small-Cell Lung Carcinoma (NSCLC) by the epidermal growth factor receptor (EGFR) kinase inhibitor erlotinib, trade name Tarceva.

This issue of IP News Quarterly will look at the background and prior art discussed, the PTAB's decision, the Federal Circuit Court's reversal, and how this decision could affect pharmaceutical patent defense moving forward.



Erlotinib

Background and Prior Art

On November 9, 2000, OSI Pharmaceuticals, Inc. filed United States Patent Application No. 09/711,272, which matured into Patent No. 6,900,221 (the '221 patent). The '221 patent disclosed the synthesis of erlotinib hydrochloride (free base pictured above), and use of erlotinib HCl in the treatment of NSCLC by the mechanism of EGFR inhibition. And while the overall failure rate for a drug entering clinical trials in the United States is around 90%, for NSCLC drugs which entered the clinic from 1990-2005, there was a 99.5% failure rate. This evidences the difficulty of developing new therapies in this field around the time of the '221 patent.

The structure and synthesis of erlotinib, the fact that it was an EGFR inhibitor, and the fact that such inhibition was useful for the treatment of lung cancer in mammals was previously disclosed by Pfizer Inc. in US Patent No. 5,747,498 and WO 96/30347, which is the first prior art cited by the appellees against the '221 patent. The second prior art was a 1997 review article written by Jackson Gibbs which states that 1) erlotinib and another compound, ZD-1839, were inhibitors of EGFR, 2) they showed efficacy against NSCLC in preclinical models, and 3) were progressing into further clinical trials. The third prior art was OSI Pharmaceuticals' 1998 Form 10-K, which gives a summary of a company's financial condition and performance, and stated that 1) erlotinib targets a number of cancers, including NSCLC, via the mechanism of EGFR inhibition, 2) that it passed Phase I clinical trials, and 3) that it was entering Phase II trials in the United States. The specific cancer being targeted in these Phase I and II trials was not mentioned.

On November 20, 2015, Apotex, a generic drug company, filed a request for Inter Partes Review of claims 44-47 and 53 of the '221 patent, directed towards the treatment of NSCLC in mammals using erlotinib. This request was granted by the PTAB on January 9, 2017. The Inter Partes Review focused on whether the prior art discussed above made the treatment of NSCLC by erlotinib obvious with a reasonable expectation of success at the date of filing. A decision was issued on Jaunary 8, 2018 on Case IPR2016–01284 (the IPR).

The PTAB's Decision

After reviewing the evidence, The Patent Trial and Appeal Board concluded that the combination of Pfizer's Patent No. 5,747,498 with Gibbs' review article or OSI's Form 10-K made the '221 patent's claims obvious with a reasonable expectation of success. All parties agreed that while Pfizer's Patent No. 5,747,498 disclosed and claimed 1) the structure of erlotinib, 2) its use in the treatment of lung cancer, and 3) its mechanism of action, but that the Pfizer patent did not specifically teach erlotinib for the treatment of NSCLC (the IPR pg 25).

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Did You Know?

A typical FDA approved drug takes on average 10-15 years to develop and costs around 2 billion dollars from start to finish. The reason for this is that drugs entering clinical trials have about a 90% failure rate and so the one drug that makes it through needs to be able to recoup the costs lost on the other ones. This is especially true for drugs which fail in later phases of clinical trials. Clinical trials in the US are broken up into three phases, which get larger and thus more expensive with each step. Phase I tests the compound on a small group of healthy volunteers in order to test safety and dosing. Phase II tests the drug on a medium sized group of patients with the target disease. This phase has the highest failure rate as it is the first phase to test efficacy in humans. Phase III is a larger and broader efficacy test and is the most expensive. Drug patents ideally help companies protect their investment and reward their innovation and research.

Thus, the key question was whether Pfizer's Patent No. 5,747,498 could be combined with Gibbs' review article and/or OSI's Form 10-K, and whether this combination led to a reasonable likelihood of success.

OSI's arguments focused on the fact that none of the references gave a reasonable likelihood of success since no prior art shows the effective use of erlotinib to treat NSCLC. OSI argued that while Gibbs' review article stated that both erlotinib and ZD-1839 showed preclinical efficacy in NCSLC, the references cited to back up these claims only discuss ZD-1839 (the IPR pg 35-36). Additionally, while OSI's Form 10-K states that erlotinib targets NSCLC and other cancers by inhibiting EGFR, and that it was going into clinical trials for the treatment of cancer, it does not give any indication as to what cancer(s) the clinical trials were for, or whether any work had been done which demonstrated that erlotinib could treat NSCLC in mammals. Form 10-K only stated that erlotinib targets the EFGR oncogene present in NSCLC, among other potentially more promising therapeutic candidates (the IPR pg 32-33). Taken together, OSI argues, neither prior art provides a reasonable expectation of success of overcoming the abysmally high failure rate of NSCLC drugs in the clinic.

Apotex argued that the requirement for clinical data or FDA approval is not necessary since the debated claims are for treating mammals, not specifically humans. Thus, all that is required is the idea that NSCLC can be treated with erlotinib in mammals. Apotex argues that the Gibbs review article would have been taken as valid, despite not having fully supportive references, as he is an esteemed pharmacologist and never made an attempt to correct the mistake (the IPR pg 39-40). Similarly, while no data was given, "OSI's 10-K was only required to lead the ordinary artisan to the treatment of non-small cell lung cancer." (the IPR pg 33). Thus, Apotex argued, since OSI's 10-K and Gibbs' article both state that erlotinib targets EGFR in NSCLC, and Pfizer's Patent No. 5,747,498 shows that inhibition of EFGR by erlotinib effectively treats cancer, treating NSCLC by EGFR inhibition was obvious with a reasonable likelihood of success at the time of the filing of the '221 patent.

The Board ultimately sided with Apotex, focusing mainly on the fact that "proof of efficacy, such as demonstration of clinical efficacy in human non-small cell lung cancer patients, is not required to demonstrate obviousness of the challenged claims" as the claims were directed towards the treatment of NSCLC in mammals in general, and not humans in particular (the IPR pg 34).

The Federal Circuit Court's Reversal

As stated above, on appeal, OSI Pharm., LLC v. Apotex Inc., No. 2018-1925, (Fed. Cir. Oct. 4, 2019), the Federal Circuit Court reversed the PTAB's decision and agreed with OSI that "The Board's finding of a reasonable expectation of success is not supported by substantial evidence." (2018-1925 pg 20). The Federal Circuit Court dismissed the Gibbs article in view of the fact that it was not supported by citations, as well as Gibbs' own admission that he did not know of a reference that supported the claim that erlotinib treated NSCLC at the time the article was published (2018-1925 pg 14-15). Thus, OSI's 10-K form was the only other viable prior art. In response to this document, The Federal Circuit Court sided with OSI, stating that "[t]here is nothing in OSI's 10-K suggesting the existence of erlotinib preclinical efficacy data that is specific to NSCLC. . . . And just because the EGFR is targeted by a drug does not necessarily mean the drug will *treat* NSCLC" as claimed (2018-1925 pg 17, emphasis added). Therefore, similar to the PTAB, The Federal Circuit Court concluded that the prior art "contain[s] no data or other promising information regarding erlotinib's efficacy in treating NSCLC." (2018-1925 pg 16). However, in contrast to the PTAB's decision, they state that "[t]he lack of . . . efficacy data or other indication of success here is significant because of the highly unpredictable nature of treating NSCLC, which is illustrated by the over 99.5% failure rate of drugs entering Phase II." (2018-1925 pg 16).

Pharmaceutical Patent Defense Moving Forward

The Federal Circuit Court was very clear to point out that they "do not hold today that efficacy data is always required for a reasonable expectation of success. Nor or are we requiring 'absolute predictability of success'." (2018-1925 pg 18). However, with this case, pharmaceutical patent owners have an added line of defense against obviousness and reasonable likelihood of success arguments, namely the unpredictability of success in the drug market. While other factors will effect other cases, this argument potentially can be used in situations similar to the one discussed in this issue of IP News Quarterly. Whether these arguments stand, and whether limits are given which further define what "highly unpredictable nature of treating [a disease]" means will be an interesting follow-up study.

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