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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC., APOTEX CORP., APOTEX PHARMACEUTICALS HOLDINGS INC., AND APOTEX HOLDINGS, INC.,
Petitioner,

v.

OSI PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2016-01284
Patent 6,900,221 B1

Before LORA M. GREEN, RAMA G. ELLURU, and ZHENYU YANG, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Apotex Inc., Apotex Corp., Apotex Pharmaceuticals Holdings Inc., and Apotex Holdings, Inc., ("Apotex" or "Petitioner") filed a Petition requesting an *inter partes* review of claims 44–47 and 53 of U.S. Patent No. 6,900,221 B1 (Ex. 1001, "the '221 patent"). Paper 3 ("Pet."). OSI Pharmaceuticals, Inc. ("OSI" or "Patent Owner") filed a Preliminary Response to the Petition.[1] Paper 7 ("Prelim. Resp.").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition and the Preliminary Response, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of the challenged claims. Accordingly, we institute an *inter partes* review of claims 44–47 and 53 of the '221 patent.

A. Related Proceedings

According to Patent Owner, the '221 Patent is presently at issue "in *OSI Pharms. LLC. et al. v. Apotex Inc. et al.*, Case No. 1:15-cv-00772-SLR (D. Del. Sept. 2, 2015) and *OSI Pharms. LLC. et al. v. Breckenridge Pharms. Inc. et al.*, Case No. 1:15-cv-01063-SLR (D. Del. Nov. 17, 2015), which are consolidated in lead Case No. 1:15-00772-SLR." Paper 5, 3–4. Patent Owner further identifies a number of closed matters involving the

[1] OSI further identifies Astellas US LLC, Astellas US Holding, Inc., Astellas Pharma Inc., and Genentech, Inc., as real parties-in-interest. Paper 5, 1.

'221 patent including *OSI Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, Case No. 1:09-cv-00185-SLR (D. Del. Mar. 19, 2009). *Id*.

B. The '221 Patent (Ex. 1001)

The '221 patent is generally directed to the B polymorph of N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride. Ex. 1001, Abstract. The patent further discloses that "N-(3-ethyny lphenyl)-6, 7-bis(2-methoxyethoxy)-4-quinazolinamine, in either its hydrochloride or mesylate forms, or in an anhydrous and hydrous form, is useful in the treatment of hyperproliferative disorders, such as cancers, in mammals." *Id.* at 1:21–25. The '221 patent references U.S. Patent No. 5,747,498 to Schnur, and incorporates it by reference in its entirety. *Id.* at 1:27–29. In addition, the '221 patent notes that Example 20 of that patent refers

> to [6,7-bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride, which, the patent discloses, is an inhibitor of the erbB family of oncogenic and protooncogenic protein tyrosine kinases, such as epidermal growth factor receptor (EGFR), and is therefore useful for the treatment of proliferative disorders, such as cancers, in humans.

Id. at 1:29–35.

According to the '221 patent, the method of treating cancer using the disclosed compound

> may be for the treatment of a cancer selected from brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological and thyroid cancer.
>
> The method may also be for the treatment of a cancer selected from non-small cell lung cancer (NSCLC), refractory ovarian cancer, head and neck cancer, colorectal cancer and renal cancer.

Id. at 4:23–30.

C. Challenged Claims

Petitioner challenges claims 44–47 and 53 of the '221 patent. Claim 44 is the only independent challenged claim, is representative, and is reproduced below:

> 44. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HFV), Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7 - bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier.

Ex. 1001, 35:26–36 (emphasis added).

Dependent claim 45 specifies that the treatment comprises further a palliative or neo-adjuvant/adjuvant monotherapy. *Id.* at 35:37–39. Dependent claim 46 specifies that that the treatment comprises blocking epidermal growth factor receptors ("EGFR"), and claim 47 specifies that the method is for the treatment of tumors that express EGFRvIII. *Id.* at 35:40–44. Dependent claim 53 specifies that the method is for the treatment of non-small cell lung cancer ("NSCLC"). *Id.* at 35:64–65.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 44–47 and 53 of the '221 patent on the following grounds (Pet. 4–5):

References	Basis	Claims Challenged
Schnur[2] and OSI's 10K[3] or Gibbs[4]	§ 103	44–46 and 53
Schnur, Gibbs or Wakeling,[5] and Moscatello[6]	§ 103	47
Schnur	§ 102(b)	44–47 and 53

Petitioner relies also on the Declaration of Giuseppe Giaccone, M.D., Ph.D. (Ex. 1002), as well as the Declaration of Laurence S. Lese, Esq. (Ex. 1012).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. *See* 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard).

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[2] Schnur et al., U.S. Patent No. 5,747,498, issued May 5, 1998 (Ex. 1009) ("Schnur").

[3] Annual Report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the Fiscal Year Ended September 30, 1998, Commission File Number 0-15190, OSI Pharmaceuticals, Inc. (Ex. 1011) ("OSI's 10K").

[4] J.B. Gibbs, "*Anticancer Drug Targets: Growth Factors and Growth Factor Signaling*," 105 J. CLIN. INV. 9–13 (2000) (Ex. 1010) ("Gibbs").

[5] A.E. Wakeling *et al.*, "*Specific Inhibition of Epidermal Growth Factor Receptor Tyrosine Kinase by 4-Anilinoquinazolines*," 38 BREAST CANCER RESEARCH AND TREATMENT 67–73 (1996) (Ex. 1013) ("Wakeling").

[6] D.K. Moscatello et al., "*Constitutive Activation of Phosphatidylinositol 3-Kinase by a Naturally Occurring Mutant Epidermal Growth Factor Receptor*," 273 J. BIOL. CHEM. 200–206 (1998) (Ex. 1014) ("Moscatello").

Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner contends that the terms of the claim should have their ordinary and customary meaning (Pet. 13), as does Patent Owner (Prelim. Resp. 17). On the present record, we agree, and determine that none of the claim terms require explicit construction for purposes of this Decision. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs, Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Anticipation by Schnur

Petitioner contends that the '221 patent claims the benefit of three priority applications, and to the extent that the earliest priority application, 60/164,907 ("the '907 provisional"), is found to disclose the use of erlotinib to treat NSCLC, Schnur "must also be found to disclose treatment of NSCLC with erlotinib." *Id.* at 44–46.

Patent Owner argues that we should invoke our discretion under 35 U.S.C. § 325(d) and deny the anticipation challenge over Schnur. Prelim.

Resp. 47. According to Patent Owner, the issue of whether the challenged claims are rendered unpatentable by Schnur has been considered previously by both the United States Patent and Trademark Office ("Office") and a federal district court. *Id.*

Patent Owner asserts further that the Petition acknowledges that Schnur does not disclose treatment of NSCLC, and, as the Petitioner also acknowledges, that was the reason given in the Statement of Reasons for Allowance in allowing the challenged claims to issue. *Id.* at 47–48 (citing Pet. 44–45, Appendix C; Ex. 1006).

We have discretion under 35 U.S.C. § 325(d) to reject a petition when the same or substantially the same prior art or arguments were presented previously in another proceeding before the Office. The relevant portion of that statute is reproduced below:

> In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

35 U.S.C. § 325(d).

Although a petitioner may have sound reasons for raising art or arguments similar to those previously considered by the Office, the Board weighs petitioners' desires to be heard against the interests of patent owners, who seek to avoid harassment. *See* H.R. Rep. No. 112-98, pt.1, at 48 (2011) (AIA proceedings "are not to be used as tools for harassment or a means to prevent market entry through repeated litigation and administrative attacks on the validity of a patent. Doing so would frustrate the purpose of the section as providing quick and cost effective alternatives to litigation.").

As Patent Owner notes (Prelim. Resp. 20), Schnur was explicitly considered by the Office during examination of the '221 patent. In fact, the Examiner noted that the specific cancers recited by the claim considered by the Examiner "are not found in Schnur." Ex. 1006. Moreover, we note that the Petition acknowledges that Schnur does not disclose NSCLC as a hyperproliferative order, noting rather that Schnur discloses lung cancer generally. *See*, *e.g.*, Pet. 26. Petitioner bases its anticipation challenge on the proposition that to the extent that the '907 provisional discloses treatment of NSCLC, Schnur also discloses treatment of NSCLC. Petitioner, however, is conflating the requirements of 35 U.S.C. § 102 for anticipation with those of 35 U.S.C. § 120 for claiming the benefit of a filing date to an earlier filed application. Thus, balancing the competing interests involved and taking full account of the facts and equities involved in this particular matter, we exercise our discretion, under 35 U.S.C. § 325(d), to deny the Petition and decline to institute *inter partes* review based on anticipation by Schnur.

C. Obviousness over Schnur and OSI's 10-K or Gibbs

Petitioner asserts that claims 44–46 and 53 are rendered obvious by the combination of Schnur and OSI's 10-K or Gibbs. Pet. 23–35. Petitioner presents a claim chart demonstrating where the limitations of the challenged claims may be found in the relied upon references. Pet., Appendix A. According to Petitioner, "[a]nalysis of the obviousness of claims 44-46 and 53 over *Schnur* in view of *Gibbs* or *OSI's 10-K* is presented in the alternative in the event that the Patent Owner attempts to antedate *Gibbs* in order to remove it as prior art to these claims." *Id.* at 23.

Patent Owner contends that Petitioner has not established a reasonable likelihood that claims 44–46 and 53 are rendered obvious by the

combination of references relied upon by Petitioner. Prelim. Resp. 18–33. Patent Owner asserts further that we should only institute as to only one of either OSI's 10-K or Gibbs, as those references have essentially the same disclosure. *Id.* at 32.

i. Overview of the Prior Art

a. Schnur (Ex. 1009)

Schnur "relates to 4-(substituted phenylamino) quinazoline derivatives which are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals." Ex. 1009, 1:9–11. Schnur recognizes that there is a continuing need for anti-cancer pharmaceuticals. *Id.* at 1:64–67. Schnur notes that it is known that a cell may become cancerous through transformation of a portion of its DNA into an oncogene, many of which "encode proteins which are aberrant tyrosine kinases capable of causing cell transformation." *Id.* at 1:20–25. According to Schnur:

> Receptor tyrosine kinases are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a transmembrane domain, and an intracellular portion which functions as a kinase to phosphorylate specific tyrosine residues in proteins and hence to influence cell proliferation. It is known that such kinases are frequently aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer. It has also been shown that epidermal growth factor receptor (EGFR) which possesses tyrosine kinase activity is mutated and/or overexpressed in many human cancers such as brain, lung, squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid tumors.

Id. at 1:30–44. Thus, Schnur teaches that is known that inhibitors of receptor tyrosine kinases "are useful as [ ] selective inhibitors of the growth of mammalian cancer cells." *Id.* at 1:45–47.

Of the 4-(substituted phenylamino) quinazoline derivatives taught by Schnur, Schnur teaches that [6-7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3- ethynylphenyl)amine is preferred (*id.* at 3:47–48; 4:8–9), and specifically discloses its synthesis (*id.* at 22:30–49 (Example 20)).

Schnur teaches:

> The active compounds of this invention are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), erbB2, HER3, or HER4 and thus are all adapted to therapeutic use as antiproliferative agents (e.g,. anticancer) in mammals, particularly humans. In particular. the compounds of this invention are therapeutants or prophylactics for the treatment of a variety of human tumors (renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, various head and neck tumors), and other hyperplastic conditions such as benign hyperplasia of the skin (e.g .. psoriasis) or prostate (e.g., BPH). It is, in addition, expected that a quinazoline of the present invention may possess activity against a range of leukemias and lymphoid malignancies.

Id. at 14:1–16.

b. Overview of OSI's 10K (Ex. 1011)

OSI's 10K is a filing with the Securities and Exchange Commission ("SEC") by OSI Pkarmaceuticals, Inc. Ex. 1011, 1. Petitioner provides also the Declaration of Mr. Lese, Esq., whose "entire professional career has focused on the practice of securities law and concomitantly corporate law."

Ex. 1012 ¶ 1. Mr. Lese provides declaration testimony reviewing the process of OSI's filing with the SEC (*id.* ¶¶ 16–23). Mr. Lese opines:

> I therefore conclude that, as of the last week of December 1998, any person could have accessed OSI's annual report on Form 10-K for its fiscal year ended September 30, 1998 using the EDGAR system within 24 to 48 hours of, December 23, 1998.

Id. ¶ 25.

> OSI's 10 K discloses
>
> > With its collaborative partner Pfizer, OSI has focused since 1986 on the discovery and development of novel classes of orally active, molecularly targeted, small molecule anticancer drugs based on oncogenes and tumor suppressor genes and the fundamental mechanisms underlying tumor growth. *The first of these programs to yield a clinical candidate, CP-358,774, which targets a variety of cancers including* ovarian, pancreatic, *non-small cell lung* and head and neck, achieved a significant milestone with the completion of Phase I safety trials and the initiation of Phase II clinical trials in the United States in cancer patients. *CP-358,774 is a potent, selective and orally active inhibitor of the epidermal growth factor receptor, a key oncogene in these cancers*. In addition, two other compounds, CP-564,959 and CP-609,754, have been identified and are in advanced stages of pre-clinical development. Nine other targets are in active R&D at OSI. CP-564,959 is being developed as an orally available, potent and selective inhibitor of a key protein tyrosine kinase receptor involved in blood vessel growth or angiogenesis. Angiogenesis is induced by solid tumors which require nutrients that will enable growth. The Company believes that the ability to safely and effectively inhibit this process represents one of the most exciting areas of cancer drug development. CP-609,754 is an orally active inhibitor of the ras oncogene, which is another important target involved in many major tumors including colon and bladder. The types of novel anticancer drugs being developed in the OSI/Pfizer collaboration are expected to be safer and more effective than standard chemotherapeutic agents.

Ex. 1011, 5–6 (emphasis added).

c. Gibbs (Ex. 1010)[7]

Gibbs provides "a broad overview of a growth factor signal transduction system, with a focus on those points that have been translated to drugs or clinical candidates." Ex. 1010, 9. Gibbs notes, however, that "[d]ue to editorial restrictions limiting the number of reference citations, much of the clinical data gleaned from abstracts is not listed in the references," and points the reader to another reference. *Id.*

Gibbs teaches:

> The EGF receptor is also the target for the development of inhibitors of the intracellular tyrosine kinase domain. ZD-1839 and CP-358,774, competitive inhibitors of ATP binding to the receptor's active site, are currently in clinical trials (12, 13). Their mechanism of action has led to some concern about safety, given the variety and physiological significance of protein kinases and other enzymes that bind ATP. However, these compounds appear to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer.

Id. at 10.

Gibbs provides also Table 1, which sets forth examples of inhibitors of growth factor signaling, and their development status, which is reproduced below:

[7] We note that at this stage of the proceeding, Patent Owner does not argue that Gibbs in not prior art under 35 U.S.C. § 102(a). Rather, Patent Owner merely states it "reserves the right" to antedate Gibbs should any ground including Gibbs be instituted. Prelim. Resp. 32 n. 10. Thus, for purposes of this decision, we assume that Gibbs is prior art to the challenged claims under 35 U.S.C. § 102(a).

Table 1
Examples of inhibitors of growth factor signaling for cancer treatment

Target	Compound	Mechanism of action	Development status
HER2/c-neu	Trastuzumab	mAb	Launched as Herceptin™
EGF receptor	C225	mAb	Phase III
	E7.6.3	mAb	Preclinical
	ZD-1839	Kinase inhibitor	Phase II
	CP-358,774	Kinase inhibitor	Phase II
	PD-168,393	Kinase inhibitor	Preclinical
PDGF receptor	SU-101	Kinase inhibitor	Phase III
IGFR	AS ODN	Antisense	Preclinical
Ras	ISIS-2503	Antisense	Phase II
	R115777	FTI	Phase II
	SCH 66336	FTI	Phase II
	L-778,123	FTI	Phase I
	BMS-214662	FTI	Phase I
Raf	ISIS-5132	Antisense	Phase II
	ZM 336372	Kinase inhibitor	Preclinical
	L-779,450	Kinase inhibitor	Preclinical
MEK	PD-184352	Kinase inhibitor	Preclinical
	U0126	Kinase inhibitor	Preclinical
PKC	ISIS-3521	Antisense	Phase II
	CGP 41251	Kinase inhibitor	Phase II
	UCN-01	Kinase inhibitor	Phase I
PI 3'-kinase	LY 294002	Kinase inhibitor	Preclinical

Id.

ii. Analysis

Petitioner relies on Schnur for teaching a genus of compounds that includes erlotinib, and disclosing it as a preferred compound. Pet. 24 (citing Ex. 1009, 3:47–48, 4:8–9, 38:13–39:12, 39:33–40:65; Ex. 1002 ¶ 93). According to Petitioner, although Schnur "discloses that the compounds can be administered to a mammal for the treatment of a hyperproliferative disorder" (*id.* (citing Ex. 1009, 5:49–52), the only difference between Schnur and the invention of challenged claims 44 and 53 is that Schnur "does not expressly identify 'NSCLC' as a hyperproliferative disorder" (*id.* at 26 (citing Ex. 1005, 23, Ex. 1006, 2)). Petitioner notes, however, that

Schnur "discloses that erlotinib is useful to treat, *inter alia*, 'lung cancer.'" *Id.* (citing Ex. 1009, 14:1–6).

Petitioner relies on Gibbs for teaching that CP-358,774, which Petitioner contends is anhydrous erlotinib hydrochloride, is "a kinase inhibitor 'with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer,' and had entered Phase-II clinical trials." *Id.* at 27 (citing Ex. 1010, 9–10, Table 1).

Petitioner relies on OSI's 10K for teaching that CP-358,774 is "a clinical candidate that had 'achieved a significant milestone with the completion of Phase I safety trials and the initiation of Phase II clinical trials in the United States in cancer patients.'" *Id.* at 28 (citing Ex. 1011, 6). Petitioner relies on OSI's 10K also for its disclosure "that CP-358,774 is a potent, selective and orally active inhibitor of the EGFR and being used to target ovarian, pancreatic, non-small cell lung, and head and neck cancers." *Id.* (citing Ex. 1011, 6).

Petitioner asserts, therefore, that Gibbs or OSI's 10K would have pointed an ordinary artisan towards erlotinib from the compounds of Schnur (*id.* at 28 (citing Ex. 1002 ¶¶ 102–105)), and would have also taught its use to treat NSCLC (*id.* (citing Ex.1010, 10, Ex. 1011, 6, E. 1002 ¶ 106)). Moreover, Petitioner asserts, the teachings of Gibbs or OSI's 10K would have provided a reasonable expectation of success of achieving the method of challenged claim 44. *Id.* at 29 (citing Ex. 1002 ¶¶ 105, 109).

Patent Owner responds that Petitioner has not established that either Gibbs or OSI's 10K "relate[ ] to any compound disclosed in Schnur, let alone erlotinib, specifically." Prelim. Resp. 19. According to Patent Owner, Gibbs or OSI's 10K refer to CP-358,774, which the Petition characterizes as

anhydrous erlotinib hydrochloride, but does not cite any evidence to support that characterization. *Id.* at 19–20. Patent Owner contends "[t]o the extent this missing teaching may be buried elsewhere in portions of Apotex's expert declarations or exhibits but never referenced in the Petition itself, it would be improper to rely on such materials to provide a key teaching necessary to establish any alleged motivation to combine." *Id.* at 20 (citing 37 C.F.R. § 42.104(b)(5)). Thus, Patent Owner asserts, as Petitioner has failed to establish that "CP-358,774" refers to any compound in Schnur, Petitioner has failed to supply any reason as to why the ordinary artisan would combine Schnur with either Gibbs or OSI's 10K. *Id.* at 22.

We do not find Patent Owner's argument persuasive at this stage of the proceeding. Dr. Giaccone, Petitioner's expert, declares:

> During joint clinical development of erlotinib between OSI and Pfizer, and then subsequently, only OSI, the hydrochloride salt of erlotinib was commonly referred by the identifier CP-358,774, which was prepared as set forth in PCT Pub. No. WO 96/30347. (*See* Ex. **1016**[8] at 4839, col. 1; *See also* V.A. Pollack *et al.*, "Inhibition of Epidermal Growth Factor Receptor-Associated Tyrosine Phosphorylation in Human Carcinomas with CP-358,774: Dynamics of Receptor Inhibition In Situ and Antitumor Effects in Athymic Mice," *J. Pharmacol. Exp. Ther.* 291(2):739-748 (Nov. 1999) (*"Pollack*," Ex. 1015) at 740 ("CP-358,774 . . . a colorless, crystalline, anhydrous compound, was synthesized in our laboratories (Arnold and Schnur, 1998)).)

[8] Moyer et al., *Induction of Apoptosis and Cell Cycle Arrest by CP-358,774, an Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase*. 57 CANCER RESEARCH 4838–4848 (1997) ("Moyer").

Ex. 1002 ¶ 29. That statement is supported by Moyer, which defines "CP-358,774" as "[6,7-Bis(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynylphenyl) amine." Ex. 1016, 4839.

Although we acknowledge that Petitioner may not have explicitly directed our attention to paragraph 29 of the Declaration of Dr. Giaccone, Petitioner does direct us to paragraph 28 in discussing the structure of erlotinib (*see* Pet. 24 n. 3), and, thus, based on the specific facts of the instant proceeding, we determine that Petitioner's failure to specifically reference paragraph 29 of the Declaration of Dr. Giaccone is not fatal to the Petition for purposes of institution.

Patent Owner argues further that neither the Petition nor the Declaration of Mr. Lese, Petitioner's expert, establish why the ordinary artisan (i.e., a medical oncologist) would look to OSI's 10K, a financial report filed with the United States Securities Exchange Commission, for "information about an experimental cancer treatment." Prelim. Resp. 22–23.

Again, we do not find this argument persuasive at this stage of the proceeding. Schnur relates to the use of 4-(substituted phenylamino) quinazoline derivatives, such as [6-7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3- ethynylphenyl) amine, that is, erlotinab, and would direct the ordinary artisan interested in using those compounds for the treatment of hyperproliferative disorders, such as cancer, to look at groups and companies developing those compounds. Thus, we are not persuaded on the record presently before us that artisans interested in the compounds of Schnur would not have been aware of the efforts of others, such as that represented by OSI's 10K.

Patent Owner contends also that Petitioner has failed to demonstrate that the ordinary artisan "would have had a reasonable expectation of success in combining Schnur with the OSI 10-K or Gibbs to achieve the claimed invention." Prelim. Resp. 23. Specifically, Patent Owner asserts that Petitioner and its expert, Dr. Giaccone, erroneously assert that OSI's 10-K and Gibbs "disclose studies involving treatment of NSCLC patients with erlotinib." *Id.* at 25–26 (citing Ex. 1002 ¶¶ 68, 72, 109, 119; Pet. 10, 11, 29).

As to OSI's 10-K, Patent Owner asserts that document "does not disclose that any Phase II clinical trial had been initiated for erlotinib for any particular indication, including NSCLC, let alone that any Phase II trial had produced positive results," but only "generally refers to a Phase II study for CP-358,774 in "'cancer patients.'" *Id.* at 26 (citing Ex. 1011, 5–6).

As for Gibbs, Patent Owner asserts that "Gibbs merely identifies the 'development status' of CP-358,774 as Phase II, without identifying the cancer indication for which CP-358,774 is being evaluated in the study." *Id.* (citing Ex. 1010, 10 (Table 1)). Moreover, Patent Owner argues that Gibbs does not provide data for CP-358,774, and the reference it cites that relates to CP-358,774 "reports on mouse xenograft studies in head and neck cancer cell lines—i.e., not NSCLC." *Id.* at 26–27 (citing Ex. 1010, 10 (which references Moyer)). Thus, Patent Owner contends, although Gibbs mentions NSCLC, it is not supported by underlying data or any citation to an underlying source. *Id.* at 27. In fact, Patent Owner argues, the only reference that discusses NSCLC pertains to ZD-1839, a structurally distinct

compound. *Id.* (citing Ex. 2006[9]). Patent Owner contends, therefore, that the ordinary artisan would "have appreciated that the statement in Gibbs that 'these compounds appear to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer,' does not teach that favorable clinical results had been obtained from treating NSCLC patients with erlotinib." *Id.* at 28.

In addition, Patent Owner argues that neither of Gibbs or OSI's 10K could have disclosed using erlotinib for treating NSCLC in patients, or reported favorable data reporting the same, as "the first patient in a Phase II study of erlotinib in NSCLC was first dosed on January 25, 2000—after Gibbs published on January 1, 2000 and over a year after the filing of the OSI 10-K." *Id.* at 28 (citing Ex. 2004, 6, Ex. 2007 (Cover Page and Table of Contents)). Patent Owner asserts that, at most, Gibbs and OSI's 10K indicate that Phase I studies of CP-358,774 "have been completed, and that a Phase II trial in an undisclosed indication has commenced." *Id.* at 29. The Declaration of Petitioner's expert, Dr. Giaccone, Patent Owner asserts, only "includes conclusory statements suggesting that, merely because erlotinib had been administered to humans, [the ordinary artisan] would have expected erlotinib to treat NSCLC." *Id.* (citing Ex. 1002 ¶¶ 112, 120, 130). According to Patent Owner, the ordinary artisan would have understood that "simply administering a compound to a human provides no expectation regarding its therapeutic efficacy in treating any particular disease." *Id.*

[9] J. R. Woodburn et al., *ZD1839, an epidermal growth factor tyrosine kinase inhibitor selected for clinical development*, 38 PROCEEDINGS AM. ASS'N CANCER RESEARCH 633 (1997).

Patent Owner contends that "most anticancer compounds—including most inhibitors of tyrosine kinases (e.g., EGFR)—fail in clinical trials, including Phase III trials." *Id.* at 30 (citing Ex. 2008[10] for its disclosure that "only about 5% of new oncology compounds advanced from human trial to FDA approval, and that from 1990-2005, ***only seven of the 1,631*** new drugs tested in Phase II clinical trials for NSCLC obtained FDA approval"; Ex. 2009[11] for its disclosure that "only 15% of Phase III trials evaluated between 1973-1994 involving chemotherapy agents for the treatment of advanced NSCLC showed a statistically significant prolongation in the survival of the patient"). Thus, according to Patent Owner, the ordinary artisan would understand that "nothing about identifying and developing effective therapies for NSCLC would have been routine or predictable." *Id.*

Patent Owner's arguments are not persuasive at this stage of the proceeding. OSI's 10K teaches that Phase I trials of CP-358,774, i.e., erlotinib, had been completed, and that Phase II trials were commencing. Ex. 1011, 5–6. OSI's 10K specifically teaches also that the compound targets non-small cell lung cancer. *Id.* Similarly, Gibbs teaches CP-358,774 was in clinical trials, and had good anti-cancer activity in patients with non-small cell lung cancer. Ex. 1010, 10. Table I of Gibbs shows that the development status of the compound is Phase II. *Id.* Thus, both OSI's 10K and Gibbs demonstrate that erlotinib was known to be active against non-small cell lung cancer, and that Phase II trials were at least being

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[10] Ramaswamy Govindan, *Phase III failure rates in oncology drugs unacceptable*, 16 ONCOLOGY NEWS INT'L 1 (Aug. 1, 2007).

[11] O.S. Breathnach et al., *Twenty-Two Years of Phase III Trials for Patients with Advanced Non-Small Cell Lung Cancer: Sobering Results*, 19 J. CLINICAL ONCOLOGY 1734, 1742 (2001).

contemplated. Thus, both OSI's 10K and Gibbs provide a reason to use erlotinib, as taught by Schnur, to treat non-small cell lung cancer, with a reasonable expectation of success. *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (noting that all that is required is a reasonable expectation of success, not absolute predictability of success).

We do not find Patent Owner's assertions and evidence that erlotinib may not have actually entered Phase II clinical trials, nor Patent Owner's evidence that many agents may fail at the Phase III stage, fatal to institution. As noted above, both Gibbs and OSI's 10K teach the use of erlotinib to treat non-small cell lung cancer, and Schnur teaches the use of 4-(substituted phenylamino) quinazoline derivatives, with erlotinib being one of its preferred compounds, in the treatment of hyperproliferative diseases, such as cancers, in mammals. Ex. 1009, 1:9–11. Thus, based on the record currently before us, we determine that Petitioner has sufficiently shown that the ordinary artisan would have combined Schnur with Gibbs or OSI's 10K, with a reasonable expectation of treating non-small cell lung cancer.

As to Patent Owner's argument that the only reference cited by Gibbs that discusses NSCLC pertains to ZD-1839, a structurally distinct compound, we note that Gibbs also teaches that a number of citations directed to clinical data were left out, pointing the reader to another reference. Ex. 1010, 9. Thus, at this stage of the proceeding based on the record currently before us, we take at face value the teachings of Gibbs as summarized above.

We conclude, therefore, that the Petition demonstrates a reasonable likelihood of success of demonstrating that challenged claims 44 and 53 are rendered obvious by the combination of Schnur and OSI's 10-K or Gibbs.

Patent Owner does not present separate arguments as to claims 45 and 46, Thus, we determine, after reviewing the Petition and supporting evidence, that Petitioner has also shown a reasonable likelihood that those claims are rendered obvious by the combination of Schnur and OSI's 10-K or Gibbs.

We have considered Patent Owner's argument that we should only institute on Schnur as combined with one of Gibbs or OSI's 10K. As Patent Owner acknowledges, however, Petitioner has demonstrated a reason as to why the grounds are not redundant to one another—that is—Patent Owner may antedate Gibbs. Thus, we decline to exercise our discretion and institute on only one of Schnur as combined with Gibbs or OSI's 10K.

iii. Conclusion

After considering the Petition and Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood that claims 44–46 and 53 are rendered obvious by the combination of Schnur and OSI's 10-K or Gibbs.

D. Obviousness over Schnur and Gibbs or Wakeling, and Moscatello

Petitioner asserts that claim 47 is rendered obvious by the combination of Schnur, Gibbs or Wakeling, and Moscatello. Pet. 35–44. Petitioner presents a claim chart demonstrating where the limitations of the challenged claims may be found in the relied upon references. Pet., Appendix B. According to Petitioner, "[a]nalysis of the obviousness of claim 47 over *Schnur* in view of *Gibbs* or *Wakeling* is presented in the alternative in the event that the Patent Owner attempts to antedate *Gibbs* in order to remove it as prior art to claim 47." *Id.* at 35.

Patent Owner contends that Petitioner has not established a reasonable likelihood that claim 47 is rendered obvious by the combination of references relied upon by Petitioner. Prelim. Resp. 33–42. Patent Owner

asserts further that we should only institute as to only one of either Gibbs or Wakeling, contending that the Petition does not argue that the grounds are non-redundant. *Id.* at 41–42.

i. Overview of Wakeling (Ex. 1013)

Wakeling teaches that "[s]ince the mitogenic action of EGF is mediated by ligand-induced autophosphorylation of the EGF receptor (EGFR), and EGFR is commonly overexpressed in solid human tumours, inhibitors of receptor tyrosine kinase activity (RTK) could prove to be effective antitumour agents." Ex. 1013, Summary. Wakeling reports the properties of aniline-quinazoline derivatives that "inhibit EGF·RTK activity and selectively inhibit EGF-stimulated tumour cell growth without affecting basal or insulin-like growth factor 1 (IGF-1)/insulin stimulated growth." *Id.* at 68.

ii. Overview of Moscatello (Ex. 1014)

Moscatello teaches that "[t]he most frequently found alteration of the epidermal growth factor receptor (EGFR) in human tumors is a deletion of exons 2–7. This receptor, termed EGFRvIII, can transform NIH 3T3 cells, and the frequent expression of this variant implies that it confers a selective advantage upon tumor cells *in vivo*." Ex. 1014, Abstract. Moscatello teaches that the EGFRvIII variant has been identified in non-small cell lung carcinomas. *Id.* at 200.

iii. Analysis

Petitioner notes that claim 47 depends from claim 44, and adds the limitation that the method is used in "tumors that express EGFRvIII." Pet. 36 (citing Ex. 1001, 35:43–44). Petitioner notes further that Schnur teaches that the antitumor properties of the disclosed compounds, which include

erlotinib, are based on inhibiting phosphorylation at the intracellular EGFR tyrosine kinase gene. *Id.* at 36 (citing Ex. 1009, 14:1–15:47; Ex. 1002 ¶¶ 59, 134).

Petitioner relies on Gibbs for teaching that "erlotinib is one of several leading compounds in clinical trials for cancer treatment that function by inhibiting intracellular ATP binding sites on the EGFR." *Id.* (citing Ex. 1010, 10; Ex. 1002 ¶¶ 66, 135). Petitioner relies on Wakeling for teaching that "aberrant expression of EGFR is common in solid tumors of epithelial origin." *Id.* Petitioner relies on Wakeling also for establishing that erlotinib "is part of a well-known class of 4-anilinoquinazoline compounds that share a basic chemical structure and function to treat cancer by inhibiting intracellular ATP binding sites on the EGFR in tumor cells." *Id.* (citing Ex. 1013, Summary, 67–69, Table 1; Ex. 1002 ¶ 136). Petitioner contends, therefore, that the ordinary artisan would have expected that erlotinib would exert its anti-tumor effect through the inhibition of EGFR. *Id.* at 37 (citing Ex. 1002 ¶ 137).

Petitioner relies on Moscatello for teaching "that overexpression of EGFR is implicated in the abnormal growth of many tumors, including tumors of the lung, and that a common genetic variant—'EGFRvIII'—had been identified in a number of cancers, including NSCLC tumors." *Id.* (citing Ex. 1014, 200; Ex. 1002 ¶¶ 82, 138). Moscatello teaches also, Petitioner contends, that similarly to EGFR, EGFRvIII is also inhibited at the intracellular kinase domain by 4-anilinoquinazoline. *Id.* (citing Ex. 1014, 202; Ex. 1002 ¶¶ 87, 88, 138).

According to Petitioner:

> Since *Moscatello* teaches that the 4-anilinoquinazoline compound, tyrphostin AG1478, prevents EGFRvIII

> phosphorylation at the intracellular tyrosine kinase domain, a person of ordinary skill in the art would reasonably expect based on *Schnur* in combination with *Gibbs* or *Wakeling* that other 4-anilinoquinazoline compounds would function similarly. (**Ex. 1002**, ¶ 139.)

Id. at 38.

Petitioner contends that the ordinary artisan would have combined Schnur, Gibbs or Wakeling, and Moscatello "because each of these publications concerns a class of compounds (4-anilinoazoquinolines) that includes erlotinib for treating cancer, and characterizing the mechanism by which these compounds (including erlotinib) interact with tumors, which includes inhibiting EGFR tyrosine kinase in tumors of epithelial origin." *Id.* at 39 (citing Ex. 1002 ¶ 142). Petitioner asserts further that Moscatello teaches that EGFRvIII was known to be prevalent in NSCLC, and demonstrates that it is subject to inhibition by a 4-anilinoquinazoline compound that target the intracellular tyrosine kinase domain. *Id.* at 41–42 (citing Ex. 1014, 202, 205–206). According to Petitioner, the ordinary artisan would have had a reason to combine the references given the structural similarities between erlotinib and AG1478. *Id.* at 38, 40–43 (citing Ex. 1002 ¶¶ 77, 139, 147, 150).

As to the combination based on Gibbs, Patent Owner reiterates its argument that the ordinary artisan would not have any reason to combine Schnur with Gibbs "given the Petition's failure to demonstrate that the CP-358,774 compound referenced in Gibbs is a compound disclosed by Schnur (i.e., erlotinib)," asserting further that Moscatello does not remedy that disclosure. Prelim. Resp. 34; *see also id.* at 39 (arguing the same). That argument is not persuasive for the reasons set forth above. Thus, we conclude on the record currently before us that Petitioner has established a

reasonable likelihood that claim 47 is rendered obvious by the combination of Schnur, Gibbs, and Moscatello

Patent Owner responds as to the alternate combination based on Wakeling that the Petition does not provide a reason as to why the ordinary artisan would have combined Wakeling, Moscatello, and Schnur to arrive at the invention of challenged claim 47. *Id.* Specifically, Patent Owner argues that Wakeling relates to the inhibition of EGFR "by a small genus of fifteen 4-anilinoquinazoline compounds." *Id.* (citing Ex. 1013, 67, 68). Moscatelo, Patent Owner asserts, "discloses *in vitro* studies using the small molecule tyrphostin AG1478 as an EGFR inhibitor to evaluate whether the phosphatidylinositol 3-kinase enzyme in cells expressing EGFRvIII was an effector in DNA synthesis induced by EGFR." *Id.* at 34–35 (citing Ex. 1014, 205). And the genus of Schnur, Patent Owner asserts, which includes thousands of 4-anilinoquinazoline compounds, of which erlotinib was one of 105 exemplified compounds, does not include either the compounds of Wakeling or the compounds of Moscatello. *Id.* at 35. Patent Owner asserts that as the compounds are structurally distinct from one another, and as the ordinary artisan would understand that small differences in chemical structure may have a large impact on biological activity and pharmacokinetic properties, the ordinary artisan would not have a reason to combine any of Schnur, Wakeling, and Moscatello. *Id.* at 35–38.

Patent Owner argues further as to the combination of Schnur, Wakeling, and Moscatello that neither Wakeling nor Moscatello discuss erlotinib, or any compound that has been successfully used in mammals to treat EGFRvIII, and, thus, there would be no reason to focus on erlotinib. *Id.* at 39–40. In particular, Patent Owner argues that Moscatello only

provides *in vitro* data demonstrating that AG1478 inhibits EGFRvIII, and does not suggest that the compounds could be used to treat tumors in vivo. *Id.* at 40 (citing Ex. 1013, 72 ("The ***potential*** for *in vivo* antitumour action of TK inhibitors has already been demonstrated with animal models, but ***much further work will be needed*** before the clinical utility of TK inhibition can be evaluated.")). Thus, Patent Owner asserts, the Petition fails to provide a reasonable expectation of success of combining Schnur, Wakeling, and Moscatello to arrive at the incention of challenged claim 47. *Id.* at 41.

We agree with Patent Owner that Petitioner has failed to establish a reasonable likelihood that the combination of Schnur, Wakeling, and Moscatello renders challenged claim 47 obvious. Claim 47 depends from challenged claim 44, and, thus, incorporates the limitations of that claim. What Petitioner has failed to do is present any evidence or argument that either Wakeling or Moscatello teaches that compound required by the claimed method, erlotinib, may be used to treat any of the conditions specifically recited by the method of claim 44, that is, "NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HFV), Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases in a mammal." In that regard, we note that in its claim chart, as to the requirements of claim 44, Petitioner points to the claim chart for claim 44. Pet., Appendix B (citing Pet., Appendix A). Although Petitioner relied on Gibbs in its challenge of independent claim 44, it did not rely on Wakeling, and, thus, the claim chart also does not explain how Wakeling ties the compound required by the claimed method, erlotinib any of the conditions treated by the method of claim 44.

iv. Conclusion

Petitioner has demonstrated a reasonable likelihood that claim 47 is rendered obvious by the combination of Schnur, Gibbs, and Moscatello. We determine, however, that Petitioner has failed to demonstrate a reasonable likelihood that claim 47 is rendered obvious by the combination of Schnur, Wakeling, and Moscatello

E. Secondary Considerations

Patent Owner argues that objective evidence of non-obviousness, such as "long-felt need, failure of others, unexpected results and commercial success, support the non-obviousness of the challenged claims of the '221 patent." Prelim. Resp. 42–45.

Secondary considerations, when present, must "be considered en route to a determination of obviousness." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (citation omitted). Secondary considerations may include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). To be relevant, evidence of nonobviousness must be commensurate in scope with the claimed invention. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (citing *In re Tiffin*, 448 F.2d 791, 792 (CCPA 1971)); *In re Hiniker Co.*, 150 F.3d 1362, 1369 (Fed. Cir. 1998).

Our Decision on Institution is not a "determination of obviousness" in the same sense as the Federal Circuit wrote in *Transocean*. Rather, a Decision on Institution decides whether a "reasonable likelihood" exists for

such a determination to be made at a later time. *Compare* 35 U.S.C. § 314(a) (authorizing *inter partes* review only if "there is a reasonable likelihood that the petitioner would prevail"), *with* 35 U.S.C. § 316(e) (placing the burden on petitioner of "proving a proposition of unpatentability by a preponderance of the evidence"). Accordingly, our analysis in this Decision focuses on whether Petitioner has established a reasonable likelihood of success based on the current record. *Id.* § 314(a); *see also* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,765 (Aug. 14, 2012) ("The 'reasonable likelihood' standard is a somewhat flexible standard that allows the Board room to exercise judgment."). In view of our analysis above, we determine that it would be premature at this stage of the proceeding to deny institution based on the secondary considerations evidence. We will permit the parties to develop a more complete record during discovery before considering such evidence, and any final decision will be based on the full record developed during the trial, including any evidence of secondary considerations.

III. CONCLUSION

For the foregoing reasons, we are persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 44–47 and 53 of the '221 patent is unpatentable under 35 U.S.C. §103(a).

Our determinations at this stage of the proceeding are based on the evidentiary record currently before us. This decision to institute trial is not a final decision as to patentability of the claim for which *inter partes* review is instituted. Our final decision will be based on the full record developed during trial.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. §314(a), an *inter partes* review is hereby instituted on the following grounds:

Claims 44–46 and 53 rendered obvious by the combination of Schnur and OSI's 10-K or Gibbs; and

Claim 47 rendered obvious by the combination of Schnur, Gibbs, and Moscatello.

FURTHER ORDERED that no other proposed grounds of unpatentability are authorized; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this Decision.

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