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.,
Petitioners,

v.

OSI PHARMACEUTICALS, INC.,
Patent Owner.

U.S. Patent No. 6,900,221
Issue Date: May 31, 2005
Title of Patent: Stable Polymorph on N-(3-ethylphenyl)-6,7-bis(2methoxyethoxy)-4-quinazolinamine hydrochloride, Methods of Production, and Pharmaceutical uses thereof

---

Case No.: T.B.D.

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,900,221 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42

TABLE OF CONTENTS

TABLE OF CONTENTS i

LIST OF EXHIBITS iv

I. INTRODUCTION 1

II. MANDANTORY NOTICES 1

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1)) 2

B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2)) 2

C. Identification of Counsel (37 C.F.R. § 42.8(b)(3)) 2

D. Service Information (37 C.F.R. § 42.8(b)(4)) 3

III. CLAIMS FOR WHICH REVIEW IS REQUESTED (37 C.F.R. § 42.104(b)(1)) 3

IV. GROUNDS FOR STANDING AND PROCEDURAL STATEMENT (37 C.F.R. § 42.104(a)) 3

V. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED 3

VI. THRESHOLD REQUIREMENT FOR INTER PARTES REVIEW 4

VII. STATEMENT OF REASONS FOR THE RELIEF REQUESTED 4

A. Overview of the ’221 Patent 5

B. Relevant Prosecution History of the ’221 Patent and Reasons for Allowance of the Challenged Claims 7

C. Priority Date of the Challenged Claims 9

D. Prior Litigation Involving the ’221 Patent 10

E. Level of Ordinary Skill in the Art 12

F. Claim Construction (37 C.F.R. § 42.104(b)(3)) 13

G. Patents and Printed Publications Relied Upon (37 C.F.R. § 42.104(b)(2)) 13

1. *Schnur* (Ex. 1009) 13

2. *Gibbs* (Ex. 1010) 17

3. *OSI's 10-K* (Ex. 1011) 18

4. *Wakeling* (Ex. 1013) 19

5. *Moscatello* (Ex. 1014) 21

H. Unpatentability of the Challenged Claims (37 C.F.R. § 42.104(b)(4)) 22

1. Ground I: Claims 44-46 and 53 are Unpatentable Under 35 U.S.C. § 103(a) (pre-AIA) as Obvious over *Schnur* in View of *Gibbs* or *OSI's 10-K* 22

a) The Prior Art Teaches or Suggests Each Element of Independent Claim 44 and Dependent Claim 53 23

b) The Prior Art Teaches of Suggests Each Element of Dependent Claim 45 30

c) The Prior Art Teaches or Suggests Each Element of Dependent Claim 46 31

d) The Rationale to Combine *Schnur* with *Gibbs* or *OSI's 10-K* 33

2. Ground II: Claim 47 is Unpatentable under 35 U.S.C. § 103(a) (pre-AIA) as Obvious Over *Schnur* in View of *Gibbs* or *Wakeling*, Further in View of *Moscatello* 35

a) *Schnur* in View of *Gibbs* or *Wakeling* Teach or Suggest That Erlotinib Was One of a Class of Compounds Having Similar Properties 36

b) *Moscatello* Provides a Reasonable Expectation That Erlotinib, Like Other Compounds Described by *Schnur* and *Wakeling* or *Gibbs*, Would Treat Tumors That Express EGFRvIII 37

c) Rationale to Combine *Schnur* and *Gibbs* or *Wakeling* with *Moscatello* 39

3. Ground III: In the Alternative, Claims 44-47 and 53 are Unpatentable Under 35 U.S.C. § 102(b) (pre-AIA) as Anticipated by *Schnur* 44

VIII. PETITIONER PRESENTS NEW GROUNDS OF UNPATENTABILITY 46

IX. THE ASSERTED GROUNDS ARE NON-CUMULATIVE AND NON-REDUNDANT 46

X. CONCLUSION 47

XI. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103 47

XII. WORD COUNT CERTIFICATION UNDER 37 C.F.R. §§ 42.24(A) 47

APPENDIX A – Claim Chart: Ground I (Obviousness of Claims 44-46 and 53 Over *Schnur* in View of *Gibbs* or *OSI's 10-K*)

APPENDIX B – Claim Chart: Ground II (Obviousness of Claim 47 Over *Schnur* in View of *Gibbs* or *Wakeling*, and *Moscatello*)

APPENDIX C – Claim Chart: Ground III (Anticipation of Claims 44-47 and 53 By *Schnur* If Priority is Accorded to the '907 Application)

EXHIBIT LIST (37 C.F.R. § 42.63(e))

Petitioners' Ex. No.	Description
1001	U.S. Patent No. 6,900,221, titled "Stable Polymorph on N-(3-ethylphenyl)-6,7-bis(2methoxyethoxy)-4-S hydrochloride, Methods of Production, and Pharmaceutical uses thereof," issued May 31, 2005
1002	Declaration of Giuseppe Giaccone, M.D., Ph.D.
1003	Excerpt from Prosecution History of U.S. Patent No. 6,900,221, Amendment dated June 19, 2002
1004	Excerpt from Prosecution History of U.S. Patent No. 6,900,221, Office Action dated August 30, 2002
1005	Excerpt from Prosecution History of U.S. Patent No. 6,900,221, Amendment dated February 28, 2003
1006	Excerpt from Prosecution History of U.S. Patent No. 6,900,221, Notice of Allowance dated June 18, 2003
1007	Provisional Appl. No. 60/164,907, filed November 11, 1999
1008	Provisional Appl. No. 60/193,191, filed March 30, 2000
1009	U.S. Patent No. 5,747,498, titled "Alkynyl and Azido-Substituted 4-Anilinoquinazolines," issued May 5, 1998
1010	J.B. Gibbs, "Anticancer drug targets: growth factors and growth factor signaling," *The Journal of Clinical Investigation 105*(1):9-13 (Jan. 2000)
1011	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.
1012	Declaration of Laurence S. Lese, Esq.
1013	A.E. Wakeling *et al.*, "Specific inhibition of epidermal growth factor receptor tyrosine kinase by 4-anilinoquinazolines," *Breast Cancer Research and Treatment 38*:67-73 (1996)
1014	D.K. Moscatello *et al.*, "Constitutive Activation of Phosphatidylinositol 3-Kinase by a Naturally Occurring Mutant Epidermal Growth Factor Receptor," *The Journal of Biological Chemistry 273*(1): 200-206 (January 1998)

1015	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," *The Journal of Pharmacology and Experimental Therapeutics 291*(2):739-748 (1999)
1016	J.D. Moyer *et al*., "Induction of Apoptosis and Cell Cycle Arrest by CP-358,774, an Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase," *Cancer Research 57*:4838-48 (1997)
1017	V. Rusch *et al*., "The Epidermal Growth Factor Receptor and its Ligands as Therapeutic Targets in Human Tumors," *Cytokine & Growth Factor Reviews 7*(2):133-141 (1996) ("*Rusch*").
1018	T. Cerny, "Expression of epidermal growth factor receptor (EGF-R) in human lung tumours," *British Journal of Cancer 54*:265-69 (1986)
1019	B.R. Voldborg *et al*., "Epidermal growth factor receptor (EGFR) and EGFR mutations, function and possible role in clinical trials," *Annals of Oncology 8*:1197-1206 (1997)
1020	M. Lee *et al.*, "Epidermal Growth Factor Receptor Monoclonal Antibodies Inhibit the Growth of Lung Cancer Cell Lines," *Journal of the National Cancer Institute Monographs* (13):117-123 (1992)
1021	H. Masui *et al*., "Growth Inhibition of Human Tumor Cells in Athymic Mice by Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies," *Cancer Research 44*:1002-7 (1984)
1022	I.E. Garcia de Palazzo *et al*., "Expression of Mutated Epidermal Growth Factor Receptor by Non-Small Cell Lung Carcinomas," *Cancer Research 53*:3217-20 (1993)
1023	C.J. Wikstrand, "Cell Surface Localization and Density of the Tumor-associated Variant of the Epidermal Growth Factor Receptor, EGFRvIII," *Cancer Research 57*:4130-40 (1997)
1024	D. Veale *et al*., "The relationship of quantitative epidermal growth factor receptor expression in non-small cell cancer to long term survival," *British Journal of Cancer 68*:162-65 (1993)
1025	M. Haeder *et al.,* "Epidermal Growth Factor Receptor Expression in Human Lung Cancer Cell Lines," *Cancer Research 48*:1132-36 (1988)
1026	D. Veale *et al*., "Epidermal growth factor receptors in non-small cell lung cancer," *British Journal of Cancer 55*:513-16 (1987)

1027	I. Linnoila, "Pathology of Non-Small Cell Lung Cancer. New Diagnostic Approaches," *Hematol Oncol Clin North Am. 4*(6):1027-51 (1990)
1028	*OSI Pharmaceuticals, Inc., Pfizer, Inc., and Genentech Inc. v. Mylan Pharmaceuticals Inc*., Civil Action No. 09-cv-185-SLR (D. Del.), Slip Op. dated May 1, 2012

TABLE OF AUTHORITIES

Cases

Impax Labs., Inc. v. Aventis Pharma Inc., 468 F.3d 1366, 1383 (Fed. Cir. 2006) 11

Rassmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1325-26 (Fed. Cir. 2005) 11

Graham v. John Deere Co., 383 U.S. 1, 17 (1966) 22

In re Merck & Co., Inc., 800 F.2d 1091, 1097 (Fed. Cir. 1986) 29

Geo. M. Martin Co. v. Alliance Machine System Intern. LLC, 618 F.3d 1294, 1302 (Fed. Cir. 2010) 34

Amgen Inc. v. Hoeschst Marion Roussel, Inc., 314 F.3d 1313, 1357 (Fed. Cir. 2003) 34

Statutes

35 U.S.C. § 102 ..... 3, 5, 7, 11, 14, 17-19, 21, 23, 35, 44-46

35 U.S.C. §103 ..... 3, 4, 23, 30-35, 46

35 U.S.C. § 314(a) 4

35 U.S.C. § 119(e) 9, 10

Other Authorities

65 Fed. Reg. 54633 (Sept. 8, 2000) 8, 27

Regulations

37 C.F.R. § 42.8(a)(1) 1

37 C.F.R. § 42.8(b)(1) 1

37 C.F.R. § 42.10(b) 1

37 C.F.R. § 42.8(b)(2) 2

37 C.F.R. § 42.8(b)(3) 2

37 C.F.R. § 42.8(b)(4).....3

37 C.F.R. § 42.104(b)(1).....3

37 C.F.R. § 42.104(a).....3

37 C.F.R. § 42.6(c).....4

37 C.F.R. § 42.104(b)(3).....13

37 C.F.R. § 42.104(b)(2).....14

37 C.F.R. § 42.104(b)(4).....22

37 C.F.R. § 1.104(e).....8, 27

37 C.F.R. § 42.15(a).....46

37 C.F.R. § 42.103 46

37 C.F.R. § 42.24(a).....46

I. INTRODUCTION

In accordance with 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-42.80 and 42.100-42.123, Petitioners Apotex Inc., Apotex Corp., Apotex Pharmaceuticals Holdings Inc., and Apotex Holdings, Inc. (collectively "Apotex" or "Petitioners") petition for *Inter Partes* Review of claims 44-47 and 53 of U.S. Patent No. 6,900,221 to Norris, *et al.*, titled "Stable Polymorph on N-(3-ethylphenyl)-6,7-bis(2methoxyethoxy)-4-quinazolinamine hydrochloride, Methods of Production, and Pharmaceutical uses thereof" ("the '221 patent," **Ex. 1001**). Concurrently filed herewith is a Power of Attorney pursuant to 37 C.F.R. § 42.10(b).

This Petition demonstrates that there is a reasonable likelihood that Petitioners will prevail on at least one of the challenged claims, and therefore respectfully request that *Inter Partes* Review be instituted. Further, for the reasons set forth herein, and in the accompanying Exhibits, Petitioners respectfully submit that claims 44-47 and 53 of the '221 patent should be canceled as unpatentable.

II. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

Apotex Inc., Apotex Corp., Apotex Pharmaceuticals Holdings Inc., and Apotex Holdings, Inc. are the real parties-in-interest for Petitioners.

Apotex Inc. is an Ontario corporation organized under Canadian laws, and is wholly owned by Apotex Pharmaceuticals Holdings Inc., which itself is wholly

owned by Apotex Holdings, Inc. Both Apotex Pharmaceuticals Holdings Inc. and Apotex Holdings, Inc. are Ontario corporations. Apotex Corp. is a Delaware corporation and is ultimately wholly owned by Apotex Holdings, Inc. None of Apotex Inc., Apotex Corp., Apotex Pharmaceuticals Holdings Inc., and Apotex Holdings, Inc. are publicly traded companies.

According to U.S. Patent Office ("PTO") records, the assignee of the '221 patent is OSI Pharmaceuticals, Inc. (Melville, NY) ("OSI" or "Patent Owner").

B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))

The '221 patent is presently at issue in the following patent infringement lawsuits:

- *OSI Pharmaceuticals, LLC and Genentech, Inc. v. Apotex Inc. and Apotex Corp.*, Civil Action No. 1:15-cv-00772-SLR (D. Del); and
- *Pfizer Inc., OSI Pharmaceuticals, LLC and Genentech, Inc. v. Breckenridge Pharmaceutical, Inc. and Natco Pharma Ltd.*, Civil Action No. 1:15-cv-01063-SLR (D. Del.).

C. Identification of Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel	Back-Up Counsel
William Blake Coblentz (Reg. No. 57,104) COZEN O'CONNOR 1200 19th Street, N.W. Washington, D.C. 20036 Telephone No.: 202-912-4837 Fax. No.: 202-861-1905	Aaron S. Lukas, Ph.D. (Reg. No. 59,443) COZEN O'CONNOR 1200 19th Street, N.W. Washington, D.C. 20036 Telephone No.: 202-912-4823 Fax. No.: 202-861-1905

Email: wcoblentz@cozen.com	Email: alukas@cozen.com

D. Service Information (37 C.F.R. § 42.8(b)(4))

Please direct all correspondence to lead counsel and back-up counsel at the contact information above. Petitioners consent to service by electronic mail at the email addresses set forth above.

III. CLAIMS FOR WHICH REVIEW IS REQUESTED (37 C.F.R. § 42.104(b)(1))

Petitioner respectfully requests review of claims 44-47 and 53 of the ’221 patent, and cancellation of those claims as unpatentable.

IV. GROUNDS FOR STANDING AND PROCEDURAL STATEMENT (37 C.F.R. § 42.104(a))

As required by 37 C.F.R. § 42.104(a), Petitioners certify that the ’221 patent is available for *Inter Partes* Review and that the Petitioners are not barred or estopped from requesting *Inter Partes* Review on the grounds identified in this Petition.

V. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED

Petitioners request *inter partes* review and cancellation of claims 44-47 and 53 of the ’221 patent on one or more of the grounds under 35 U.S.C. §§ 102 and 103 set forth herein. The ’221 patent is to be reviewed under pre-AIA §§ 102 and 103. Petitioners’ detailed statement of the reasons for the relief requested is set forth below in the section titled “Statement of Reasons for Relief Requested.” In

accordance with 37 C.F.R. § 42.6(c), copies of the exhibits are filed herewith. In addition, this Petition is accompanied by the Declaration of Giuseppe Giaccone, M.D., Ph.D. ("Giaccone Decl.," **Ex. 1002**).

VI. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

A petition for *Inter Partes* Review must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition." 35 U.S.C. § 314(a). This Petition meets this threshold. Further, for each of the grounds of unpatentability proposed, there is a reasonable likelihood that Petitioners will prevail with respect to at least one of the challenged claims.

VII. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

As set forth in detail below, claims 44-47 and 53 of the '221 patent are unpatentable based on the following grounds:

Ground I: Claims 44-46 and 53 are Unpatentable Under 35 U.S.C. § 103(a) (pre-AIA) as Obvious Over *Schnur* In View of *OSI's 10-K* or *Gibbs*.

Ground II: Claim 47 is Unpatentable under 35 U.S.C. § 103(a) (pre-AIA) as Obvious Over *Schnur* and *Gibbs* or *Wakeling*, in view of *Moscatello*.

Ground III: In the Alternative, Claims 44-47 and 53 are Unpatentable Under 35 U.S.C. § 102(b) (pre-AIA) as Anticipated by *Schnur*.

A. Overview of the '221 Patent

The '221 patent is titled "Stable Polymorph on N-(3-Ethynylphenyl)-6, 7-Bis (2-Methoxyethoxy)-4-Quinazolinamine Hydrochloride, Methods of Production, and Pharmaceutical Uses Thereof." The compound "N-(3-Ethynylphenyl)-6, 7-Bis (2-Methoxyethoxy)-4-Quinazolinamine" is commonly known as erlotinib. (*See* **Ex. 1002** at ¶¶ 28 and 31.) Further, the Abstract of the '221 patent discloses that:

> The present invention relates to a stable crystalline form of N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-4-quinazolinamine [*i.e.,* erlotinib] hydrochloride designated the B polymorph, its production in essentially pure form, and its use. The invention also relates to the pharmaceutical compositions containing the stable polymorph B form of N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-4-quinazolinamine as hydrochloride, as well other forms of the compound, and to methods of treating hyperproliferative disorders, such as cancer, by administering the compound.

(**Ex. 1001** at 1, Abstract.)

Thus, both the Title and Abstract of the ’221 patent indicate that the claimed invention is directed to a new, stable crystalline form of erlotinib, and methods of using the same to treat hyperproliferative disorders. (**Ex. 1001** at Abstract; col. 7, l. 64–col. 11, l. 33.) Indeed, the vast majority of the claims of the ’221 patent refer to compositions and methods of treatment that require polymorph B of erlotinib.

However, claims 44-47 and 53 of the ’221 patent include no limitation on the crystalline form of erlotinib used to practice the claimed methods. Instead, claims 44-47 and 53 broadly claim the use of erlotinib to treat a variety of hyperproliferative disorders without any limitation regarding the crystalline form of the active ingredient. (*See* **Ex. 1001** at col. 35, l. 26–col. 36, l. 19; **Ex. 1002** at ¶ 32.) Specifically, independent claim 44 of the ’221 patent requires:

> 44. A method for the treatment of NSCLC (non-small cell lung cancer) . . . 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**, col. 35, ll. 26-36; col. 35, l. 66–col. 36, l. 19.) Claims 45-47 and 53 depend directly from claim 44, and likewise do not include any limitations that further require a specific crystalline form of erlotinib. (*See* **Ex. 1001**, col. 35, ll. 37-65.) Thus, unlike the vast majority of other claims in the ’221 patent, claims

44-47 and 53 include no limitation as to the crystalline form of erlotinib that is administered to practice the claimed methods of treatment.

B. Relevant Prosecution History of the '221 Patent and Reasons for Allowance of the Challenged Claims

The prosecution history of the '221 patent shows that claims 44-47 and 53 were allowed to issue on the basis that the use of erlotinib to treat the disorders recited in claim 44 was not known in the prior art. Claims 44-47 and 53 of the '221 patent correspond to independent claim 64 and dependent claims 65-67, and 88 that were pending during prosecution. Pending claims 64-67 were entered by way of an amendment dated June 28, 2002, and pending claim 88 was entered by way of an amendment dated March 6, 2003. (*See* **Ex. 1003** (Amendment dated June 19, 2002) at 28-29; **Ex. 1006** (Amendment dated February 28, 2003) at 37.)

Pending claims 64-67 were rejected under 35 U.S.C. § 102(e) (pre-AIA) as anticipated by U.S. Patent No. 5,747,498 ("*Schnur*", **Ex. 1010**). (*See* **Ex. 1004** at 10-11 (citing **Ex. 1010** at col. 14, ll. 6-16, 28; col. 16, ll. 46-51; claims 28 and 29).) The PTO found that each and every limitation in claims 64-67 were disclosed by *Schnur* and communicated to OSI that "[c]laims 62-68 are rejected under 35 U.S.C. 102(e) as being anticipated by *Schnur* ('498). Applicant (OSI Pharmaceuticals Inc. or "OSI") admit that the prior art material [*Schnur*] and the composition made from it contain polymorph B [of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride]." (**Ex. 1004** at 10, ¶ 15.)

OSI argued that, whereas *Schnur* discloses the use of erlotinib to treat lung cancer, the use of erlotinib to treat non-small cell lung cancer (NSCLC) is not mentioned or disclosed. (*See* **Ex. 1005** at 23; **Ex. 1002** at ¶ 34.) OSI further added claim 88 which depended on claim 64 and narrowed the treatment to NSCLC.

The PTO subsequently allowed pending claims 64-67 and 88 to issue as claims 44-47 and 53 of the '221 patent based on a finding that the claims were "drawn to treatment of specific cancers by any polymorph of the claimed compounds. These specific cancers are not found in *Schnur* ('498)." (*See* **Ex. 1006** (Notice of Allowance dated June 18, 2003) at 6; **Ex. 1002** at ¶ 35.)

Thus, the PTO found that each and every limitation of claims 44-47 and 53 were disclosed in *Schnur* except for the treatment of NSCLC as specified in OSI's February 28, 2003 Office Action Response. (**Ex. 1005** at 23; **Ex. 1006** at 2; **Ex. 1002** at ¶ 36.) OSI did not respond to the PTO's Reasons for Allowance, and therefore is presumed to have acquiesced to the PTO's factual findings.[1]

[1] 37 CFR § 1.104(e); *see* 65 Fed. Reg. 54633 (Sept. 8, 2000) ("The deletion of this statement from the rule should require applicant to set forth his or her position in the file if he or she disagrees with the examiner's reasons for allowance, or be subject to inferences or presumptions to be determined on a case-by-case basis by a court reviewing the patent, the Office examining the patent in a reissue or reexamination proceeding . . . .").

As discussed below, facts not available to the PTO during prosecution of the '221 patent conclusively show that a person of ordinary skill in the art would have reasonably expected erlotinib to be effective in treating at least NSCLC in view of the prior art. Thus, the knowledge of a person of ordinary skill in the art in view of the prior art discloses, teaches, or suggests every limitation of the challenged claims, including the subject matter the Office found missing from the prior art in the undisputed reason for allowance.

C. Priority Date of the Challenged Claims

The earliest priority date to which claims 44-47 and 53 should be accorded under 35 U.S.C. § 119(e) is March 30, 2000. The '221 patent was filed on November 9, 2000, and issued on May 31, 2005. The '221 patent claims priority to the following Provisional Applications:

Appl. No.	**Filing Date**
60/164,907	November 11, 1999
60/193,191	March 30, 2000
60/206,420	May 23, 2000

(*See* **Ex. 1001** at col. 1, ll. 8-13.) However, methods of using erlotinib to treat the hyperproliferative disorders recited in claims 44-47 and 53, and specifically NSCLC, were not recited in Provisional Appl. No. 60/164,907 ("the '907 application"). (*See* **Ex. 1007**; **Ex. 1002** at ¶ 38.) Instead, the '907 application

merely discloses the use of erlotinib hydrochloride (*i.e.,* the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine) to treat lung cancer in the same manner as described in *Schnur*. (*See* **Ex. 1002** at ¶ 38, discussing **Ex. 1007** at 6, l. 8 to 8, l. 8; and 10, l. 3 to 11, l. 24; *compare* **Ex. 1009** at col. 14, ll. 1-30.) Therefore, under 35 U.S.C. § 119(e) claims 44-47 and 53 should not be accorded a priority date of November 11, 1999, due to a failure by the '907 application to satisfy the requirements under 35 U.S.C. § 112, first paragraph. Namely, the use of erlotinib to treat NSCLC is not mentioned or disclosed in the '907 application.

The first written disclosure concerning the use of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine (*i.e.,* erlotinib) to treat NSCLC as recited in claims 44-47 and 53 is found in Provisional Appl. No. 60/193,191 ("the '191 application"), filed March 30, 2000. (*See* **Ex. 1008** (Provisional Appl. No. 60/193,191) at 1, ll. 20-26; 2, l. 21–3, l. 30; 4, ll. 10-13; and 7, claims 1-10; **Ex. 1002** at ¶ 37.) Accordingly, pursuant to 35 U.S.C. § 119(e), the earliest priority date to which claims 44-47 and 53 can claim benefit is March 30, 2000.

D. Prior Litigation Involving the '221 Patent

The '221 patent was previously asserted by the Patent Owner in a district court litigation (*OSI Pharmaceuticals, Inc., Pfizer, Inc., and Genentech Inc. v.*

Mylan Pharmaceuticals Inc., Civil Action No. 09-cv-185-SLR (D. Del.)).[2] There, claim 53 of the '221 patent was found not anticipated by the prior art—namely, *Schnur* and an abstract entitled "Development of a Potent, Specific Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase (CP-358,774) as an Anti-Cancer Therapeutic Agent" by Kenneth K. Iwata *et al*.

The district court found that claim 53 of the '221 patent was not anticipated by *Schnur* on the basis that an oncologist would not read *Schnur* to teach that every compound disclosed therein (including erlotinib) was actually effective for the treatments that are disclosed. (*See* **Ex. 1028** (District Court Opinion) at 36-37.) However, absent evidence to the contrary, "proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation." *See Impax Labs., Inc. v. Aventis Pharma Inc*., 468 F.3d 1366, 1383 (Fed. Cir. 2006); *Rasmusson v. SmithKline Beecham Corp*., 413 F.3d 1318, 1325-26 (Fed. Cir. 2005).

Relevant to the Grounds set forth herein, the district court also found that claim 53 was not obvious in view of the prior art because "a person of ordinary skill in the art would not have had a reasonable expectation that inhibiting EGFR would result in the treatment of NSCLC." (*See* **Ex. 1028** at 44.) While not binding on these proceedings, this finding is also legally irrelevant because the

[2] Also involved in this prior litigation were U.S. Reissue Patent No. RE41,065 (a reissue of *Schnur*), and U.S. Patent No. 7,087,613.

question is not whether a disclosure of EGFR inhibition would lead to a reasonable expectation of success, but instead whether *Schnur*'s disclosure of erlotinib's use for treating lung cancer would lead a person of ordinary skill in the art to reasonably expect efficacy in treating NSCLC.

The district court also found that the Patent Owner set forth evidence to show that others had tried, and failed to obtain FDA-approval for drugs to treat NSCLC. (*See* **Ex. 1028** at 44.) To the extent that the Patent Owner attempts to introduce such evidence of the failure by others here, Petitioners respectfully submit that such evidence is legally irrelevant. First, there is no requirement in the plain language of claims 44 or 53 that the claimed method of treating NSCLC be FDA-approved. Second, to the extent that there was skepticism as to whether erlotinib would be useful to treat NSCLC, the prior art disclosures of erlotinib's use to treat lung cancer (*Schnur*), and in particular to treat NSCLC (*OSI's 10-K* and *Gibbs*) would have given more than a reasonable expectation of success. As discussed at length in Dr. Giaccone's Declaration (**Ex. 1002** at ¶¶ 18-30 and 91-154.), a person of ordinary skill in the art reviewing *Schnur*'s disclosure of erlotinib to treat lung cancer would have effectively read this as a disclosure of erlotinib's use to treat NSCLC. The fact that secondary references—*OSI's 10-K* and *Gibbs*—further disclose this explicitly only proves that there was nothing unexpected about erlotinib's usefulness in treating NSCLC. Third, and finally, any

findings that there was a long-felt need or a failure by others to develop an FDA-approved treatment for NSCLC would have been satisfied by the prior art—namely, *Schnur*, which discloses the use of erlotinib to treat lung cancer.

E. The Level of Ordinary Skill in the Art

A person of ordinary skill in the art relevant to the challenged claims of the '221 patent would have a medical degree and at least some specialized training in oncology, and more particularly, specialized training in thoracic oncology. (*See* **Ex. 1002** at ¶ 52.) A person of ordinary skill in the art would also have several years of clinical experience, and a substantive understanding and experience using the medications and therapies effective for treating various lung cancers at the relevant time. (*See* **1002** at ¶ 52.) A person of ordinary skill in the art may have collaborated with others having expertise in pharmaceutical formulation development and pharmaceutical drug development. (**Ex. 1002** at ¶ 51.)

F. Claim Construction (37 C.F.R. § 42.104(b)(3))

The words recited in the challenged claims of the '221 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation of the claim language. Petitioners do not believe that OSI attributed any special meanings to the terms used in the challenged claims of the '221 patent when the broadest reasonable interpretation standard is applied. (*See* **Ex. 1002** at ¶¶ 54 and 55.) Petitioners' positions regarding the scope of the claims should not

be construed as an assertion regarding the appropriate claim scope in other adjudicative forums, where a different claim interpretation standard may apply.

G. Patents and Printed Publications Relied Upon (37 C.F.R. 42.104(b)(2))

Petitioners rely on the following patents and printed publications.

1. *Schnur* (Ex. 1009)

U.S. Patent No. 5,747,498 ("*Schnur*", **Ex. 1009**) was published on May 5, 1998, which is more than one year before the earliest priority date of claims 44-47 and 53 of the '221 patent. Accordingly, *Schnur* is prior art to claims 44-47 and 53 of the '221 patent under 35 U.S.C. § 102(b) (pre-AIA).

Schnur identifies that the disclosure includes an "invention . . . to a method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1." (**Ex. 1009** at col. 5, ll. 49-52.)

Schnur specifies that the compound of claim 1 is a class of 4-anilinoquinazoline compounds that 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." (**Ex. 1009** at Title; col. 14, ll. 1-6.) Of which, *Schnur* specifically identifies [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-

ethynylphenyl)-amine or erlotinib as a "specific preferred compound" of that class. (**Ex. 1009** at col. 3, ll. 47-48; col. 4, ll. 8-9.) *Schnur* also teaches how to make erlotinib and the hydrochloride salt thereof in Example 20. (**Ex. 1009** at col. 22, ll. 30-49.)

Additionally, *Schnur* recognizes that inhibiting phosphorylation of EGFR at the intracellular tyrosine kinase domain with preferred compounds such as erlotinib is the underlying mechanism to prevent tumor growth. (**Ex. 1009** at col. 1, ll. 30-63; col. 14, ll. 35-41.) Further, *Schnur* discloses that the compounds, including erlotinib, are suitable for use in the treatment of hyperproliferative disorders such as lung cancer. (*See* **Ex. 1009** at col. 5, ll. 56-60; col. 14, ll. 6-13.)

Schnur discloses that the compounds can be prepared as pharmaceutically acceptable salts, such as an acid-addition salt, and "can exist in solvated, as well as unsolvated forms, such as the hydrated forms." (**Ex. 1009** at col. 13, ll. 25-26; ll. 30-36.) In discussing *Schnur*, the '221 patent expressly admits that *Schnur* teaches an anhydrous form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride. (**Ex. 1001** at col. 8, ll. 43-45; col. 13, ll. 13-15.) Further, the '221 patent acknowledges that *Schnur* discloses a mixture of polymorphs A and B of erlotinib hydrochloride, and that the mixture is anhydrous. (*See* **Ex. 1001** at col. 8, ll. 43-45; col. 13, ll. 13-15.)

Effective dosages described in *Schnur* are taught to be dependent on the subject being treated, on the severity of the affliction, on the manner of administration and on the judgment of the prescribing physician. (**Ex. 1009** at col. 15, ll. 55-58.) In general, the effective dosages are disclosed to be in the range of approximately 0.001-100 mg/kg, preferably 1 to 35 mg/kg in single or divided doses. (**Ex. 1009** at col. 15, ll. 58-61.) For an Average 70 kg human, the taught amount would be from 0.05 to 7 g/day, preferably 0.2 to 2.5 g/day. (**Ex. 1009** at col. 15, ll. 61-62.)

Schnur discloses that a specific amount of active compound, such as a therapeutically-effective amount of erlotinib, comprise various pharmaceutical compositions for administration. Specifically, *Schnur* provides that the composition may be a tablet, capsule, pill, powder, a solution, parenteral injection, an emulsion, cream, ointment, or suppository. (**Ex. 1009** at col. 15, l. 63 – col. 16, l. 1.) *Schnur* further teaches that methods to prepare the listed pharmaceutical compositions are known to those of skill in the art and incorporates by reference *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easter, Pa., 15th Edition (1975) (**Ex. 1002**, ¶ 61; **Ex. 1009** at col. 16, ll. 41-45.)

Schnur also discloses that administration of erlotinib includes suitable pharmaceutical carriers which include inert diluents or fillers, water and various organic solvents. (**Ex. 1009** at col. 15, l. 63 – col. 16, l. 8; col. 16, ll. 21-22.)

Schnur further discloses that compounds such as erlotinib can be administered with "one or more other antitumor substances," and that "[s]uch conjoint treatment may be achieved by way of the simultaneous, sequential, cyclic or separate dosing of the individual components of the treatment." (**Ex. 1009** at col. 16, ll. 46-51.) Thus, *Schnur* discloses the use of the disclosed compounds (including erlotinib) along with a neo-adjuvant/adjuvant monotherapy—that is, an additional anti-tumor treatment given along with (before or after) treatment with erlotinib to treat, *inter alia*, lung cancer. (**Ex. 1002**, ¶¶ 62, 115.)

Schnur was also cited by the PTO during prosecution of the '221 patent, and applied against the pending claims that would eventually issue as claims 44-47 and 53 of the '221 patent.

2. *Gibbs* (Ex. 1010)

An article authored by J.B. Gibbs and titled "Anticancer drug targets: growth factors and growth factor signaling," was published in January 2000, which was before the earliest priority date of claims 44-47 and 53 of the '221 patent. Accordingly, *Gibbs* is prior art to claims 44-47 and 53 of the '221 patent under 35 U.S.C. § 102(a) (pre-AIA). *Gibbs* was not of record during the prosecution of the application leading to the '221 patent.

Gibbs is a review article that provides an "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** at 9, col. 1.) *Gibbs* discloses that CP-358,774 (*i.e.,* anhydrous erlotinib hydrochloride) achieves its anti-tumor activity by targeting the EGFR, and that erlotinib had entered Phase II clinical trials. (*See* **Ex. 1010** at 9, col. 1; 10, col. 1, Table 1.) Further, *Gibbs* discloses that erlotinib was shown to have good anti-cancer activity "with an acceptable therapeutic index, particularly in patients with NSCLC." (**Ex. 1010** at 10, col. 1.)

Gibbs also establishes that erlotinib is part of a well-known class of compounds which have anti-cancer properties by inhibiting ATP from binding to intracellular tyrosine kinase domains on EGFR. (**Ex. 1010** 10, col. 1; **Ex. 1002** ¶ 66.)

3. *OSI's 10-K* (Ex. 1011)

OSI Pharmaceuticals Inc.'s annual report (*OSI's 10-K*, **Ex. 1011**) was electronically filed with the Securities and Exchange Commission on December 23, 1998, and published by the Securities and Exchange Commission as of the last week of December 1998. (*See* Declaration of Laurence S. Lese, Esq. (**Ex. 1012**).) The publication date is more than one year before the earliest priority date of claims 44-47 and 53 rendering it prior art under 35 U.S.C. § 102(b) (pre-AIA). *OSI's 10-K* was not before the PTO during the prosecution of the application leading to the '221 patent.

OSI's 10-K provides that erlotinib was a publicly known orally active inhibitor of the epidermal growth factor receptor that treats non-small cell lung cancer (NSCLC) as of December 23, 1998. (**Ex. 1011** at 6). *OSI's 10-K* further discloses to the public that Phase I studies for erlotinib were completed and that Phase II studies had already begun. (**Ex. 1011** at 6). The disclosure that erlotinib completed Phase I clinical studies and was in the process of Phase II clinical studies for an NSCLC indication informs a person of ordinary skill in the art that erlotinib was administered to a human for the treatment of NSCLC.. (**Ex. 1002**, ¶72; **Ex. 1011** at 6.)

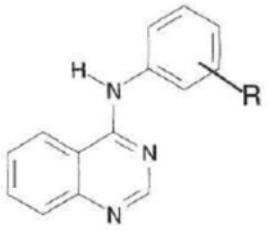
4. *Wakeling* (Ex. 1013)

An article authored by A.E. Wakeling and coauthors titled "Specific inhibition of epidermal growth factor receptor tyrosine kinase by 4-anilinoquinazolines," was published in 1996, which was more than one year before the earliest priority date of claims 44-47 and 53 of the '221 patent. Accordingly, *Wakeling* is prior art to claims 44-47 and 53 of the '221 patent under 35 U.S.C. § 102(b) (pre-AIA). *Wakeling* was not before the PTO during the prosecution of the application leading to the '221 patent.

Wakeling teaches a person of ordinary skill in the art a class of molecules that inhibit EGFR tyrosine kinase activity to block tumor cell proliferation. (**Ex.**

1013 at 68, col. 1.) The class of molecules with such properties all share the base structure shown below:

Table 1. Biological activity of anilino-quinazoline derivatives



Compound	Substituent	Inhibition of EGF-RTK IC50 (μM)	Inhibition of EGF stimulated KB cells IC50 (μM)	Inhibition of basal KB cell growth IC50 (μM)
1	H	0.55	12.5	38
2	o-Cl	1	>12.5	25
3	m-Cl	0.04	1.2	15
4	p-Cl	0.5	3.6	6
5	m-F	0.12	4.7	25
6	m-Br	0.02	0.8	12.5
7	m-I	0.07	1.1	12.5
8	m-OMe	0.7	10–100	>10
9	m-Me	0.18	2.4	16.5
10	m-NMe_2	0.52	11	12.5
11	m-OH	0.66	7.3	28
12	m-NO_2	0.07	2.7	12.5
13	m-CF_3	0.16	3.9	12.5
14	m-CN	0.2	7.6	19
15	m-SMe	0.5	7.8	12.5

(**Ex. 1033** at 68, Table 1.)

The *in vitro* testing shown in Table 1 indicates that the preferred substructures have the "R" group substituted at the meta position. (**Ex. 1013** at Summary; 68, Table 1; 69, col. 1; **Ex. 1002**, ¶ 77.) A person of ordinary skill in the art would have understood that this class of compounds all function similarly and predictably as anti-tumor agents by inhibiting intracellular EGFR tyrosine kinase binding domains. (*See generally* **Ex. 1013**; **Ex. 1002**, ¶ 73-80.)

Wakeling also discloses that prior knowledge regarding the role of epidermal growth factors in the proliferation of various solid tumors of epithelial origin was well established over about a decade of research starting in the mid-1980s. (**Ex. 1013** at 67; **Ex. 1002** ¶ 74.)

5. *Moscatello* (Ex. 1014)

An article authored by D.K. Moscatello and coauthors titled "Constitutive Activation of Phophatidylinositol 3-Kinase by a Naturally Occurring Mutant Epidermal Growth Factor Receptor," was published in January 1998, which was more than one year before the earliest priority date of claims 44-47 and 53 of the '221 patent. Accordingly, *Moscatello* is prior art to claims 44-47 and 53 of the '221 patent under 35 U.S.C. § 102(b) (pre-AIA). *Moscatello* was not before the PTO during the prosecution of the application leading to the '221 patent.

Moscatello discloses a study that examined inhibition of normal EGFR and the variant EGFRvIII using a 4-anilinoquinazoline tyrosine kinase domain inhibitor of EGFR, tyrphostin AG1478. (**Ex. 1002**, ¶82; **Ex. 1014** at 202 and 205-206.) *Moscatello* also reports from prior studies that NSCLC cells include both normal EGFR as well as the variant EGFRvIII, and that both are susceptible to inhibition by compounds that prevent phosphorylation and downstream cell signaling events, which down-regulates tumorigenesis and tumor growth. (**Ex. 1002**, ¶82; **Ex. 1014** at 202 and 205-206.)

According to *Moscatello*, the cell signaling events impeded by a 4-anilinoquinazoline TKI, such as AG1478, prevented phosphorylation which regulated tumor growth, morphological transformation, and cell death by both normal EGFR and the variant EGFRvIII. (**Ex. 1002**, ¶83; **Ex. 1014** at 206.)

H. Unpatentability of the Challenged Claims (37 C.F.R. § 42.104(b)(4))

In resolving the question of the obviousness of the claim, the following underlying factual determinations must be considered: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; and (3) the level of skill in the art; and (4) secondary considerations of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

For the purposes of the obviousness analyses set forth herein a person of ordinary skill in the art would have a medical degree and at least some specialized training in oncology, and more particularly, specialized training in thoracic oncology. (*See* **Ex. 1002** at ¶ 52.) A person of ordinary skill in the art would also have several years of clinical experience, and a substantive understanding and experience using the medications and therapies effective for treating various lung cancers at the relevant time. (*See* **1002** at ¶ 52.) A person of ordinary skill in the art may have collaborated with others having expertise in pharmaceutical formulation development and pharmaceutical drug development. (**Ex. 1002** at ¶ 51.)

1. Ground I: Claims 44-46 and 53 are Unpatentable Under 35 U.S.C. § 103(a) (pre-AIA) as Obvious Over *Schnur* in View of *Gibbs* or *OSI's 10-K*

As discussed in § VII. C, the earliest priority date that should be accorded to claims 44-46 and 53 of the '221 patent is March 30, 2000.

As discussed in § VII. G, based on its priority date, *Schnur* and *OSI's 10-K* are prior art to the challenged claims under 35 U.S.C. § 102(b) (pre-AIA), whereas *Gibbs* is prior art to the challenged claims under 35 U.S.C. § 102(a) (pre-AIA). Analysis 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.

A claim chart summarizing where each and every element of claims 44-46 and 53 can be found in the prior art disclosures of *Schnur*, *Gibbs*, and *OSI's 10-K* is provided in **Appendix A**.

a) The Prior Art Teaches or Suggests Each Element of Independent Claim 44 and Dependent Claim 53

Independent claim 44 requires the following:

> 44. A method for the treatment of NSCLC (non-small cell lung cancer) . . . 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** at col. 35, ll. 26-36.) Dependent claim 53 requires each limitation of claim 44 but narrows the condition treated to only NSCLC. (**Ex. 1001** at col. 35, ll. 64-65.)

Schnur discloses a genus of compounds that includes erlotinib. (*See* **Ex. 1009** at, e.g., col. 38, l. 13 – col. 39, l. 12.) *Schnur* expressly discloses erlotinib (*i.e.,* "[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine") as a preferred compound, and in fact erlotinib is one of 49 preferred compounds specifically identified in claim 8 of *Schnur*.[3] (*See* **Ex. 1009** at col. 3, ll. 47-48; col. 4, ll. 8-9; col. 39, l. 33 – col. 40, l. 65; **Ex. 1002**, ¶ 93.)

Schnur discloses that the compounds can be administered to a mammal for the treatment of a hyperproliferative disorder. (**Ex. 1009** at col. 5, ll. 49-52 ("[t]he invention further relates to a method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1.")) *Schnur* also claims "[a] method

[3] The compound disclosed in *Schnur* claim 8 as "[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine," is the same compound as "N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine," which is disclosed in the '221 patent—both are "erlotinib." (*See* **Ex. 1002**, ¶ 28.)

of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1"; "wherein said hyperproliferative disorder is cancer"; and "wherein said cancer is brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, esophageal, gynecological or thyroid cancer." (*See* **Ex. 1009** at col. 41, ll. 55-63.)

The therapeutically effective amount can depend on the subject being treated, on the severity of the affliction, on the manner of administration, and on the judgment of a prescribing physician. (*See* **Ex. 1009** at col. 15, ll. 55-58.) Generally, a therapeutically effective dosage is in the range of approximately 0.001-100 mg/kg, preferably 1 to 35 mg/kg in single or divided doses. (**Ex. 1009** at col. 15, ll. 58-61.) For an Average 70 kg human, a therapeutically effective amount is from 0.05 to 7 g/day, preferably 0.2 to 2.5 g/day. (**Ex. 1009** at col. 15, ll. 61-62.) *Schnur*'s disclosure of the therapeutically effective dose is identical to that disclosed by the '221 patent. (*Compare* **Ex. 1009** at col. 15, ll. 55-62, *with* **Ex. 1001** at col. 24, ll. 19-27, *and* **Ex. 1001** at col. 24, ll. 33-43; col. 30, ll. 29-35.)

Schnur discloses that a specific amount of active compound, such as a therapeutically-effective amount of erlotinib, comprise various pharmaceutical compositions for administration and are prepared by methods known to those of skill in the art and cites *Remington's Pharmaceutical Sciences*., Mack Publishing

Company, Easter, Pa., 15th Edition (1975), which is a reference guide well known to a person of ordinary skill in the art. (**Ex. 1009** at col. 16, ll. 41-45; **Ex. 1002** ¶ 96.) *Schnur* provides that the composition may be a tablet, capsule, pill, powder, a solution, parenteral injection, an emulsion, cream, ointment, or suppository. (**Ex. 1009** at col. 15, l. 63 – col. 16, l. 1.)

Further, *Schnur* expressly discloses that the pharmaceutical composition additionally includes a carrier, and identifies suitable carriers to "include inert diluents or fillers, water and various organic solvents." (**Ex. 1009** at col. 15, l. 63 – col. 16, l. 8; col. 16, ll. 21-22.)

In sum, the only difference between *Schnur* and claims 44 and 53 is that *Schnur* does not expressly identify "NSCLC" as a hyperproliferative disorder. (*See* **Ex. 1005** at 23; *see also* **Ex. 1006** at 2.) Instead, *Schnur* only discloses that erlotinib is useful to treat, *inter alia*, "lung cancer." (**Ex. 1009** at col. 14, ll. 1-6.) As discussed in § VII. B, the PTO reached the same conclusion during prosecution of the '221 patent, and allowed claim 44 to issue because it was "drawn to treatment of specific cancers by any polymorph of the claimed compounds. These specific cancers are not found in *Schnur* ('498)." (**Ex. 1006** at 2.) Accordingly, the only reason claim 44 (and claims 45-47 and 53 that depend therefrom) was allowed to issue was because *Schnur* does not include a verbatim disclosure of

NSCLC. OSI did not respond to the PTO's Reasons for Allowance, and therefore acquiesced to the PTO's reason for allowance.[4]

During prosecution of the '221 patent, the PTO never rejected any of the challenged claims over *Schnur* in view of any additional prior art disclosures related to erlotinib. (*See* § VII. B; **Ex. 1004**; **Ex. 1006**.) Nonetheless, a person of ordinary skill in the art would have been aware of *Gibbs* and/or *OSI's 10-K*, and would have read *Schnur*'s disclosure in view of this contemporaneous prior art. (*See* **Ex. 1002** at ¶ 101.) Neither *Gibbs* nor *OSI's 10-K* were before the PTO during prosecution of the '221 patent. (*See* **Ex. 1001**, pp. 1-3.)

Gibbs teaches that CP-358,774 (*i.e.,* anhydrous erlotinib hydrochloride) was a kinase inhibitor "with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer," and had entered Phase-II clinical trials. (*See* **Ex. 1010** at 9, col. 1; 10, col. 1, Table 1.)

[4] 37 CFR § 1.104(e); *see* 65 Fed. Reg. 54633 (Sept. 8, 2000) ("The deletion of this statement from the rule should require applicant to set forth his or her position in the file if he or she disagrees with the examiner's reasons for allowance, or be subject to inferences or presumptions to be determined on a case-by-case basis by a court reviewing the patent, the Office examining the patent in a reissue or reexamination proceeding . . . .").

OSI's 10-K discloses that CP-358,774 (*i.e.,* anhydrous erlotinib hydrochloride) was 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." (**Ex. 1011** at 6.) *OSI's 10-K* further discloses 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. (**Ex. 1011** at 6.)

Accordingly, a person of ordinary skill in the art viewing *Gibbs* or *OSI-s 10-K* would have understood that of all the specific compounds disclosed by *Schnur*, erlotinib was the most preferred, and in fact had entered Phase II clinical trials. Therefore, a person of ordinary skill in the art would have no need to choose erlotinib from the preferred compounds disclosed by *Schnur*, but instead would have been guided by *Gibbs* or *OSI's 10-K* directly to erlotinib as the preferred compound useful to treat the conditions disclosed in *Schnur*. (**Ex. 1002** at ¶¶ 102 - 105.)

Moreover, whereas *Schnur* in view of *Gibbs* or *OSI's 10-K* teaches and suggests the preferred use of erlotinib to treat lung cancer, *Gibbs* or *OSI's 10-K* would have further instructed a person of ordinary skill in the art to use erlotinib to treat NSCLC in humans. (**Ex. 1010** at 10, col. 1; **Ex. 1011** at 6; **Ex. 1002** at ¶ 106.) Therefore, notwithstanding the fact that a person of ordinary skill in the art

would have equated *Schnur*'s disclosure of the treatment of lung cancer as synonymous with the treatment of NSCLC (*See* **Ex. 1002**, ¶¶ 19, 20 and 107.), the preferred use of erlotinib to treat NSCLC is made explicit when *Schnur* is viewed through the lens of *Gibbs* or *OSI's 10-K*. (*See* **Ex. 1002**, ¶ 107.)

Further, the combination of *Schnur* with *Gibbs* or *OSI's 10-K* would have predictably yielded claim 44. The threshold for predictability merely requires a reasonable expectation that the beneficial result will be achieved. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). In the present case, the combination of the prior art establishes more than a reasonable expectation that the compound erlotinib as described in *Schnur* would treat NSCLC in a mammal. *Schnur* provides that compounds, including erlotinib, were known to treat lung cancer in a mammal, and further establishes that the effective dosage range, pharmaceutical compositions, carriers, and administration thereof were also known. (**Ex. 1009** at col. 14, l. 1 – col. 16, 1. 51; **Ex. 1002**, ¶ 109.) *Gibbs* or *OSI's 10-K* directs a person of ordinary skill in the art to choose erlotinib as the compound in *Schnur* to treat NSCLC in a mammal. (**Ex. 1010** at 9, col. 1, **Ex. 1011** at 6, **Ex. 1002** at ¶¶ 105 and 109.) Accordingly, a person of ordinary skill in the art would have done nothing more than apply erlotinib as taught in *Schnur* to treat NSCLC as taught in *Gibbs* or *OSI's 10-K* to predictably yield claim 44. (**Ex. 1002**, ¶ 109.)

Had the PTO been apprised of *Gibbs* or *OSI's 10-K*, claim 44 would have been rejected during prosecution because each of these prior art references specifically directs a person of ordinary skill in the art to the single preferred compound disclosed in *Schnur*, erlotinib, and its use to treat NSCLC. This evidence would have negated the only reason for allowance given by the PTO as to claim 44 and dependents thereof. (**Ex. 1002**, ¶113; *see* **Ex. 1005** at 23; *see also* **Ex. 1006** at 2.)

Accordingly, each and every limitation of claims 44 and 53 is taught or suggested by the prior art, thereby rendering claims 44 and 53 unpatentable under 35 U.S.C. § 103(a).

b) The Prior Art Teaches or Suggests Each Element of Dependent Claim 45

Claim 45 further limits the method recited in claim 44 such that "the treatment further comprises a palliative or neoadjuvant/adjuvant monotherapy." (**Ex. 1001**, col. 35, ll. 37-39.)

Schnur teaches that the disclosed compounds, among them erlotinib, can be administered with "one or more other antitumor substances," and that "[s]uch conjoint treatment may be achieved by way of the simultaneous, sequential, cyclic or separate dosing of the individual components of the treatment." (**Ex. 1009** at col. 16, ll. 46-51; **Ex. 1002**, ¶¶ 62 and 115.) Thus, a person of ordinary skill in the art would have recognized that *Schnur* discloses the use of the disclosed

compounds (including erlotinib) along with a neo-adjuvant/adjuvant monotherapy—that is, an additional anti-tumor treatment given before or after treatment with erlotinib—to treat, *inter alia*, lung cancer. (**Ex. 1002**, ¶¶ 62, 115 and 116.)

Further, a person of ordinary skill in the art reading *Schnur* in view of *Gibbs* or *OSI's 10-K* would have recognized that erlotinib, in particular, was the preferred compound disclosed by *Schnur*, that erlotinib was particularly useful to treat NSCLC (the most prevalent of the two main forms of lung cancer), and that such treatment of NSCLC could be achieved by administering a therapeutically effective dose of erlotinib along with a neo-adjuvant/adjuvant monotherapy. (**Ex. 1002**, ¶¶ 62, 115 and 116.)

Accordingly, each and every limitation of claim 45 would have been obvious to a person of ordinary skill in the art in view of the prior art, and this claim is therefore unpatentable under 35 U.S.C. § 103(a).

c) The Prior Art Teaches or Suggests Each Element of Dependent Claim 46

Claim 46 depends from claim 44 and adds a further limitation that the treatment comprise blocking epidermal growth factor (EGF) receptors. (**Ex. 1001** at col. 35, ll. 40-42.)

Schnur discloses that "[t]he active compounds of this invention [which includes erlotinib] are potent inhibitors of the erbB family of oncogenic and

protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), . . . and thus are all adapted to therapeutic use as antiproliferative agents (*e.g.,* anticancer) in mammals." (**Ex. 1009** at col. 14, ll. 1-6; **Ex. 1002**, ¶ 122.) Thus, *Schnur* specifically teaches that the 4-anilinoquinazoline compounds disclosed (including erlotinib) block EGFR phosphorylation as the underlying treatment for lung cancer. (**Ex. 1002**, ¶¶59 and 122; **Ex. 1009** at col. 14, l. 1 – col. 15 l. 48.)

Gibbs also discloses that CP-358,774 (*i.e.,* anhydrous erlotinib hydrochloride) is part of a well-known class of compounds which have anti-cancer properties by inhibiting ATP from binding to intracellular tyrosine kinase domains on EGFR, and further specifies that this is the mechanism exploited to treat NSCLC. (**Ex. 1010** at 9, col. 1, Table 1; **Ex. 1002** ¶ 66 and 123.)

Similarly, *OSI's 10-K* discloses that erlotinib is a potent inhibitor of EGFR, which is key to the treatment of NSCLC. (**Ex. 1011** at 6).

Therefore, all three references—*Schnur*, *Gibbs*, and *OSI's 10-K*—teach a person of ordinary skill in the art that erlotinib treats cancer by inhibiting EGFR. (**Ex. 1002**, ¶ 125; *see* **Ex. 1009**; *see also* **Ex. 1010**; **Ex. 1011**.)

As discussed above, person of ordinary skill in the art reading *Schnur* in view of *Gibbs* or *OSI's 10-K* would have been directed to a method of treating NSCLC in a human by administering a therapeutically effective amount of a

pharmaceutical composition comprising erlotinib with a carrier. What is more, a person of ordinary skill in the art would have known that NSCLC was the only form of lung cancer that could be treated by inhibiting EGFR, and that small cell lung cancer tumors did not respond to treatment with EGFR inhibitors. (**Ex. 1002**, ¶126.) Therefore, *Schnur* in view of *Gibbs* or *OSI's 10-K* would have provided a reasonable expectation that the therapeutically effective amount of erlotinib would treat NSCLC by blocking EGFR. (**Ex. 1002**, ¶ 126.)

Accordingly, each and every limitation of claim 46 is taught or suggested by the prior art, thereby rendering claim 46 unpatentable under 35 U.S.C. § 103(a).

d) The Rationale to Combine *Schnur* with *Gibbs* or *OSI's 10-K*

A person of ordinary skill in the art would have been motivated to combine the teachings of *Schnur* with *Gibbs* or *OSI's 10-K*. On the one hand, *Schnur* discloses a genus of preferred compounds (that includes anhydrous N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride) that are useful for treating cancer in humans through EGFR inhibition. (*See* **Ex. 1002**, ¶¶ 59 and 128.) On the other hand, *Gibbs* and *OSI's 10-K* are contemporaneous prior art references published soon after *Schnur* that specify precisely which of the compound disclosed in *Schnur* had in fact been tested in a clinical setting. (**Ex. 1002** ¶¶ 101-106, 110, 118 and 128.) Moreover, both *Gibbs* and *OSI's 10-K*

disclose that erlotinib had entered clinical testing to treat NSCLC. (**Ex. 1002** ¶¶ 101 – 106, 110, 118 and 128.)

The teachings of these prior art references differ only in that *Schnur* teaches a genus of compounds that includes erlotinib for use to treat lung cancer while *OSI's 10-K* and *Gibbs* specify that the compound anhydrous erlotinib hydrochloride to treat a type of lung cancer called NSCLC. (**Ex. 1002** ¶¶ 106-109 and 129.) Therefore, a person of ordinary skill in the art would have found it obvious to view *Schnur* through the further disclosure of *Gibbs* or *OSI's 10-K* because each of these references expressly disclose the same molecule, for blocking the same therapeutic target, in the same field of treatment. (**Ex. 1002**, ¶¶ 101-109 and 129.)

Schnur explicitly discloses the administration of therapeutically effective amounts of erlotinib to treat lung cancer, of which NSCLC is the predominant disease state. (**Ex. 1002**, ¶ 18-30 and 59-61.) Because the prior art is presumed to be enabled for that which it discloses under 35 U.S.C. § 103, further evidence such as actual completed clinical trials in cancer patients is not required. *See Geo. M. Martin Co. v. Alliance Machine System Intern. LLC*, 618 F.3d 1294, 1302 (Fed. Cir. 2010); *see also Amgen Inc. v. Hoeschst Marion Roussel, Inc.*, 314 F.3d 1313, 1357 (Fed. Cir. 2003).

Further, *Gibbs* and *OSI's 10-K* both report that erlotinib had completed Phase I studies and initiated Phase II studies. (**Ex. 1010** at 10, Table 1; **Ex. 1011** at 6.) A person of ordinary skill in the art would have understood this meant erlotinib was administered to humans, thereby providing further confirmation that erlotinib would have been reasonably expected to treat NSCLC in mammals. (**Ex. 1002**, ¶¶ 67, 72 and 130.)

In view of the foregoing, a person of ordinary skill in the art would have been motivated to combine the teachings of *Schnur* with *Gibbs* or *OSI's 10-K* to arrive at subject matter of claims 44-46 and 53 of the '221 patent.

2. Ground II: Claim 47 is Unpatentable under 35 U.S.C. § 103(a) (pre-AIA) as Obvious Over *Schnur* in View of *Gibbs* or *Wakeling*, Further in View of *Moscatello*

As discussed in § VII. G, each of *Schnur*, *Wakeling*, and *Moscatello* are prior art to the challenged claims under 35 U.S.C. § 102(b) (pre-AIA), whereas *Gibbs* is prior art to the challenged claims under 35 U.S.C. § 102(a) (pre-AIA). Analysis 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.

A claim chart summarizing where each and every element of claim 47 can be found in the prior art disclosures of *Schnur*, *Gibbs*, *Wakeling*, and *Moscatello* is provided in **Appendix B**.

a) *Schnur* in View of *Gibbs* or *Wakeling* Teach or Suggest That Erlotinib Was One of a Class of Compounds Having Similar Properties

Claim 47 depends from claim 44 and further specifies that the method of treatment is used in "tumors that express EGFRvIII." (**Ex. 1001**, col. 35, ll. 43-44.)

Schnur teaches that the anti-tumor properties of erlotinib for treating, *inter alia*, lung cancer, is based on inhibiting phosphorylation at the intracellular EGFR tyrosine kinase domain. (**Ex. 1009** at col. 14, l. 1 – col. 15, l. 47; **Ex. 1002 ¶¶** 59 and 134.)

Gibbs teaches 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. (**Ex. 1002**, ¶¶ 66 and 135; **Ex. 1010** 10, col. 1.)

Wakeling teaches that aberrant expression of EGFR is common in solid tumors of epithelial origin, which include tumors of the lungs, mouth, kidneys, breast, and vulva. (**Ex. 1013** at 67-68; **Ex. 1002 ¶¶** 73-80 and 136.) *Wakeling* also establishes that erlotinib, as taught in *Schnur*, 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. (**Ex. 1002**, ¶ 136; **Ex. 1013** at summary, 67-68, Table 1, 69.)

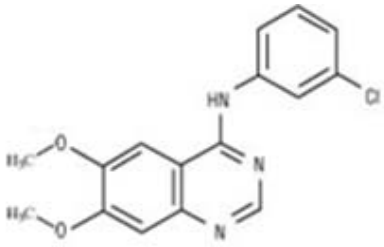
Therefore, a person of ordinary skill in the art reading *Schnur* in view of *Gibbs* or *Wakeling* would have recognized erlotinib as one of the leading compounds within the class of 4-anilinoquinazolines, and reasonably expected that erlotinib's anti-tumor effects operated by a similar mechanism to that of other 4-anilinoquinazoline compounds—through the inhibition of EGFR. (**Ex. 1002**, ¶ 137.)

b) *Moscatello* Provides a Reasonable Expectation That Erlotinib, Like Other Compounds Described by *Schnur* and *Wakeling* or *Gibbs*, Would Treat Tumors That Express EGFRvIII

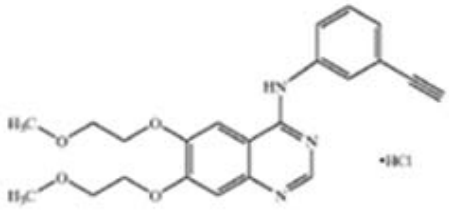
Moscatello teaches that overexpression of EGFR is implicated in the abnormal growth of many tumors, including tumors of the lung, and that a common genetic variant—"EGFRvIII"—had been identified in a number of cancers, including NSCLC tumors. (**Ex. 1002**, ¶¶ 82 and 138; **Ex. 1014** at 200, col. 2.) *Moscatello* further teaches that EGFRvIII, like normal EGFR, can be inhibited at the intracellular tyrosine kinase domain by a 4-anilinoquinazoline to prevent cell signaling activation that is important to tumorigenesis. (**Ex. 1002**, ¶¶ 88 and 138; **Ex. 1014** at 202.) Specifically, *Moscatello* exposed normal EGFR and the variant EGFRvIII to tyrphostin AG1478, a 4-anilinoquinazoline compound, and observed that cell signaling in both EGFR and EGFRvIII and tumor growth was inhibited. (**Ex. 1002**, ¶¶ 87, 88 and138; **Ex. 1014** at 202.) Thus, *Moscatello* teaches that the intracellular tyrosine kinase domains in both

normal EGFR and the variant EGFRvIII are involved in tumorigenesis and tumor cell growth, and that these processes can be inhibited by a 4-anilinoquinazoline (tyrphostin AG1478) that directly blocks the receptors. (*See* **Ex. 1002**, ¶ 138; **Ex. 1014** at 202, 205-206.)

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.) This is particularly true given the structural similarity between AG1478 and erlotinib (shown below). (**Ex. 1002**, ¶ 139.)



Tyrphostin AG1478



N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride

Indeed, the teachings of *Schnur* in view of *Gibbs* or *Wakeling* in combination with *Moscatello* would have led a person of ordinary skill in the art to reasonably conclude that tyrphostin AG1478 and erlotinib would affect tumors of epithelial origin expressing the mutant EGFRvIII in the same way. (**Ex. 1002**, ¶ 140.) Therefore, a person of ordinary skill in the art reviewing *Schnur* and *Gibbs*

or *Wakefield* in view of *Moscatello* would have recognized that because erlotinib was an EGFR inhibitor of phosphorylation at the intracellular tyrosine kinase domain, like AG1478, erlotinib would inhibit EGFRvIII. (**Ex. 1002**, ¶ 140.)

For these reasons, each and every limitation of claim 47 would have been obvious to a person of ordinary skill in the art in view of the prior art, and this claim is therefore unpatentable.

c) *Rationale to Combine Schnur and Gibbs or Wakeling with Moscatello*

A person of ordinary skill in the art would have been motivated to combine the teachings of *Schnur* and *Gibbs* or *Wakeling* with *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. (**Ex. 1002**, ¶ 142.)

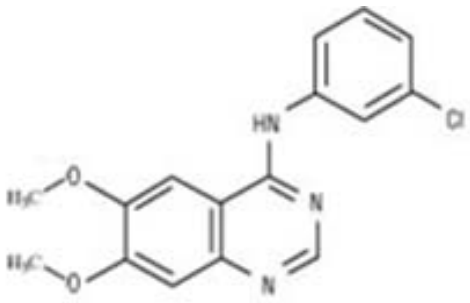
Where their teachings differ, they offer complementary approaches for addressing their common problem of combating hyperproliferation of tumor cells by inhibiting EGFR. (**Ex. 1002**, ¶ 143.) Because these references address the same field and the same issues, a person of ordinary skill in the art would have looked to their complementary disclosures.

Schnur, *Gibbs*, *Wakeling*, and *Moscatello* are generally directed to the treatment of cancer, and in particular the use of drugs that treat certain types of

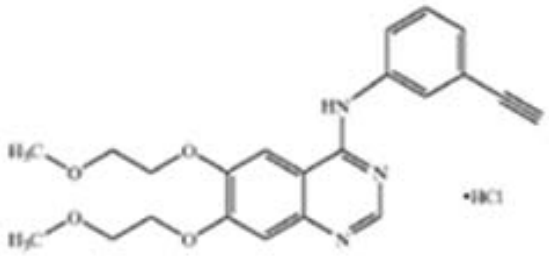
cancer by inhibiting the intracellular tyrosine kinase domain of EGFR. (**Ex. 1002**, ¶¶ 59, 66, 78, 117 and 135.)

Schnur teaches that 4-anilinoquinazoline compounds such as erlotinib treat tumor growth in lung cancer by inhibiting EGFR phosphorylation at the intracellular tyrosine kinase domain. (**Ex. 1002**, ¶¶ 59 and 145; **Ex. 1009** at col. 1, ll. 30-63; col. 14, ll. 1-34.) Impeding phosphorylation prohibits activation of a downstream signaling network involving cell proliferation, cell cycle progression, and survival. (**Ex. 1002**, ¶¶ 22, 83 and 145.)

Moscatello teaches tyrosine kinase domain inhibition of normal EGFR and the mutant EGFRvIII with tyrphostin AG1478. (**Ex. 1002** ¶ 82.) The compounds discussed by *Schnur* and *Moscatello* are members of the same class of drugs and their biological activity were well known in the art as shown in *Gibbs*. (**Ex. 1002**, ¶¶ 66 and 146; **Ex. 1010** 10, col. 1.) Therefore, *Schnur* and *Moscatello* utilize structurally similar molecules to inhibit the tyrosine kinase domain of EGFR, but *Moscatello* shows additionally that such molecules are also effective inhibitors of EGFRvIII. The molecules are shown below.



Tyrphostin AG1478



N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride

(**Ex. 1002** ¶146.)

Based on the structural and functional similarity between the compound used in *Moscatello* and the anhydrous erlotinib hydrochloride disclosed in *Schnur* and *Gibbs* or *Wakeling*, a person of ordinary skill in the art would have been motivated to utilize *Moscatello* in order to build on the teachings of *Schnur* and *Gibbs* or *Schnur* and *Wakeling*. Further, a person of ordinary skill in the art would have reasonably expected that, like the compound studied in *Moscatello*, anhydrous erlotinib hydrochloride would similarly function to inhibit EGFRvIII. (**Ex. 1002**, ¶ 147.)

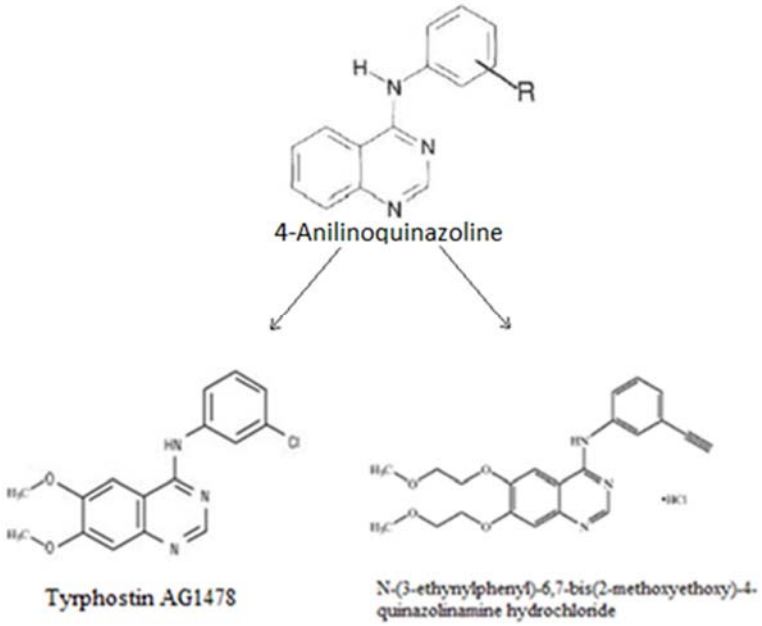
Additionally, *Schnur* and *Gibbs* teach that erlotinib hydrochloride is a potent tyrosine kinase domain inhibitor that has anticancer properties for a variety of cancers, including NSCLC. (**Ex. 1002**, ¶¶ 59, 66, 122, 123 and 148.) *Moscatello* complements these teachings by empirically proving that EGFRvIII, which was known to be prevalent in NSCLC, is subject to the same inhibition by compounds such as erlotinib that target the intracellular tyrosine kinase domain. (**Ex. 1014** at

202, 205-206.) Accordingly, a person of ordinary skill in the art would have understood *Moscatello* to be applicable to erlotinib hydrochloride for treating NSCLC tumors that express EGFRvIII. (**Ex. 1002**, ¶¶ 139 and 148.) As such, a person of ordinary skill in the art would have known that simply substituting tyrphostin AG1478 with erlotinib hydrochloride would have predictably resulted in the subject matter of claim 47. (**Ex. 1002**, ¶¶ 140 and 148.)

Reliance on prior art such as *Moscatello* in order to better understand the mechanism by which erlotinib acts in the body would have been common practice for persons of ordinary skill in the art because of the similarity between tyrphostin AG1478 and erlotinib hydrochloride. (**Ex. 1002**, ¶ 149.) Indeed, it would have been very surprising if the mechanisms underlying the activity of these two compounds were somehow different. (**Ex. 1002**, ¶ 149.) Further, EGFRvIII was known to respond poorly to extracellular ligand domain-mediated treatments. (**Ex. 1002**, ¶¶ 22 and 149; *See* **Ex. 1014**, 200.) As such, a person of ordinary skill in the art would be actively researching studies such as the one reported in *Moscatello* or would perform similar research to determine if NSCLC tumors expressing EGFRvIII are receptive to similar intracellular tyrosine kinase domain-mediated therapies. (**Ex. 1002**, ¶¶ 22 and 149.)

Wakeling teaches that both AG1478 and erlotinib are in a commonly known class of compounds that share the same basic structure and functions called

4-anilinoquinazolines which have anti-cancer effects in a variety of solid tumor cells of epithelial origin such as NSCLC. (**Ex. 1002** ¶ 73-80, 136 and 150.) Further, *Wakeling* reports that 4-anilinoquinazolines substituted at the meta position exhibited the most potent inhibitory effects on the intracellular EGFR tyrosine kinase domain, a structural property that is shared with erlotinib. (**Ex. 1002** ¶¶ 77 and 150.)



(**Ex. 1002** ¶ 150.)

Given the same base structure and function of a well-known class of molecules, a person of ordinary skill in the art would have reasonably expected that the compounds used in *Moscatello* and the anhydrous erlotinib hydrochloride disclosed in *Schnur* would function similarly to inhibit EGFRvIII. (**Ex. 1002**, ¶¶ 139 and 150.)

It was also known that cancer cells that express EGFRvIII respond poorly to treatments that bind at the extracellular ligand domain. (**Ex. 1002**, ¶¶ 22, 149 and 152; *see* **Ex. 1014**, 200.) As such, a person of ordinary skill in the art would have been motivated to combine the teachings of *Moscatello* with prior art related to compounds such as erlotinib, which was a known inhibitor of normal EGFR and functioned by binding at the intracellular tyrosine kinase domain. (**Ex. 1002**, ¶¶ 84 and 152.)

In view of the foregoing, a person of ordinary skill in the art would have been motivated to combine the teachings of *Schnur* with *Gibbs* or *Wakeling*, and look to *Moscatello* for further insight into the mechanism underlying erlotinib's efficacy as a tyrosine kinase receptor inhibitor for the treatment of NSCLC. Doing so would have provided the predictable result that is recited in claim 47 of the '221 patent.

3. Ground III: In the Alternative, Claims 44-47 and 53 are Unpatentable Under 35 U.S.C. § 102(b) (pre-AIA) as Anticipated by *Schnur*

As introduced in § VII. C above, the '221 patent claimed the benefit of three provisional applications:

Appl. No.	**Filing Date**
60/164,907	November 11, 1999
60/193,191	March 30, 2000
60/206,420	May 23, 2000

(*See* **Ex. 1001** at col. 1, ll. 8-13.)

Also discussed in § VII. C was the observation that the ’907 application and *Schnur* do not expressly identify NSCLC as a treated hyperproliferative disorder. Disclosure concerning treated conditions in the ’907 application is identical to *Schnur*. ((**Ex. 1002**, ¶ 38; **Ex. 1007** 10, l. 3 to 11, l. 27; *compare with* **Ex. 1009** col. 14, l. 1 to col. 15, l. 48.)

A claim chart summarizing that, to the extent written support for each and every element of claims 44-47 and 53 can be found in the ’907 application, such disclosure is identical to that of *Schnur* is provided in **Appendix C**.

Accordingly, if the ’907 application is found to disclose the use of erlotinib to treat NSCLC to the extent a priority claim to the ’907 application is valid for claims 44-47 and 53, *Schnur* must also be found to disclose treatment of NSCLC with erlotinib. This would negate the reason for allowing claims 44-47 and 53 rendering them anticipated by *Schnur* and invalid under 35 U.S.C. § 102(b).

VIII. PETITIONER PRESENTS NEW GROUNDS OF UNPATENTABILITY

Schnur is cited on the ’221 patent and was considered during prosecution, but the PTO did not consider *Gibbs, OSI’s 10-K*, *Wakeling* or *Moscatello*, let alone consider whether these prior art references in combination with *Schnur* rendered the challenged claims obvious under 35 U.S.C. § 103(a). Accordingly, Petitioners’ proposed grounds for unpatentability are not cumulative of the arguments presented and considered by the PTO.

IX. THE ASSERTED GROUNDS ARE NON-CUMULATIVE AND NON-REDUNDANT

Ground I is non-cumulative and non-redundant over the other grounds presented herein. Specifically, the PTO never rejected claims 44-46 or 53 of the ’221 patent as obvious under 35 U.S.C. § 103(a) over any prior art references, let alone *Schnur* in combination *Gibbs* or *OSI’s 10-K*. Instead, the PTO only made a rejection of these claims over *Schnur* under 35 U.S.C. § 102.

Ground II is non-redundant over Grounds I and III because a different claim is addressed. Further, Ground II is non-redundant over prior art rejections made during the prosecution of the ’221 patent at the PTO in that Ground II presents prior art that was not before the PTO during prosecution of the ’221 patent.

Ground III is non-redundant over Grounds I and II in that Ground III is set forth explicitly to address the patentability of claims 44-47 and 53 in the event these claims are accorded a priority date of November 11, 1999.

X. CONCLUSION

For the reasons set forth above, the challenged claims are unpatentable. Accordingly, Petitioners respectfully request that the Board grant this Petition for *inter partes* review and institute trial.

Respectfully Submitted,

Dated: June 28, 2016

/s/ W. Blake Coblentz
W. Blake Coblentz
Counsel for Petitioner
Registration No. 57,104

XI. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(a) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 50-3111.

XII. WORD COUNT CERTIFICATION UNDER 37 C.F.R. § 42.24(a)

Petitioner certifies that this Petition is 9,637 words in length, as determined by Microsoft Word® word count feature, excluding any table of contents, mandatory notices under § 42.8, certificate of service or word count, or appendix of exhibits or claim listing.

Appendix A
Claim Chart: Ground I (Obviousness of Claims 44-46 and 53 Over *Schnur* in View of *Gibbs* or *OSI's 10-K*)

Claims	**Prior Art Disclosure**
44. A method for the treatment of NSCLC (non small cell lung cancer) . . . in a mammal . . .	*Schnur* **Ex. 1009** at col. 5, ll. 53-60 ("In a preferred embodiment, the method of treating hyperproliferative disorders includes those wherein said hyperproliferative disorder is cancer. In another preferred embodiment, the method of treating hyperproliferative disorders includes those wherein said hyperproliferative disorder is . . . lung, . . . cancer.") *Schnur* **Ex. 1009** at col. 14, ll. 6-14 ("In particular, the compounds of this invention are therapeutants or prophylactics for the treatment of a variety of human tumors (. . . lung, . . . tumors), and other hyperplastic conditions . . . .") *Schnur* **Ex. 1009** at claims 12-14 (col. 41, ll. 55-63) ("12. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1"; "[13.] wherein said hyperproliferative disorder is cancer"; and "[14.] wherein said cancer is . . . lung . . . cancer.") *Gibbs* **Ex. 1010** at 10, Table 1: Target | Compound | Mechanism of Action | Development Status EGF receptor | CP-358,774 | Kinase inhibitor | Phase II *Gibbs* **Ex. 1010** at 10, col. 1 ("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. 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.") *OSI's 10-K* **Ex. 1011** at 6 ("CP-358,774 . . . which targets a variety of cancers including . . . non-small cell lung . . . , 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.")
. . . 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, . . .	*Schnur* **Ex. 1009** at col. 3, ll. 47-48, col. 4, ll. 8-9 ("Specific preferred compounds of formula I include . . . [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-amine . . . .") *See also Schnur* **Ex. 1009**, claim 8 (col. 39, ll. 33-34, col. 40, ll. 1-2). *Schnur* **Ex. 1009** at col. 5, ll. 49-52 ("The invention further relates to a method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound.") *Schnur* **Ex. 1009** at col. 15, ll. 55-62 ("The amount of active compound administered will, of course, be dependent on the subject being treated, on the severity of the affliction, on the

	manner of administration and on the judgement of the prescribing physician. However, an effective dosage is in the range of approximately 0.001-100 mg/kg, preferably 1 to 35 mg/kg in a single or divided doses. For an average 70 kg human, this would amount to 0.05 to 7 g/day, preferably 0.2 to 2.5 g/day.") *Schnur* **Ex. 1009** at claims 3 and 12 (col. 39, ll. 15-18 and 55-58) ("3. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a pharmaceutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier." and "12. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1.") *Gibbs* **Ex. 1010** at 10, col. 1 ("CP-358,774, competitive inhibitors of ATP binding to the receptor's active site, are currently in clinical trials. . . . [T]hese 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.") *OSI's 10-K* **Ex. 1011** at 6 ("CP-358,774 . . . which targets a variety of cancers including . . . non-small cell lung . . . , 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.")
. . . and a carrier.	*Schnur* **Ex. 1009** at col. 5, ll. 44-48 ("The

	invention further relates to a pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.") *Schnur* **Ex. 1009** at col. 16, ll. 3-6 ("The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient.") *Schnur* **Ex. 1009** at col. 16, ll. 21-23 ("Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents.") *Schnur* **Ex. 1009** at col. 16, ll. 41-45 ("Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, *see Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easter, Pa., 15th Edition (1975).")
45. The method of claim 44, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.	*Schnur* **Ex. 1009** at col. 16, ll. 46-51 ("The hyperproliferative disease treatment described above may be applied as a sole therapy or may involve, in addition to the active compound, one or more other antitumor substances. Such conjoint treatment may be achieved by way of the simultaneous, sequential, cyclic or separate dosing of the individual components of the treatment.")
46. The method of claim 44, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).	*Schnur* **Ex. 1009** at col. 1, ll. 40-47 ("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 . . . lung, . . . tumors. Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as a selective inhibitors of the growth of mammalian cancer cells.") *Schnur* **Ex. 1009** at col. 14, ll. 1-6 ("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), . . . and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans.") *See also Schnur* **Ex. 1009**, col. 14, l. 31 – col. 15, l. 48. ("The in vitro activity of the active compounds in inhibiting the receptor tyrosine kinase (and thus subsequent proliferative response. e.g., cancer) may be determined by the procedure detailed below. . . .") *Gibbs* **Ex. 1010** at 10, Table 1: Target | Compound | Mechanism of Action | Development Status EGF receptor | CP-358,774 | Kinase inhibitor | Phase II *Gibbs* **Ex. 1010** at 10, col. 1 ("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.") *OSI's 10-K* **Ex. 1011** at 6 ("CP-358,774 is a potent, selective and orally active inhibitor of the epidermal growth factor receptor, a key oncogene in these cancers.")
53. The method of claim 44 for	*Schnur* **Ex. 1009** at col. 5, ll. 53-60 ("In a

the treatment of non-small cell lung cancer (NSCLC).	preferred embodiment, the method of treating hyperproliferative disorders includes those wherein said hyperproliferative disorder is cancer. In another preferred embodiment, the method of treating hyperproliferative disorders includes those wherein said hyperproliferative disorder is . . . lung, . . . cancer.") *Schnur* **Ex. 1009** at col. 14, ll. 6-14 ("In particular, the compounds of this invention are therapeutants or prophylactics for the treatment of a variety of human tumors (. . . lung, . . . tumors), and other hyperplastic conditions . . . .") *Schnur* **Ex. 1009** at claims 12-14 (col. 41, ll. 55-63) ("12. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1"; "[13.] wherein said hyperproliferative disorder is cancer"; and "[14.] wherein said cancer is . . . lung . . . cancer.") *Gibbs* **Ex. 1010** at 10, col. 1 ("However, these compounds [ZD-1839 and CP-358,774] appear to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with non–small cell lung cancer.") *OSI's 10-K* **Ex. 1011** at 6 ("CP-358,774 . . . which targets a variety of cancers including . . . non-small cell lung . . . , 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.")

Appendix B

Claim Chart: Ground II (Obviousness of Claim 47 Over *Schnur* in View of *Gibbs* or *Wakeling*, and *Moscatello*)

Claim	**Prior Art Disclosure**
44. A method for the treatment of NSCLC (non small cell lung cancer) . . . 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.	*See* **Appendix A** (above).
47. The method of claim 44, for use in treatment of tumors that express EGFRvIII.	*Schnur* **Ex. 1009** at col. 1, ll. 40-47 ("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 . . . lung, . . . tumors. Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as a selective inhibitors of the growth of mammalian cancer cells.") *Schnur* **Ex. 1009** at col. 14, ll. 1-6 ("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), . . . and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans.") *See also Schnur* **Ex. 1009**, col. 14, l. 31 – col.

	15, l. 48. ("The in vitro activity of the active compounds in inhibiting the receptor tyrosine kinase (and thus subsequent proliferative response. e.g., cancer) may be determined by the procedure detailed below. . . .") *Gibbs* **Ex. 1010** at 10, Table 1: Target | Compound | Mechanism of Action | Development Status EGF receptor | CP-358,774 | Kinase inhibitor | Phase II *Gibbs* **Ex. 1010** at 10, col. 1 ("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.") *Wakeling* **Ex. 1013** at 67 (Summary) ("Since the mitogenic action of EGF is mediated by ligand-induced autophosporylation 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. . . . The most potent 4-anilinoquinazolines ($IC_{50} \approx 20nM$) have small non-polar meta substituents on the aniline ring, ...") *See also Wakeling* **Ex. 1013** at 68 (Table 1). *Wakeling* **Ex. 1013** at 67 ("Since the first report almost ten years ago that the presence of the epidermal growth factor receptor (EGFR) in some human breast tumours indicates a poor prognosis, it has become clear that aberrant expression of EGFR and other members of the EGF (*erb*B) family of receptors occurs in many common solid tumours of epithelial origin . . . .")

	Moscatello **Ex. 1014** at Abstract ("The 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.") *Moscatello* **Ex. 1014** at 200, col. 1 ("Overexpression of EGFR has been implicated in the pathogenesis of many human tumors, including those derived from the brain, breast, lung, ovary, prostate, and skin.") *Moscatello* **Ex. 1014** at 200, col. 2 ("We therefore investigated the possible role played by this enzyme in transformation by the EGFRvIII, and we now report that PI 3-kinase is constitutively activated in EGFRvIII-transformed cells and is essential for transformation by this receptor variant.") *Moscatello* **Ex. 1014** at 202, col. 1 ("Preincubation of cells with tyrphostin AG1478, a highly specific inhibitor of the EGF receptor kinase, reduced the phophotyrosine-associated PI 3-kinase activity in cells expressing either receptor (Fig. 2), suggesting that the EGF receptor tyrosine kinase activity is directly involved in PI 3-kinase activation in these cells.") *Moscatello* **Ex. 1014** at 206 ("We found that PI 3-kinase inhibitors inhibited both monolayer growth in low serum and anchorage-independent growth of cells expressing normal EGF receptor and EGFRvIII.")

Appendix C

Claim Chart: Ground III (Anticipation of Claims 44-47 and 53 By *Schnur* If Priority is Accorded to the '907 Application)

Claim	**The '907 Application**	***Schnur* (Ex. 1009)**
44. A method for the treatment of NSCLC (non small cell lung cancer) . . . in a mammal . . .	*'907 application* **Ex. 1007** at 10, ll. 3-13 ("The compounds of the present invention are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), . . . and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans. In particular, the compounds of the present invention are useful in the prevention and treatment of a variety of human hyperproliferative disorders such as malignant and benign tumors of the . . . lung, . . . and other hyperplastic conditions . . . .)	*Schnur* **Ex. 1009** at col. 14, ll. 1-14 ("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), . . . 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 (. . . lung, . . . tumors), and other hyperplastic conditions . . . .")
. . . comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised	*'907 application* **Ex. 1007** at 7, ll. 8-10 ("The invention also relates to a pharmaceutical composition for treating a disease in a mammal which comprises a	*Schnur* **Ex. 1009** at col. 3, ll. 47-48, col. 4, ll. 8-9 ("Specific preferred compounds of formula I include . . . [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)-

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, . . .	therapeutically effective amount of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride . . . .") *See also '907 application* **Ex. 1007** at 7, ll. 17-19. *'907 application* **Ex. 1007** at 11, l. 34 – 12, l. 2 ("The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration and the judgement of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to about 7 g/day, preferably about 0.2 to about 2.5 g/day.") *'907 application* **Ex. 1007** at claim 2 (17, ll. 6-8) ("2. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which	amine . . . .") *See also Schnur* **Ex. 1009**, claim 8 (col. 39, ll. 33-34, col. 40, ll. 1-2). *Schnur* **Ex. 1009** at col. 5, ll. 49-52 ("The invention further relates to a method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound.") *Schnur* **Ex. 1009** at col. 15, ll. 55-62 ("The amount of active compound administered will, of course, be dependent on the subject being treated, on the severity of the affliction, on the manner of administration and on the judgement of the prescribing physician. However, an effective dosage is in the range of approximately 0.001-100 mg/kg, preferably 1 to 35 mg/kg in a single or divided doses. For an average 70 kg human, this would amount to 0.05 to 7 g/day, preferably 0.2 to 2.5 g/day.") *Schnur* **Ex. 1009** at claims

	comprises a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.	3 and 12 (col. 39, ll. 15-18 and 55-58) ("3. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a pharmaceutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier." and "12. A method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1.")
. . . and a carrier.	*'907 application* **Ex. 1007** at 7, ll. 8-10 ("The invention also relates to a pharmaceutical composition for treating a disease in a mammal which comprises a therapeutically effective amount of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride and a pharmaceutically acceptable carrier.") *'907 application* **Ex. 1007** at 12, ll. 25-27 ("The	*Schnur* **Ex. 1009** at col. 5, ll. 44-48 ("The invention further relates to a pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.") *Schnur* **Ex. 1009** at col. 16, ll. 3-6 ("The

	pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.") *'907 application* **Ex. 1007** at 12, ll. 31-32 ("Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents.") *'907 application* **Ex. 1007** at 13, ll. 7-10 ("Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, *see Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easter, Pa., 5th Edition (1975).")	pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient.") *Schnur* **Ex. 1009** at col. 16, ll. 21-23 ("Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents.") *Schnur* **Ex. 1009** at col. 16, ll. 41-45 ("Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, *see Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easter, Pa., 15th Edition (1975).")
45. The method of claim 44, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.	*'907 application* **Ex. 1007** at 12, ll. 6-18 ("The active compound may be applied as a sole therapy or may involve one or more other anti-tumour substances,	*Schnur* **Ex. 1009** at col. 16, ll. 46-51 ("The hyperproliferative disease treatment described above may be applied as a sole therapy or may involve, in

	for example those selected from, ... Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.")	addition to the active compound, one or more other antitumor substances. Such conjoint treatment may be achieved by way of the simultaneous, sequential, cyclic or separate dosing of the individual components of the treatment.")
46. The method of claim 44, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).	*'907 application* **Ex. 1007** at 10, ll. 3-16 ("The compounds of the present invention are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), . . . and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans. *'907 application* **Ex. 1007** at 1, ll. 8-14, *discussing Schnur* ("United States Patent No. 5,747,498, issued May 5, 1998, which is incorporated herein by reference in its entirety, 10 refers, in Example 20, to [6, 7-bis(2-methoxyethoxy)-quinazolin-4-yl]-(3-	*Schnur* **Ex. 1009** at col. 14, ll. 1-6 ("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), . . . and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans.")

	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.")	
47. The method of claim 44, for use in treatment of tumors that express EGFRvIII.	*'907 application* **Ex. 1007** at 10, ll. 3-16 ("The compounds of the present invention are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), . . . and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans. *'907 application* **Ex. 1007** at 1, ll. 8-14, *discussing Schnur* ("United States Patent No. 5,747,498, issued May 5, 1998, which is incorporated herein by reference in its entirety, 10 refers, in Example 20,	*Schnur* **Ex. 1009** at col. 14, ll. 1-6 ("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), . . . and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans.")

	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.")	
53. The method of claim 44 for the treatment of non-small cell lung cancer (NSCLC).	*'907 application* **Ex. 1007** at 10, ll. 3-13 ("The compounds of the present invention are potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), . . . and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans. In particular, the compounds of the present invention are useful in the prevention and treatment of a variety of human hyperproliferative disorders such as	*Schnur* **Ex. 1009** at col. 14, ll. 1-14 ("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), . . . 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 (. . . lung, . . . tumors), and other

	malignant and benign tumors of the . . . lung, . . . and other hyperplastic conditions . . . .)	hyperplastic conditions . . . .”)

CERTIFICATE OF SERVICE

The undersigned certifies, in accordance with 37 C.F.R. §§ 42.6(e)(4) and 42.105, that service was made on the Patent Owner as detailed below.

Date of service: June 28, 2016

Manner of service FEDERAL EXPRESS

Documents served Petition for *Inter Partes* Review Under 35 U.S.C. § 312 and 37 C.F.R. § 42.104;
Petitioners' Exhibit List; and
Exhibits 1001 – 1028.

Persons Served Chief Executive Officer
OSI Pharmaceuticals, LLC.
1 Astellas Way
Northbrook, IL 60062

/s/ W. Blake Coblentz
W. Blake Coblentz
Counsel for Petitioner
Registration No. 57,104