Filed on behalf of Patent Owner Genentech, Inc. by

David L. Cavanaugh (Reg. No. 36,476)
Rebecca A. Whitfield (Reg. No. 73,756)
Robert J. Gunther, Jr. (*Pro Hac Vice*)
Lisa J. Pirozzolo (*Pro Hac Vice*)
Kevin S. Prussia (*Pro Hac Vice*)
Andrew J. Danford (*Pro Hac Vice*)
WILMER CUTLER PICKERING
HALE AND DORR LLP
1875 Pennsylvania Ave., NW
Washington, DC 20006

Adam R. Brausa (Reg No. 60,287)
Daralyn J. Durie (*Pro Hac Vice*)
DURIE TANGRI LLP
217 Leidesdorff Street
San Francisco, CA 94111

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO. LTD.[1]
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00804
U.S. Patent 6,627,196

PATENT OWNER'S RESPONSE

[1] Case IPR2017-01958 has been joined with this proceeding.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Constitutional Provisions

Other Authorities

I. INTRODUCTION[2]

The'196 patent inventors discovered that trastuzumab, the first antibody ever approved to treat breast cancer, could be administered on a three-week dosing regimen without compromising the safety or efficacy shown with weekly administration. Prior to trastuzumab's approval in September 1998, chemotherapy was the most common breast-cancer treatment. But for the estimated 25-30% of patients afflicted with virulent HER2-positive breast cancer, the prognosis was poor and life expectancy following a diagnosis was 12-18 months. Oncologists welcomed the introduction of trastuzumab, which finally gave these patients hope.

[2] The Board previously terminated IPR2017-01958 and joined it to the instant proceeding, IPR2017-00804. (IPR2017-01958, Paper 9.) In its motion for joinder, Petitioner Samsung Bioepis argued, and the Board agreed, that Samsung's petition was "essentially a copy of" and "substantially identical to" Hospira's petition; that Samsung's petition "relies solely on the same prior art analysis and expert testimony submitted by Hospira;" and that Samsung is merely participating in an "understudy capacity." (IPR2017-01958, Paper 1 at 1-5; IPR2017-01958, Paper 9 at 5.) Thus, while this response cites to Hospira's petition and evidence, Patent Owner's argument and evidence apply equally to Samsung's petition.

Efforts to better understand and use this new therapy did not end when trastuzumab was first approved for weekly administration to treat metastatic breast cancer. Use of targeted antibody therapy to destroy or inhibit cancer cell growth was a novel approach that had been largely unsuccessful until the late 1990s. In addition, the biologic mechanism of trastuzumab differed dramatically from chemotherapy. With chemotherapy, clinicians sought to kill as many cancer cells as possible without causing side effects that were even worse than the cancer being treated. In contrast, trastuzumab was known to specifically target breast-cancer cells. Nevertheless, much remained to be studied and learned about this groundbreaking therapy.

The prior art relied upon by Petitioners reveals the extent to which skilled artisans were still learning about trastuzumab, and does not support the contention that the claimed dosing regimens would have been obvious. There is no dispute that the prior art only described weekly administration of trastuzumab, and that the authors of the prior art opted for weekly dosing based on the very same pharmacokinetic data upon which Petitioners rest their case. Indeed, Petitioners' own clinical expert—a co-author of one of Petitioners' three prior art references—has proffered no evidence from the late 1990s that he or any other oncologist ever suggested an extended dosing interval for trastuzumab. Petitioners thus base their obviousness case on conclusory expert testimony referencing a generalized desire

for "convenience," "quality of life," and "compliance" that is nowhere evident in the prior art. In short, there is nothing in the prior art mentioning the claimed extended dose interval or the alleged motivation.

Petitioners' proof of "reasonable expectation of success" is no more compelling. In the face of varied and conflicting data, Petitioners' pharmacokinetics expert oversimplified his analysis, and then relied upon data in the prior art that would support his position while ignoring data that would not. For example, Petitioners' expert conceded that while the prior art taught that trastuzumab had "dose dependent" kinetics (*i.e.*, varying half-life depending upon dose), he assumed a single half-life when performing his analysis. Even worse, when confronted with prior art disclosing half-lives for trastuzumab ranging from 1.7 days to 12 days, Petitioners' expert opted to plug into his equations the longest reported half-life and to ignore prior art data reporting a shorter half-life. In defending these choices, Petitioners' expert sought to justify his analysis on the grounds that he "used the best information available at the time," but the prior art did not disclose sufficient detail such that a skilled artisan could accurately model an extended interval dosing regimen for a drug with non-linear kinetics like trastuzumab. (Ex. 2037, Jusko Dep., at 42:10-16, *see id.* at 42:10-16, 124:20-125:5.)

At bottom, Petitioners' obviousness case does not properly account for the seriousness of the disease condition at issue or the novelty of targeted cancer therapy at the time. With respect to "motivation," the prior art makes clear that convenience and compliance were not of concern to women with HER2-positive breast cancer or their physicians; treating the cancer was the driving force behind dosing regimens then being explored. Similarly, with respect to "reasonable expectation of success," there is no support for the proposition that a skilled artisan would rely on oversimplified analyses to predict pharmacokinetics for a complex and novel cancer therapy where errors could have fatal consequences.

II. TECHNOLOGY BACKGROUND

A. Trastuzumab Opened the Door to Targeted Treatment of Breast Cancer

1. Trastuzumab offered hope to women with HER2-positive breast cancer

The '196 patent is directed to the treatment of "HER2-positive" cancers, a class of cancers characterized by the overexpression of human epidermal growth factor 2 receptor ("HER2"), also known as human ErbB2. HER2-positive breast cancer is a particularly aggressive form of cancer, in which cancer cells grow and spread rapidly. (Ex. 2040, Gelmon Decl., ¶12.) HER2-positive status was associated with a high rate of tumor recurrence and spreading of the cancer to other areas of the body, as well as a shorter time to relapse. (Ex. 2041, Kopreski '96 at

433; Ex. 2042, Lehrer '93 at 1420; Ex. 2043, Slamon '87 at 179-80.) The life expectancy of HER2-positive patients in 1996 was only 18 months post-diagnosis. (Ex. 2044, Holzman '96 at 138; *see also* Ex. 2045, Hoyle '98 at 887; Ex. 2040, ¶12.)

In 1998, HER2-positive breast cancer made up 25-30% of the 180,000 yearly new breast cancer diagnoses. (*See* Ex. 1011 at 1, 5; *see also* Ex. 1013 at 9; Ex. 2040, ¶13). As a result, even before FDA approval of trastuzumab, Genentech was "swamped" by demand for trastuzumab and teamed with patient advocacy groups to design a lottery system to equitably distribute a limited supply to severely affected patients. (Ex. 2045, Hoyle '98 at 887.)

2. The biologic mechanisms of trastuzumab differed from traditional anti-cancer treatment

Until the approval of trastuzumab in September 1998, the treatment most commonly prescribed for breast cancer was chemotherapy. (Ex. 2040, ¶¶6, 29, 39.) Chemotherapy agents work by killing tumor cells, but they also kill healthy cells in the process and are thus considered non-targeted cancer treatments. (*Id.* at ¶30.) Rapidly dividing cells—such as hair follicles, cells lining the intestine, and bone marrow cells—tend to be damaged the worst, leading to symptoms such as

hair loss, gastrointestinal issues, myelosuppression, and neutropenia.[3] (*Id.*) In 1999, the goal of most chemotherapy dosing was to kill the greatest number of tumor cells without causing life-threatening toxicity. (*Id.* at ¶31; *see also* Ex. 2038, Lipton Dep., at 37:15-39:21; 45:12-46:2.) Typically, that was done by administering the largest tolerable dose followed by a dosing interval that would allow a patient time to recover before the next dose. (Ex. 2040, ¶30.)

The use of antibodies to treat cancer involved a radically different approach. In contrast to the broad-based DNA-damaging activity of chemotherapeutic agents, targeted cancer therapies interact with specific molecular targets involved in the growth, progression, and spread of cancer. (*Id.* at ¶30; Ex. 2060, Stadler 2000 at 7; *see also* Ex. 2038 at 37:20-11, 39:12-21, 47:17-19.) At the time of the invention, although numerous antibodies had been tested in patients with different cancers (including breast cancer), consistent therapeutic efficacy had not been shown. (Ex. 2002 at 649; *id.*, Table 2 (identifying failed antibody clinical trials for numerous cancers); Ex. 2040 at ¶¶14, 16.) Prior to August 1999, the FDA had approved only

[3] Myelosuppression results in a reduction of white blood cells, which can decrease a person's ability to fight infection. (Ex. 2040, ¶30.) Neutropenia occurs when a person has an abnormally low number of a particular type of white blood cell. (*Id.*) Both conditions can be life-threatening. (*Id.*)

one other antibody for use in treating cancer—Genentech's rituximab product, which was approved for non-Hodgkin's lymphoma treatment in 1997. (Ex. 2003, Reichert '09 at 388; *see also* Ex. 2038, 33:8-17.) Trastuzumab was the first antibody approved to target solid tumors and the first approved to treat breast cancer. (*Id.*; *see also* Ex. 2040, ¶15.)

At the time of the invention, most clinical investigators were well-aware of the distinctions between the newer target-based agents and classic chemotherapy agents. (Ex. 2060 at 7-8; Ex. 2038 at 37:13-39:21.) As a consequence, they appreciated that trastuzumab worked differently from traditional chemotherapy. (Ex. 1013 at 13 ("[T]he biologic action of [trastuzumab] … differs markedly from conventional anticancer agents."); *see also* Ex. 2038 at 37:15-39:21.) It was known that as a targeted cancer treatment, trastuzumab bound to HER2 receptors on HER2 cancer cells. Once there, it inhibited tumor cell growth and induced cell death by flagging HER2-overexpressing tumor cells for destruction by the body's immune system. (*See, e.g.*, Ex. 1001, 35:45-58; Ex. 1008 at 1.)

Skilled artisans also knew that for trastuzumab to be effective, adequate blood levels had to be maintained over the entire course of treatment. (Ex. 2040, ¶¶8, 36; Ex. 2039, ¶¶37-39.) Failure to maintain therapeutic serum concentrations throughout the dosing interval risked jeopardizing clinical efficacy. (Ex. 2040, ¶36; Ex. 2039, ¶39.) Preclinical studies of trastuzumab identified 10-20 µg/mL as

the target trough concentration for clinical efficacy, and early clinical studies showed that failure to reach this target was associated with a lack of clinical response. (Ex. 2040 at ¶¶36, 65; Ex. 1014 at 9; Ex. 1013 at 10.) Moreover, at the time of the invention, the weekly dosing regimens in the prior art resulted in higher mean trough concentrations for the average patient. For example, the regimen described in Baselga '96 resulted in a mean trough concentration of 54 μg/mL. (Ex. 1014 at 14, Table 6.) The 1998 Herceptin® Label (Ex. 1008, "The Label") reported that the approved weekly dosing regimen resulted in mean trough serum concentration levels of approximately 79 μg/mL. (Ex. 1008 at 1.)

B. Armed with a New Therapeutic Approach, Researchers Sought to Improve Treatment and to Learn More

1. At the time of the invention, researchers focused on improving efficacy

Trastuzumab's 1998 approval marked a breakthrough in the breast oncology field, providing patients with hope of treatment for a condition previously viewed as a death sentence. (*See* Ex. 2038 at 234:10-18; Ex. 2040, ¶24.) In the wake of the approval, skilled artisans seeking to maximize clinical outcomes for patients with HER2-positive breast cancer now focused on how trastuzumab could be used more effectively. (Ex. 2040, ¶¶24-25; Ex. 2028, Baselga 2000 at 27-33; Ex. 2046, Shak '99 at 76.). As one inventor of the '196 patent noted, trastuzumab's success prior to August 1999 offered "proof of principle," but further research was needed

to improve patient outcomes. (Ex. 2046, Shak '99 at 76). During the five years following trastuzumab's approval, hundreds of papers and abstracts were published in which researchers explored various ways to maximize the effective use of trastuzumab. (Ex. 2040 at ¶29.)

For example, in the late 1990s, skilled artisans were actively investigating how to combine trastuzumab with chemotherapy, including paclitaxel, the chemotherapy agent administered with trastuzumab in the Phase III studies that led to trastuzumab's approval. (Ex. 2040, ¶¶25, 37-38, 57; Ex. 2028 at 28.) Inspired by the favorable results of the Phase III trials reported in the Label, researchers—including coauthors of the prior art upon which Petitioners rely—studied administering paclitaxel to match weekly trastuzumab administration. (Ex. 2040, ¶¶38, 57; Ex. 2023, Seidman '98 at 3360; Ex. 2030, Perez '98 at 373; Ex. 2029, Fornier '99.) In this regimen, paclitaxel was administered more frequently than the then-standard three-week regimen. (*Id.*)

This trend was bolstered by studies reporting that that weekly paclitaxel administration had a remarkably favorable toxicity profile, with the same or better efficacy as compared to the three-week regimen. (*See* Ex. 2040, ¶38; Ex. 2023, Seidman '98 at 3353, 3357-58; Ex. 2034, Frasci '98 at 24.) Indeed, by 1999, studies showed that weekly paclitaxel was more effective than a three-week regimen. (Ex. 2026, Sikov '98 at 432 (weekly paclitaxel study had the highest

response rate in advanced breast cancer for single agent paclitaxel and suggesting further study); Ex. 2023, Seidman '98 at 3357-58 (weekly paclitaxel may have advantages over three-week dosing).) As described by a preeminent researcher in 1998, weekly paclitaxel was generating "much interest" given the high relative dose intensity and density delivered, and very modest side effects. (Ex. 2030, Perez '98 at 373, 375-76; *id.* at 385 ("Further investigation into the role of weekly paclitaxel … is ongoing."); *see also* Ex. 2034, Frasci '98 at 15 ("The weekly administration of paclitaxel has raised much interest in the last few years in view of the quite astonishing doses delivered with this schedule.").) At his deposition, Petitioner's oncology expert, Dr. Allan Lipton, conceded that this was an "important theory" that many people were exploring prior to the invention. (Ex. 2038 at 134:4-135:7; 273:7-13.)

In contrast, nothing in the prior art reflects any motivation to extend the dosing interval for trastuzumab to match the three-weekly dosing of paclitaxel, (Ex. 2038 at 173:20-174:10.) On the contrary, prominent researchers were taking the opposite approach. (Ex. 2040, ¶¶32-33, 38, 57; Ex. 2023, Seidman '98; Ex. 2028, Baselga 2000.)

2. The pharmacokinetic data in the prior art presented a complex picture

Although researchers had some understanding of how trastuzumab worked (and that it differed from chemotherapy), the experience and data available to skilled artisans regarding trastuzumab pharmacokinetics were limited and varied. The prior art taught that trastuzumab was dose-dependent and that half-life increased with dose amount when the drug was dosed weekly. But at the time of the invention, the degree to which half-life varied, and the reasons for the variance were not known.

*a. The prior art taught that trastuzumab exhibited dose-dependent (***i.e.***, non-linear) pharmacokinetics*

The prior art explicitly taught that trastuzumab exhibited dose-dependent pharmacokinetics over the dosing ranges tested. (Ex. 2039, Grass Decl., ¶¶8, 28-33.) For example, the Label reports that: "Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics." (Ex. 1008 at 1; Ex. 2037, Jusko Dep., 66:1-9.) Similarly, Baselga '96 reports: "The resulting recombinant humanized anti-p185HER2 monoclonal antibody (rhuMAb HER2) was found to be safe and to have dose-dependent pharmacokinetics in two prior phase I clinical trials." (Ex. 1013 at 9; Ex. 2037, Jusko Dep., 83:16-84:7.) Moreover, the data presented in the prior art is consistent with this conclusion. (Ex. 2039, ¶28.; *see also* Ex. 2037, Jusko Dep., 73:11-14.) A skilled artisan would

understand the prior art's teaching that trastuzumab exhibited dose-dependent pharmacokinetics to mean that trastuzumab had non-linear kinetics. (Ex. 2039, ¶¶8, 30; *see also* Ex. 2037, Jusko Dep., 66:7-13.)

In the case of drugs with linear kinetics, the half-life of a drug (*i.e.*, the time it takes for a drug's concentration in the body to decrease by half) remains the same across any dose amount or dose interval. (Ex. 2008, Gabrielsson & Weiner '97 at 145-46; Ex. 2039, ¶19.) A drug with linear kinetics is thus eliminated at a rate proportional to the drug's plasma concentration. (*Id.* at ¶¶20-21.) In contrast, for drugs with non-linear kinetics, the drug's half-life changes as its concentration in the body changes, *i.e.*, the half-life is dependent on the drug's concentration in body. (*Id.* at ¶¶22-23, 27.) That means that plasma concentrations do not change proportionally with dose or interval. (*Id.*; Ex. 2037, Jusko Dep., 65:16-19.) Thus, the pharmacokinetic parameters from one dose amount and interval cannot be reliably used to predict the effects of a different dose amount or interval. (Ex. 2039, ¶¶12-13, 24-27, 35.) More data is needed. (*Id.* at ¶¶56-60, 66)

While the prior art taught that trastuzumab had non-linear kinetics, it did not contain sufficient data from which to determine the specific characteristics or cause of the non-linearity. (Ex. 2039, ¶¶48, 56; Ex. 2037, Jusko Dep., 66:1-6, 83:16-84:7.) One such potential source of non-linear kinetics was the presence of shed antigen. (Ex. 2039, ¶¶56, 72.) "Shed antigen" refers to circulating extra-cellular

domain ECD^{HER2} "shed" from the tumor source, and circulating in the blood stream. (Ex. 2039, ¶71; Ex. 2001 at 313.) The prior art taught that 64% of patients with HER2-positive breast cancer had detectable levels of shed antigen and that the presence of shed antigen was correlated with lower trough serum concentrations of trastuzumab, lower half-life values, and the lack of a clinical response. (*See e.g.*, Ex. 1008 at 1; Ex. 1014 at 14; Ex. 1013 at 14.) Notwithstanding the relatively poor efficacy of trastuzumab in patients with high circulating levels of shed antigen, researchers noted that those patients should continue to be studied. (*See, e.g.*, Ex. 1013 at 14.)

b. The prior art did not contain the data that a skilled artisan would need to predict the efficacy and safety of alternative dosing regimens for trastuzumab

Whether a drug has linear or non-linear kinetics has significant implications for predicting the safety and efficacy of a proposed dosing regimen. (Ex. 2039, ¶¶22-27.) For drugs with linear pharmacokinetics, a pharmacokineticist can reasonably predict serum trough concentrations for different dose amounts and intervals by assuming that the drug's half-life remains constant. (*Id.* at ¶¶21, 27; *see also* Ex. 2037, Jusko Dep., 42:18-44:4.) In contrast, for drugs with non-linear pharmacokinetics, pharmacokinetic parameters such as half-life do not have the same utility as they do in a linear system because half-life is limited to the

particular concentration of the drug in the system at that very moment. (Ex. 2039, ¶¶22, 24; Ex. 2008, Gabrielsson & Weiner '97 at 124.)

The prior art contains insufficient information about the pharmacokinetics of trastuzumab for a skilled artisan to reliably predict the impact of a three-week dosing regimen on serum concentration. (Ex. 2039, ¶¶57, 66; *id.* at ¶6.) The cited prior art provides limited pharmacokinetic data derived from weekly trastuzumab administration, and does not contain the breadth of serum-concentration vs. time data that a skilled artisan would need to reliably predict serum concentrations likely to result from a three-week dosing regimen. (*Id.* at ¶¶56-66.) In fact, Petitioners' expert readily conceded that applying a linear model was the only possible way to do his calculations based on the prior art data. (Ex. 2037, Jusko Dep., 124:20-125:4; *infra* pp. 55-56.)

III. THE '196 PATENT

A. The Invention

The '196 patent discloses and claims new regimens for treating cancer with trastuzumab. The dosing regimens described in the patent feature less frequent dosing of trastuzumab as well as higher initial loading doses and higher maintenance doses. (Ex. 1001 at 1:34-35; 6:20-21; 44:29-37; 5:31-40; 34:10-27.)

The patent specification also provides important information about trastuzumab's pharmacokinetic properties that was not available in the prior art,

including information collected during a Phase III clinical trial of trastuzumab involving 213 patients. (Ex. 1001, 38:33-39:10; 39:11-31 (Table 2); 39:32-40:17, Fig. 3.) For example, Table 2 of the specification discloses weekly mean trough serum concentrations over seven weekly infusions. (Ex. 1001, 39:10-33.) Figure 3 provides additional information with respect to mean trough concentration over an even longer period of time—through 36 weeks of treatment. (*Id*. at Fig. 3.) This information about the pharmacokinetics of trastuzumab was not available in the prior art.

B. Challenged Claims

The Board instituted review of claims 1-3, 5, 7, 9-11, and 17-33. (Paper 13 at 14.) Patent Owner opposes Petitioners' arguments regarding all the challenged claims, but will refer to claims 11, 18, and 22, which depend indirectly from independent claim 1, as exemplary for this response.

Claim 1 relates to a method for treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor. The initial loading dose is at least 5 mg/kg of an anti-ErbB2 antibody; subsequent maintenance doses, comparable to or smaller than the loading dose, are separated in time "by at least two weeks." Dependent claims specify the cancer type, the loading dose amount, the maintenance dose amount(s), and the time interval between doses. For example, claim 11 requires the loading dose to be 8 mg/kg and at least one

subsequent maintenance dose to be 6 mg/kg, and the interval between doses to be three weeks.[4] Written in independent form, claim 11 reads:

> A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:
>
> administering to the patient ***an initial dose of approximately 8 mg/kg*** of the anti-ErbB2 antibody; and
>
> administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose, wherein at least one subsequent dose is ***approximately 6 mg/kg***, wherein the plurality of subsequent doses are separated in time from each other ***by at least three weeks***.[5]

[4] Challenged claims 5, 10, 11, and 30 are directed to dose intervals of at least three weeks. The remaining challenged claims require dose intervals of at least two weeks.

[5] All emphasis is added unless otherwise noted.

IV. PETITIONERS' ASSERTED REFERENCES

The Board instituted review of the challenged claims on a single ground, obviousness based on the Label in view of Baselga '96, Pegram '98, and the knowledge of a person of ordinary skill in the art. (Paper 13 at 14.)

A. Baselga '96 Does Not Disclose or Suggest the Claimed Dosing Regimen

Baselga '96 reports the results of a Phase II clinical study designed to evaluate the efficacy and toxicity of weekly trastuzumab administration in patients with HER2-positive metastatic breast cancer. (Ex. 1013 at 9; Ex. 2040, ¶19.) Forty-six patients received 250 mg of trastuzumab followed by 100 mg weekly doses. (*Id.*) According to the authors, the weekly regimen was determined to be the "optimal dose and schedule of rhuMAb HER2" based on two prior Phase I clinical trials. (*Id.* at 10.) Baselga '96 notes that trastuzumab has "documented dose dependent pharmacokinetics" and reports, for the weekly regimen tested, a mean serum half-life of 8.3 +/- 5.0 days. (*Id.* at 10-11.) Baselga '96 does not report sufficient information from which a skilled artisan could determine the type and severity of the non-linearity. (Ex. 2037, Jusko Dep., 83:14-84:7, 89:5-7; Ex. 2039, ¶¶59, 48.)

Baselga '96 indicates that the weekly regimen did not work for 11% (5 of 45) of patients with high shed antigen levels, reporting that "no anticancer

responses were observed in groups of patients with serum concentrations of $ECD^{HER2} \geq 500$ ng/mL." (Ex. 1013 at 14, 11; *see also* Ex. 2039, ¶¶72-74.) Baselga '96 further cautions that interpretation of results of further trials of drugs like trastuzumab should take shed antigen into account. (Ex. 1013 at 14, 11.)

Baselga '96 does not reference or suggest administering trastuzumab at any dosing interval other than weekly, and Dr. Lipton concedes that it does not address convenience. (Ex. 2038, Lipton Dep. at 259:13-17, 107:14-16; *see also id.* at 109:6-16.) Although Baselga '96 refers generally to preclinical studies administering trastuzumab with a chemotherapy agent such as paclitaxel (Ex. 1013 at 15), there is no mention or hint as to the desirability of administering trastuzumab on the same schedule as chemotherapy.

B. Pegram '98 Does Not Disclose or Suggest the Claimed Dosing Regimen

Pegram '98 describes the results of a Phase II clinical study in which 39 patients with metastatic breast cancer received trastuzumab in combination with the chemotherapeutic agent cisplatin. (Ex. 1014 at 8; Ex. 2040, ¶19.) Similar to Baselga '96, patients were treated with a 250 mg dose of trastuzumab followed by weekly doses of 100 mg for nine weeks. (*Id.*; *see also* Ex. 2037, Jusko Dep., 95:14-96:4.) Patients also received cisplatin about every four weeks, but not on the same day as trastuzumab. (Ex. 1014 at 8-10; Ex. 2037, Jusko Dep., 97:4-98:22.)

Pegram '98 provides only limited pharmacokinetic information on trastuzumab. (*See* Ex. 2039, ¶¶53, 60; *id.* at ¶54; Ex. 2040, ¶20.) Specifically, Table 6 of Pegram '98 reports a half-life of 11.0 ± 4.0 days for patients treated with trastuzumab and cisplatin. (Ex. 1014 at 14, Table 6; Ex. 2037, Jusko Dep., 99:14-100:4.) Pegram '98 also includes results from Baselga '96, reporting that when administered alone, trastuzumab had a mean half-life of 9.2 ± 5.3 days. (Ex. 1014 at 14, Table 6.) Pegram '98 further reports that mean maximum trough serum concentrations reached 54 µg/mL when trastuzumab was administered without chemotherapy, and 85 µg/mL when trastuzumab was administered with cisplatin. (*Id*.)

Pegram '98 reports that patients with any measurable detectable levels of shed antigen had mean trough concentrations 57% lower than those patients without detectable shed antigen (18.7 µg/ml v. 43.6 µg/mL) and had lower mean trough concentrations across all time points. (Ex. 1014 at 14; *id.* at Fig. 1; Ex. 2039, ¶¶71-72, 74.) Pegram further reports that "there was an inverse relationship between [trastuzumab] serum half-life and serum shed HER2 ECD of 0.5 µg/mL or greater." (*Id.*) Indeed, the observed half-life of trastuzumab in patients with shed antigen of 0.5 µg/ml or greater was only 2.9 days for trastuzumab alone and 4.0 days for trastuzumab plus cisplatin. (*Id.* at 14.) Approximately 16% (13 of 82) of patients in the study had shed antigen levels greater than 0.5 µg/mL.

Pegram '98 does not reference or suggest administering trastuzumab at any dosing interval other than weekly. (*See* Ex. 2037, Jusko Dep., 96:6-8; Ex. 2038 at 116:7-11.) Notably, while Petitioners' expert Dr. Lipton co-authored Pegram 1998, there is no mention of convenience or quality of life and Dr. Lipton concedes that compliance was not an issue. (Ex. 2037, Jusko Dep., at 98:7-99:12; Ex. 2038 at 118:4-8.) Nor does Pegram '98 suggest administering trastuzumab less frequently to match a chemotherapy regimen.

C. The 1998 Herceptin® Label Does Not Disclose or Suggest the Claimed Regimen

The Label (Ex. 1008) reflects the initial FDA-approved indications and dosing regimen for trastuzumab. (Ex. 1008 at 1.) Based on Phase III clinical trials, the FDA approved a regimen of a loading dose of 4 mg/kg followed by weekly maintenance doses of 2 mg/kg to treat HER2 positive metastatic breast cancer. (Ex. 1008 at 1.; *see also* 2040, ¶¶21-23.) For this regimen, the Label reported an average observed half-life of 5.8 days with a range of 1 to 32 days. (*Id.*; Ex. 2037, Jusko Dep., 60:12-21; Ex. 2039, ¶51.)

The Label reports that short duration intravenous infusions of 10 to 500 mg of trastuzumab once weekly demonstrated "dose-dependent pharmacokinetics." (Ex. 1008 at 1.) In these dose-rising studies, 10 mg doses administered weekly had an average half-life of 1.7 days and 500 mg doses administered weekly had an

average half-life of 12 days; the Label does not provide half-life information for any doses between 10 and 500 mg. (*Id.*; Ex. 2037, Jusko Dep., at 68:18-69:8; Ex. 2039, ¶58.) Nor does the Label disclose how many individuals participated in the dose rising studies. (Ex. 2037, Jusko Dep., 76:17-77:2, 78:21-79:8.) The parties' experts agree that a skilled artisan would understand from the Label that trastuzumab has "non-linear" kinetics, but there is insufficient information in the Label from which a skilled artisan could determine the scope and contours of that non-linearity. (Ex. 2037, Jusko Dep., 66:1-9; Ex. 2039, ¶¶28-30, 51.)

The Label also reports that 64% of patients studied had detectable levels of shed antigen. (Ex. 1008 at 1). The Label reports that patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations of trastuzumab. (*Id.*) But "with ***weekly*** dosing, most patients with elevated shed antigen levels achieved target trough serum concentrations" after six doses. (*Id.*).

The Label only refers to weekly dosing, and says nothing about the possibility of a three-week regimen. (Ex. 2037, Jusko Dep., 55:12-15, 57:9-13 (no single-dose studies reported in the Label); 58:9-59:8; 71:22-72:20; Ex. 2039, ¶¶51, 58.) Nor does the Label disclose or suggest a need for more convenient dosing regimens, or to dose trastuzumab on the same schedule as any chemotherapeutic agent. (*See also* Ex. 2038, at 76:10-19 ("the [L]abel doesn't give motivation").)

V. ARGUMENT

Petitioners falls short of proving obviousness in at least three key respects.

First, Petitioners' argument that in August 1999 a skilled artisan would have been motivated to administer trastuzumab less frequently for the sake of convenience, compliance or improved quality of life is unsupported by and inconsistent with the prior art. Nothing in the prior art suggests that skilled artisans treating patients having HER2-positive cancer were concerned with convenience or patient compliance in August 1999. Given the seriousness of the disease condition at issue, skilled artisans were focused on improving clinical outcomes for these patients. And even if a skilled artisan were to have a general desire for convenience, that desire could not be viewed without also considering the more important (and well-documented) concern that failure to reach therapeutic serum trough concentrations would reduce efficacy. Petitioners' myopic focus on convenience as a motivating factor in the absence of evidence that the extended dose interval would maintain efficacy ignores the realities of HER2-positive cancer treatment in the 1990s.

Second, nothing in the prior art supports the proposition that a skilled artisan would have been motivated to dose trastuzumab to match a three-week chemotherapy regimen. The prior art contains no such suggestion. To the contrary, it suggests skilled artisans were motivated to dose chemotherapy more

frequently to match the weekly schedule approved for trastuzumab. In addition, knowledge of the different biologic actions of trastuzumab would not motivate a skilled artisan to dose on the same schedule.

Third, even if a skilled artisan were motivated to try three-week dosing, there was insufficient pharmacokinetic data in the prior art to reasonably predict whether such a regimen would have been clinically effective. At the time of the invention, trastuzumab was the first antibody approved to treat solid tumors, and marked the very start of the use of targeted cancer therapy. Skilled artisans, who had previously relied primarily on chemotherapy, had little experience with antibodies, and fundamental questions remained to be addressed. Moreover, the prior art taught that trastuzumab has non-linear kinetics, a feature that Petitioners' pharmacokinetics expert has admitted presents challenges to developing a dosing regimen. To support its obviousness case, Petitioners improperly ignore the complexity of the prior art, relying on equations that do not account for non-linear kinetics and cherry-picking only convenient data. A skilled artisan would not risk patient lives in reliance on Petitioners' over-simplified analysis.

A. A Person of Ordinary Skill Would Not Have Been Motivated to Administer Trastuzumab on a Three-Week Schedule

Petitioners fail to identify any prior art that teaches or suggests any aspect of the claimed dosing regimen—either the extended dose interval or the claimed

loading and maintenance doses. Nor do Petitioners present credible evidence that a skilled artisan would have been motivated to combine the teachings of the cited art and knowledge of three-week chemotherapy dose regimens to develop a three-week dosing regimen for trastuzumab.

1. Petitioners provide no justification for selection of the claimed dose amounts

None of the prior art referenced in the instituted ground would have led to the claimed combination of loading and maintenance doses in a three-week regimen. Instead, to arrive at the claimed invention, Petitioners engage in a series of extrapolations and assumptions based on a purported "loading" dose (712 mg) that is nowhere in the prior art, and a supposed "maintenance" dose (500 mg) that had never been administered in a loading/maintenance dosing regimen at any interval, let alone at the claimed extended intervals. (Paper 1 at 37-40.) Missing from the Petition or the opinions of its experts is any plausible rationale for why a skilled artisan would select these untested doses *a priori* to devise a new dosing regimen with trastuzumab. While Petitioners and their pharmacokinetics expert suggest that a skilled artisan would have started with the 500 mg dose because it was reported to have a half-life of 12 days (Ex. 1003, ¶48) and the dose "had been successfully administered to patients" (Paper 1 at 31), neither Petitioners nor their experts provide any scientific rationale for selecting the 500 mg dose amount. (*See*

infra SectionV.B.1.b.) The only plausible explanation is that the 500 mg dose was selected because it came closest to the claimed regimen. This is classic hindsight and should be rejected as such. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig*., 676 F.3d 1063, 1072 (Fed. Cir. 2012) ("Evidence of obviousness, especially when that evidence is proffered in support of an obvious-to-try' theory, is insufficient unless it indicates that … skilled artisans would have had a reason to select the route that produced the claimed invention.'" (citing *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008))).

To overcome the absence of any rationale for selection of the claimed dose regimens, Petitioners suggest that selecting from a known range is conventional activity. (*See, e.g.*, Paper 1 at 25-26, 31-33, 45, 46-47.) But the cases on which Petitioners rely assume that there is a known and overlapping range available in a predictable art. *See, e.g.*, *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295-96 (Fed. Cir. 2012) (noting "because the prior art disclosed values overlapping the claimed ranges, the 'general conditions' of the claim [were] disclosed"); *In re Woodruff*, 919 F.2d 1575, 1576-77 (Fed. Cir. 1990) (noting all ranges overlap). That is simply not the case here. Petitioners' argument that there was a "range" of overlapping dose regimens in the prior art (*see, e.g.*, Paper 1 at 32-33) ignores the key fact that the only dosing interval disclosed was weekly. The range must

already exist in the prior art; petitioners cannot manufacture a "range" without basis.

Even more fundamentally, designing effective antibody dosing regimens for cancer treatment was not a predictable art at the time of the invention. Trastuzumab was a first-in-class antibody with a novel therapeutic mechanism and documented dose-dependent kinetics. (*See supra* Sections II.A-B.) Indeed, at the time of the invention, developing an antibody dosing regimen for clinical use was described as a "complicated task." (Ex. 2004, Casadevall '99 at 11.) And it was known that drugs that exhibit dose-dependent kinetics like trastuzumab "defy easy quantitative description and prediction." (Ex. 1022 at 3:109.) Adding to the unpredictability, trastuzumab was the first antibody to treat breast cancer and did so with a novel therapeutic mechanism. As a result, Petitioners' reliance on cases like *Applied Materials* (groove depth on an integrated circuit) and *Woodruff* (atmospheric gas quantities) is misplaced. *See, e.g.*, *In re Patel*, 566 F. App'x 1005, 1010 (Fed. Cir. 2014) (non-precedential) ("Depending on the technology, even small differences in formulations can be meaningful"); *see also Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1304 (Fed. Cir. 2015) (declining to find obvious claims that fell within disclosed ranges in the prior art where the claimed amount of ingredients "could and did materially and unpredictably alter the propert[ies] of the claimed [invention].").

Nor does Petitioners' argument find support in the readily distinguishable case of *Biomarin Pharm. Inc. v. Genzyme Therapeutic Prods., LP*, IPR2013-00537, Paper 79 (Feb. 23, 2015) (Ex. 1025), *aff'd Genzyme Therapeutic Prods. LP v. Biomarin Pharm. Inc.*, 825 F.3d 1360 (Fed. Cir. 2016). There, the Board found that claims directed to biweekly administration of a therapeutic amount of an enzyme would have been obvious to a skilled artisan where the prior art already disclosed key elements of the claimed invention. For example, the prior art not only disclosed the amount of drug to be administered (Ex. 1025 at 10-11, 16), but also that a biweekly regimen of a similar enzyme had been shown to be effective at treating a related disorder (*id.* at 11-12, 16). The prior art relied upon by Petitioners here discloses nothing of the kind—not the claimed intervals of two or three weeks, or use of longer intervals with the claimed loading and maintenance doses. And unlike in *BioMarin*, the prior art at issue here expressly teaches that trastuzumab exhibits dose-dependent kinetics and that a weekly regimen was the "optimal" regimen.

2. A skilled artisan would not have been motivated to extend the dosing interval for the sake of convenience

a. The evidence shows that in August 1999, skilled artisans were not focused on convenience

In August 1999, trastuzumab had been FDA-approved for less than a year. While it offered tremendous promise to patients diagnosed with HER2-positive

breast cancer, skilled artisans remained focused on improving efficacy. (Ex. 2040, ¶¶25, 29; Ex. 2046, Shak '99 at 76.) Indeed, in the case of metastatic breast cancer—the only indication approved at the time of the invention—efficacy was critical because every day matters where untreated patients have a life expectancy of only 10-18 months. (Ex. 2040, ¶¶12, 40; Ex. 2044, Holzman '96 at 138; *see also* Ex. 2045, Hoyle '98 at 887 ("[B]reast cancer patients who overproduce HER2 can now expect to live some 10 to 12 months after metastasis begins, a horribly rapid progression compared to six or seven years for HER2- normal patients.").)

The focus on safety and efficacy is borne out by the prior art. All references upon which Petitioners rely discuss safety and efficacy, whereas not a single one refers to convenience or compliance. (*See, e.g.*, Ex. 1014 at 9 (describing administration of cisplatin the day after trastuzumab, even when the two drugs were administered during the same week); Ex. 1008 at 1 ("Patients receiving HERCEPTIN should undergo frequent monitoring for deteriorating cardiac function."); Ex. 1013 at 10 (describing study objectives including investigating "the antitumor activity of rhuMAB HER2" and to "defin[ing] further the toxicity profile and pharmacokinetics of rhuMAb HER2").) This is because efficacy was the primary concern. (Ex. 2040, ¶¶7, 25, 30-34, 39-41, 55.)

The absence in the prior art of any suggestion of a problem with convenience or a desire to develop a less frequent dosing regimen for trastuzumab

is hardly surprising in the context of breast cancer. As Dr. Gelmon explains, if the drug does not have its intended clinical effect, convenience simply does not matter. (*Id.* at ¶40.) Dozens of researchers at the time of the invention were testing dose-dense chemotherapy treatments, which involved administering treatment more frequently than was standard, because it was believed the shortened dosing intervals would increase efficacy due to lack of time for regrowth between cycles—despite the seemingly "inconvenient" dosing regimen. (Ex. 2040, ¶¶32-34, 55; *see infra* Section V.A.2.b.) Indeed, Dr. Lipton concedes that researchers at the time of the invention were motivated to increase efficacy by administering paclitaxel weekly. (Ex. 2038 at 134:4-10, 134:19-135:14; 141:1-4; 142:8-21; 144:8-147:9; 263:17-264:1.)

Against this backdrop of clear, documentary evidence that skilled artisans working with chemotherapy agents were motivated by efficacy concerns even at the expense of convenience, Dr. Lipton presents only a generalized convenience theory. (*See, e.g.*, Ex. 2038 at 206:14-207:5 ("[T]he motivation for patient convenience is the same in any disease. Cancer, noncancer, you want to do what's most convenient for your patient."); *id* 174:11-20 ("Well, we assume we want patient convenience.").) But merely identifying a generalized concern for "convenience" untethered to the specific patient population in the claims is legally insufficient to carry Petitioners' burden. *See Rovalma, S.A. v. Bohler-Edelstahl*

GmbH & Co. KG, 856 F.3d 1019, 1025-26 (Fed. Cir. 2017) (reversing PTAB decision finding a motivation to combine, and finding a general desire for "high thermal conductivities" was insufficient to find a motivation to increase thermal conductivity beyond levels previously achieved."); *Böhler-Edelstahl GmbH & Co. KG. v. Rovalma S.A.*, IPR2015-00150, Paper 51 at 12-13 (Dec. 6, 2017) (Pollock, APJ) (finding challenged claims patentable on remand for same reason); *see also Depomed, Inc. v. Actavis Elizabeth LLC*, No. CIV.A. 12-1358 JAP, 2014 WL 4215435, at *48 (D.N.J. Aug. 25, 2014) ("general motivation to … improve compliance and possibly reduce side effects" insufficient where "certain unique characteristics of [the claimed compound] … may have dissuaded a POSA" from creating the claimed invention.).

b. A clinical oncologist would not have been motivated to dose trastuzumab on a three-week schedule like a chemotherapy agent

Petitioners also contend that a skilled artisan would have dosed trastuzumab every three weeks to align the schedules for dosing trastuzumab and chemotherapy. (Ex. 1002, ¶¶ 65-66.) But like Dr. Lipton's convenience theory, this opinion has no foundation in the prior art. (*Cf.* Ex. 1002, ¶¶ 65-66.)

At the time of the invention, skilled artisans were not considering extending trastuzumab's dosing interval. Instead, to improve efficacy, they were increasing the frequency of paclitaxel administration both when used alone and in

combination with other treatments such as trastuzumab. In numerous clinical trials, oncologists were using weekly paclitaxel. (*See* Ex. 2040, ¶38; Ex. 2023, Seidman '98 at 3353, 3357-58; Ex. 2034, Frasci '98 at 15, 24; Ex. 2030, Perez '98 at 370, 375-76; Ex. 2048, Alvarez '99 at 636; Ex. 2025, Breier '98 at 740; Ex. 2049, Mickiewicz '99 at 515; Ex. 2031, Perez '99 at 480; Ex. 2023, Seidman '98 at 2; Ex. 2026, Sikov '98 at 245; Ex. 2024, Sola '99; *see also* Ex. 2038 at 134:4-136:18, 142:8-147:9.) These studies suggested that more frequent paclitaxel administration could have significant advantages. (*See, e.g.*, Ex. 2023, Seidman '98 at 3353, 3357-58; Ex. 2034, Frasci '98 at 24; *see also* 2033, Ready 2007 at 576, 583 (study coauthored by Dr. Lipton stating that weekly paclitaxel is more effective than every-three-week paclitaxel).)

Consistent with this focus, skilled artisans at the time of the invention were motivated by trastuzumab's Phase III results to explore the weekly co-administration of trastuzumab and paclitaxel—not extending trastuzumab to match paclitaxel's three-week regimen. (Ex. 2040, ¶¶7, 38, 55-57.) For example, one author wrote "[t]he recent observation of meaningful translation of preclinical synergy into clinical benefit for the combination of paclitaxel (3-hour infusion every 3 weeks) and Herceptin … ***has motivated us to explore the weekly co-administration of these two agents*** (paclitaxel via weekly 1-hour infusion) in a phase II trial that is well underway…." (Ex. 2023, Seidman '98 at 3360.); *see also*

Ex. 2028, Baselga 2000 at 29 ("The results of preclinical studies and the pivotal phase III study have led to the design of series of follow up studies with taxanes plus trastuzumab" including "a phase II study of weekly paclitaxel plus trastuzumab in patients with metastatic breast cancer.").) It is worth noting that the artisans investigating weekly administration of paclitaxel in conjunction with weekly trastuzumab included four authors of Baselga '96. (*Compare*, Ex. 1013 at 9, *with* Ex. 2023, Seidman '98 at 3353; *cf.* Paper 1 at 36 ("It is also beneficial for the clinic to administer the combined therapies on the same schedule because they only have to prep the patient once. In addition, there is added cost to the patient's care for each visit to the clinic." (citations omitted)).)

That skilled artisans, including the co-authors of the prior art relied on by Petitioners, were not applying chemotherapy-dosing regimens or concepts to trastuzumab is hardly surprising. In August 1999, very little had been published in the literature about trastuzumab pharmacokinetics. (*See supra* Section II.B.2.) Moreover, as Baselga '96 explains, "the biologic action of [trastuzumab] … differs markedly from conventional anticancer agents" like chemotherapy. (Ex. 1013 at 13; Ex. 2040, ¶¶ 36, 53-54.) A skilled artisan would therefore have known that chemotherapy agents and targeted therapies like trastuzumab are dosed according to different principles and thus would not have expected them to be dosed on the same intervals. (*See* Ex. 2040, ¶¶36, 53-54; *supra* Section II.A.2.)

c. Dr. Lipton's conclusory reference to compliance and quality of life is insufficient to establish a motivation to combine

Dr. Lipton's conclusory and generalized assertion that a skilled artisan would have been motivated to "improve patient compliance and quality of life" is not only legally insufficient but contradicted by the contemporaneous evidence. (*cf.* Paper 1 at 33-34; Ex. 1002, Lipton Decl. ¶ 63.)

First, Dr. Lipton does not cite any reference suggesting that extending the dosing regimen of trastuzumab would improve the "quality of life" of patients with HER2-positive breast cancer. (*Cf.* Ex. 1002, Lipton Decl. ¶¶38-44; Ex. 2038 at 225:2-10.) Although Dr. Lipton cites prior art studies using the term "quality of life," none of these studies discuss quality of life for patients with HER2-positive breast cancer. (Ex. 2038 at 220:8-222:12; *cf. id.* at 319:14-15.) At best, these studies indicate that the factors most influencing quality of life in breast cancer patients were the efficacy and safety of their treatment. (*See, e.g.*, Ex. 1020 at 12 ("quality of life" measurement scores are designed to be responsive to changes in patients' health status over time); Ex. 1019 at 8 (listing "quality of life" factors including physical, cognitive, and global health assessments); Ex. 1020 at 14 (same).) Indeed, the papers cited by Dr. Lipton describe a "significant concern expressed with regard to fear of the spread of breast cancer or recurrent disease." (Ex. 1021 at 9.)

Moreover, studies at the time of the invention (but not referenced by Dr. Lipton) found that treatment with weekly trastuzumab could ***improve*** patient quality of life in comparison to treatment with chemotherapy regimens alone, even though patients were required to undergo weekly infusions of trastuzumab. (Ex. 2036, Osoba '99 at 86-87.)[6] Osoba 1999 reports that the patients who received weekly trastuzumab reported no decline in quality in life over the course of treatment, in contrast to prior studies showing deteriorating quality of life scores while patients received chemotherapy treatment alone. (*Id.* at 86-87, 84; *see also* Ex. 2040, ¶¶49-51.) Even when weekly trastuzumab was added to an every three-week regimen of paclitaxel, quality of life scores of treated patients increased as compared to every-three-week chemotherapy alone. (*Id.* at 87.) Thus, contrary to Petitioners' suggestion, the addition of two extra visits per treatment cycle to allow for the weekly administration of trastuzumab certainly did not negatively impact patient quality of life, but appeared to improve it. (Ex. 2040; ¶¶49-52; *cf.* Ex. 1002, ¶44 ("[Q]uality of life for patients with all forms of cancer has long been a concern to physicians and has been correlated with patient outcomes.").)

[6] Ex. 2036, Osoba '99, while published shortly after the priority date, presents survey data that was collected prior to the priority date and therefore represents patient concern at the time of the invention.

Second, there is no evidence that skilled artisans were concerned about "compliance" with weekly administration of trastuzumab. (Ex. 2040, ¶48.) The implication that patient compliance with weekly trastuzumab needed improvement is utterly devoid of support in the prior art and should be rejected as a motivation to combine. *See In re Nuvasive*, 842 F.3d 1376, 1383 (Fed. Cir. 2016) ("'conclusory statements' alone are insufficient" articulations of motivation to combine) (quoting *In re Sang Su Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2002).)

In contrast to Dr. Lipton's general assertions that have no specific ties to trastuzumab or HER2-positive cancer, Dr. Gelmon has offered specific evidence regarding her experience with patients taking trastuzumab in 1999. Dr. Gelmon explains that, at the time of the invention, she personally observed that patient compliance was high. (Ex. 2040, ¶43.) Moreover, as Dr. Gelmon explains, compliance was not likely to be an issue because—unlike conventional chemotherapy drugs—trastuzumab was both well tolerated with minimal side effects ***and*** effective at treating HER2-positive breast cancer. (*Id.* at 35, 44-45, 47; *compare* Ex. 2038 at 217:6-218:10 (Dr. Lipton agreeing that trastuzumab is a well-tolerated therapy with a low incidence of side effects), *and id.* at 52:18-20 ("we knew in 1999 Herceptin was effective …[and] significantly improved the outcome of cancer patients") *with* Ex. 2047, Campbell-Baird 2010 at 85 (paper coauthored by Dr. Lipton opining "[e]ffective therapies with fewer side effects would improve

treatment compliance and substantially benefit these [metastatic breast cancer] patients.").)[7]

d. Petitioners' generalized convenience argument is counter to law

i. Motivation must be viewed in the context of the prior art at issue and the perspective of a skilled artisan

Whether a skilled artisan would have been motivated to combine the prior art to achieve the claimed invention is a case-specific inquiry that must be grounded in the evidentiary record. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d

[7] Petitioners and Dr. Lipton's reliance on a statement from one of the named inventors who was serving as an expert witness in an unrelated proceeding is inapt. (*Cf.* Ex. 1002, ¶64 (citing Ex. 1017); *see also* Paper 1 at 27-28.) That proceeding involved a different invention, with different prior art, at a different period of time, through the lens of a different person of skill in the art, and therefore has no relevance here. (*See* Ex. 2037, Jusko Dep., 111:22-112:14 (Dr. Jusko asserting that his prior criticisms of an analysis that extrapolating based on a linear model pertains to the particular drug in the particular situation and "should not be generalized about any other compound."); *cf. Sanofi-Synthelabo*, 550 F.3d at 1089 ("The determination of obviousness is dependent on the facts of each case.").)

1075, 1089 (Fed. Cir. 2008) ("The determination of obviousness is dependent on the facts of each case."); *see also Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1051 (Fed. Cir. 2016) (en banc) ("[W]hether a skilled artisan would have been motivated to combine references [is] a question[] of fact."). Importantly, Petitioners must identify a particularized motivation to combine the prior art to achieve the claimed invention. *Innogenetics, N.V. v. Abbott Labs*., 512 F.3d 1363, 1373 (Fed. Cir. 2008) ("A generalized motivation to develop a method is not the kind of motivation required by the patent laws." (citations omitted)). Merely identifying a generalized concern over "patient convenience" or "patient compliance" untethered to the specific patient population in the claims is legally insufficient to carry Petitioners' burden. (*See supra* V.A.2.a.)

The need to identify a particularized motivation to solve a problem in the prior art is essential to avoid the pitfalls of hindsight bias. "[W]hile we understand that '[t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation,' we also recognize that we cannot allow hindsight bias to be the thread that stitches together prior art patches into something that is the claimed invention." *Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017) (quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 419, 421 (2007).)

ii. Petitioners' reliance on Hoffman-La Roche is misplaced

Petitioners' reliance on *Hoffman-La Roche Inc. v. Apotex, Inc.* for the general proposition that "[a] relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance" is misplaced. (Paper 1 at 34 (quoting *Hoffman-La Roche*, 748 F.3d 1326, 1329 (Fed. Cir. 2014)); Paper 13 at 13 (same).). *Hoffman-La Roche* does not stand for the proposition that a desire for convenience or patient compliance will always provide motivation to extend dosing intervals. (*Cf.* Paper 13 at 13 (citing *Hoffman-La Roche*, 748 F.3d at 1329).) *Hoffman-La Roche* addressed the specific issue of whether once monthly administration of 150 mg of the bisphosphonate ibandronate was obvious in view of prior art teaching that monthly administration of bisphosphonates (including ibandronate) improved patient compliance. *Hoffman-La Roche*, 748 F.3d at 1330 (identifying three prior art references disclosing monthly administration of ibandronate). The Federal Circuit's statement regarding convenience was clearly grounded in the specific facts of that case:

> A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance ***stemming from the inconvenience of oral bisphosphonate regimens***.
>
> Fosamax®, a prior art bisphosphonate product sold by Merck & Co.,

> was administered weekly, and several prior art references taught once monthly oral dosing of ibandronate or other bisphosphonates.

Hoffman-La Roche, 748 F.3d at 1329.

The facts that supported a finding of motivation in *Hoffman-La Roche* have no bearing upon this case, which involves a first-in-class therapeutic, a fatal disease condition, and a completely different set of prior art. (Ex. 2040, ¶¶43-47.) At the time of the invention, trastuzumab was the only antibody approved for the treatment of solid tumors and one of the first targeted cancer treatments. (Ex. 2003 at 388.) In contrast, the drug at issue in *Hoffman-La Roche*, ibandronate, was a member of a well-characterized class of drugs, bisphosphonates, that had already been efficaciously administered over the claimed dosing interval. *Hoffman-La Roche*, 748 F.3d at 1327-28, 1330.

Convenience considerations that may be applicable in the context of treatments to prevent osteoporosis have little relevance in the context of treating HER2-positive breast cancer. (Ex. 2040, ¶¶41-47.) Dr. Lipton concedes as much. (Ex. 2038 at 302:11-303:12 (comparing bisphosphates and trastuzumab is an "apples and oranges" comparison because "they're two different classes of drugs for different indications, with different mechanisms of action").) Failure to take osteoporosis medication may increase the risk of bone injury many years later, but has no short-term impact on patients. (Ex. 2040, ¶46.) Doctors therefore must

oftentimes coax patients into taking this type of preventative medication, including by making treatment regimens convenient and easy to remember. (*Id.*) In contrast, failure to take medication for HER2-positive breast cancer will typically result in death within months. (*Id.* at ¶43.) Patients thus need little additional convincing in the form of convenience to take trastuzumab. (*Id.*; *see also id.* at ¶¶42-47 (compliance was not likely to be an issue for breast-cancer patients).) In short, factual findings relevant to the motivations applicable to dosing of bisphosphonates have no relevance to motivations relating to dosing regimens for novel antibodies targeting breast cancer. (*See* Ex. 2038 at 302:11-303:12.)

3. The pharmacokinetic data in the prior art would not have motivated a skilled artisan to extend the dosing interval of trastuzumab

It is not the Patent Owner's burden to prove that a skilled artisan would have been deterred from pursuing three-week dosing. *In re Magnum Oil*, 829 F.3d 1367, 1375 (Fed. Cir. 2016) ("In an *inter partes* review, the burden of persuasion is on the petitioner to prove 'unpatentability by a preponderance of the evidence,' 35 U.S.C. § 316(e), and that burden never shifts to the patentee." (citations omitted); *but see* Paper 13 at 12 (requiring Patent Owner to establish that "an ordinary artisan would have been discouraged from extending the dosing interval to once every three weeks.") Yet here, as a factual matter, the evidence supports such a conclusion and, in any event, demonstrates that a skilled artisan would not have

been motivated to extend the dosing interval of trastuzumab. (Ex. 2039, ¶¶9-10, 67-75.)

First, the prior art's statement that weekly dosing of trastuzumab was "optimal" (Ex. 1013 at 10) would have pointed a skilled artisan away from three-week dosing. This is particularly so given that several of the extraordinarily skilled artisans in Baselga '96 later conducted trials increasing the frequency of paclitaxel administration to match the weekly administration of trastuzumab after viewing the results of the phase III trials reported in the Label. (Ex. 2023, Seidman '98 at 3353; Ex. 2028, Baselga 2000 at 29; Ex. 2039, ¶¶68-69.)

Second, a skilled artisan would have known from the prior art's report of trastuzumab's non-linear kinetics that seemingly small changes in dose amount or interval could unpredictably alter clinical effects. Pharmacokineticists and oncologists have observed that it can be exceedingly difficult to design dosing regimens for drugs with such behavior. For example, Dr. Jusko has written that, even in 2001, "[d]rugs that demonstrate nonlinear pharmacokinetic behavior can prove difficult in terms of designing dosage regimens and determining correlations between drug concentrations and effects (efficacy and toxicity)." (Ex. 2010, Mager & Jusko '01 at 519, 522; *see also* Ex. 2037, Jusko Dep., 104:6-16 ("one needs to appreciate the nature –the mechanism of the nonlinearity and severity of it.").

Third, the unpredictability generally associated with drugs having non-linear kinetics was compounded for trastuzumab given the prior art's reporting of widely varied half-life data and the potential impact of shed antigen on serum trough concentrations. (Ex. 2039, ¶¶71-75; *supra* Section V.B.1.b (describing half-life variability).) This would have been particularly concerning given the Label reports that 64% of patients studied had detectable levels of shed antigen and that "[p]atients with higher baseline shed antigen were more likely to have lower serum trough concentrations." (Ex. 1008 at 1; Ex. 2039, ¶73.) Likewise, Pegram '98 reported that circulating shed antigen was inversely related to half-life and that for patients with high levels of shed antigen, trastuzumab had a half-life of only 2.9 days. (Ex. 1014 at 4; Ex. 2039, ¶74.) It was not reported what the time course of the effect of shed antigen would be, *i.e.*, if it would increase, decrease, or reach a constant level over time. As such, while it was known that changing levels of shed antigen would result in changing half-life of trastuzumab, the potential time effect was not understood. (*Id.* at ¶ 72.) Given the data in the prior art regarding the effect of shed antigen on half-life and trough serum concentration data, a skilled artisan would have been cautious in designing a new dosing regimen for trastuzumab. (Ex. 2039, ¶¶73-75.)

Lastly, independent of trastuzumab's non-linear kinetics and the prevalence of shed antigen, a skilled artisan would have known that extending the dosing

interval of trastuzumab would have increased peak concentrations while lowering trough concentrations. (Ex. 2039, ¶38.) A skilled artisan would have been concerned that a three-week dosing regimen would have resulted in plasma trough concentrations below those previously shown to have been clinically effective. (Ex. 2040, ¶58.)

Particularly for a life-saving drug like trastuzumab, a skilled artisan would not have risked patients' lives based on generalized notions of convenience by altering a proven regimen for a first-in-class cancer therapy like trastuzumab based on the uncertainty presented in the prior art. (*Id.* at ¶¶8, 58, 65.)

B. Petitioners Have Failed to Show that a Skilled Artisan Would Have a Reasonable Expectation of Success

Petitioners have the burden of establishing that a skilled artisan would have a reasonable expectation of success that extending the trastuzumab dosing regimen to three weeks with the claimed loading and maintenance doses would be safe and effective. The reasonable-expectation-of-success inquiry is firmly rooted in the facts of the case, the context of the problem to be solved, and the claims. *See Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013) (the "expectation-of-success analysis" must match the problem to be solved); *see also Arctic Cat Inc. v. Bombardier Recreational Prod. Inc.*, No. 2017-1475, --- F.3d ----, 2017 WL 6044237, at *5 (Fed. Cir. Dec. 7,

2017) (reasonable expectation of success is a question of fact). In the context of a cancer-treatment regimen, an oversimplified pharmacokinetic analysis that glosses over the recognized deficiencies of the prior-art data by ignoring fundamental (but inconvenient) teachings fails to provide a sufficient reasonable expectation of success.

1. Dr. Jusko's analysis contradicts fundamental teachings of the prior art

The pharmacokinetic analysis upon which Petitioners rely to demonstrate reasonable expectation of success is fatally flawed in two key respects. First, Petitioners' pharmacokinetics expert erroneously applied linear pharmacokinetics to predict serum trough concentration values for a three-week regimen. This contradicted prior art teachings that trastuzumab had demonstrated non-linear kinetics. Second, Petitioners' pharmacokinetics expert impermissibly cherry-picked the data used in his calculations, ignoring data that would not support a reasonable expectation of success, while electing to use data that would most strongly support his opinions. These errors render his conclusions fundamentally unreliable.

a. Petitioners' application of linear pharmacokinetics to support their position is erroneous

i. The prior art does not support application of linear pharmacokinetics

Petitioners' pharmacokinetics expert, Dr. William Jusko, concedes that the prior art taught that trastuzumab had non-linear kinetics. (Ex. 2037, Jusko Dep., 42:10-43:3; 67:18-20; *see also* Ex. 2039, ¶¶28-30, 34.) He also concedes that a drug with non-linear kinetics will not have the same half-life at different drug concentrations, doses, and intervals. (Ex. 2037, Jusko Dep., 68:18-69:2.) Notwithstanding this teaching in the prior art, Dr. Jusko used linear pharmacokinetic equations to estimate the predicted serum trough concentrations of trastuzumab over a three-week interval. (Ex. 1003, ¶¶ 46-66, 69-71; Ex. 2037, Jusko Dep., 42:10-16; Ex. 2039, ¶¶12, 16.) Similarly, all of the equations used by Dr. Jusko assume that the half-life, elimination rate constant, and volume of distribution of trastuzumab remain constant as the dose amount changes and as the concentration of the drug changes in the bloodstream.[8] (*Id.* at 43:8-16, 43:20-44:4,

[8] Dr. Jusko's reliance on a single half-life appears in paragraph 49 of his declaration. There, he uses a 12-day half-life to calculate an elimination rate constant of 0.05776 $days^{-1}$. (Ex. 1003, ¶49.) Dr. Jusko then used this elimination

45:13-15, 48:2-51:21, 67:14-20; Ex. 2039, ¶¶12, 16; *see also id.* at ¶¶22-25).) This was error.

For drugs with non-linear kinetics, pharmacokinetic parameters such as half-life do not remain constant but change as a function of the concentration of the drug in the plasma. (Ex. 1022 at 3:109; Ex. 2008, Gabrielsson & Weiner '97 at 123; Ex. 2038, ¶¶22-25, 27, 34-36; *see also* Ex. 2037, Jusko Dep., 73:11-18 (agreeing that the Label teaches that "the rate at which trastuzumab is cleared from the bloodstream changes with dose amount.").) Thus, the half-life of trastuzumab was known to change with dose amount and dose interval. For these reasons, a skilled artisan would not expect the half-life derived from weekly administration of trastuzumab to accurately predict the concentration of a different dose amount at a different dosing interval. (Ex. 2039, ¶¶40-47, ¶¶49-55, 57; Ex. 1013 at 10 (pharmacokinetic data collected weekly); Ex. 1014 at 9-10 (same).)

To the extent that Dr. Jusko relies on Baselga '96's application of a one-compartment model to support his assumption that a skilled artisan would have assumed linear kinetics in developing an alternative dosing regimen, that too was error. (Ex. 2039, ¶¶31-33, 63-64, 52; *cf*. Ex. 1003, ¶¶33-35; *id*. at ¶ 33 ("Serum

---

rate constant to determine serum trough concentrations. (*See, e.g.*, *id.* at ¶¶50-56, 59-61.)

levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." (quoting Ex. 1013 at 10.)); Ex. 2037, Jusko Dep., 88:8-14.) Whether a drug has non-linear kinetics over a given dose interval is independent of the question of whether a one or two compartment model best fits the data. (Ex. 2039, ¶32.) Thus, Baselga '96's reported use of a one-compartment linear model to describe the data collected from the weekly administration of 100 mg of trastuzumab cannot be read in isolation from the statement in Baselga '96 that trastuzumab has dose-dependent pharmacokinetics. (*See id.* at ¶¶31-32; *see also, W.L. Gore & Assocs., Inc. v. Garlock, Inc*., 721 F.2d 1540, 1550 (Fed. Cir. 1983) (a prior art reference must be considered in its entirety); M.P.E.P. § 2141.02(VI) (same).) A skilled artisan reading Baselga '96 in its entirety would understand that while the one-compartment linear model may have been descriptive of the data collected over a weekly dosing interval of a single dose amount, it could not be used to reliably predict what would happen over a longer dosing interval or a different dose amount. (Ex. 2039, ¶¶31-32.)

Likewise, the Label's report of a single half-life for each dose amount does not support a conclusion that a linear model is appropriate. (Ex. 2039, ¶65; *cf.* Ex. 1003, ¶34.) The fact that the Label only reports a single half-life does not indicate that a one-compartment linear model was used. (Ex. 2039, ¶65.) Even for drugs that are modelled according to a two-compartment model a single half-life is often

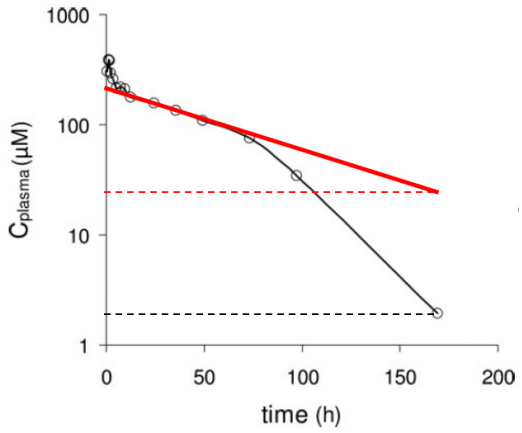
reported on the product label. (*Id.*; *compare, e.g.*, Ex. 2076, 2007 Ativan® Label at 1 (reporting a single mean half-life), *and* Ex. 2078, 2011 Onfi® Label at 14-15 (same), *with* Ex. 2077, Greenblatt at 57-62 (reporting two and three compartment models for lorazepam (Ativan®)), *and* Ex. 2079, Jawad & Richens '84 at 873-76 (describing elimination of clobazam (Onfi®) as biexponential).) Moreover, FDA guidelines for the format of the pharmacokinetics section of an application did not require the reporting or identification of a particular multicompartment analysis. (Ex. 2075 at 3-4, 6.)

ii. Linear pharmacokinetic equations likely overestimate trough concentrations after three weeks

A skilled artisan would have known that applying linear kinetics to data from weekly administration of a dose-dependent drug such as trastuzumab to predict trough concentrations for a three-week trastuzumab regimen would likely overestimate serum trough concentrations. (Ex. 2039, ¶¶13, 40-47.) Petitioners' expert agreed that the Label teaches that the rate at which trastuzumab is cleared from the bloodstream changes with dose amount and that as the dose amount decreases, clearance increases. (Ex. 2037, Jusko Dep., 73:11-18, 75:1-4.) This is consistent with the prior art's reporting of shorter half-lives for smaller doses of trastuzumab. (*See, e.g.*, Ex. 1008 at 1 (reporting 1.7-day half-life for 10 mg dose, 5.8-day half-life for 4 mg/kg loading dose and 2 mg/kg maintenance doses, and 12-

day half-life 500 mg doses.) A skilled artisan would thus expect the half-life of trastuzumab to decrease as its concentration decreases in the plasma. (Ex. 2039, ¶¶25, 43; Ex. 2037, Jusko Dep., 73:11-14, 75:1-4.) Dr. Jusko's equations, which assume that the half-life of trastuzumab remains constant over a three-week interval, do not account for this, and instead assumed a higher half-life (and lower rate of elimination) throughout the three-week interval than would have been expected. (Ex. 2039, ¶¶43-44; *see also id.* at ¶¶45-47.)

The anti-cancer agent indisulam provides a real-world example of how incorrectly assuming a constant half-life measured over a short interval could greatly overestimate the predicted serum concentration over a longer interval. (Ex. 2039, ¶26; Ex. 2052, Zandvliet '06 at 1041.) As Dr. Grass explains, the graph below shows a plasma concentration vs. time profile of indisulam. If a skilled artisan were to predict the serum concentration of indisulam after 175 hours using ***only*** the data collected from the first 50 hours and assuming the half-life would remain constant (*i.e.*, assume linear kinetics as depicted by the red line), the predicted serum concentration would be an overestimate of the measured serum concentration by at least an order of magnitude:



(*See id*. at 1045, Fig. 6 (edited for clarity, red and dotted lines added); Ex. 2039, ¶26.)

It is for these reasons that skilled artisans, including Dr. Jusko, have urged caution in predicting the behavior of drugs with non-linear kinetics. (*See, e.g.*, Ex. 1022 at 3:109 ("dose-dependent … kinetic behaviors defy easy quantitative description and prediction."); Ex. 2007 at 153; Ex. 2010 at 519, 522.) This is particularly true where, as here, the type and degree of non-linearity have not been described in the art. (*See* Ex. 1022 at 3:109 (after identifying non-linear behavior, the next steps "involve determining the parameters affected and the likely mechanisms of the nonlinearity."); Ex. 2037, Jusko Dep., 104:6-16 ("one needs to appreciate the … mechanism of the nonlinearity and the severity of it,"); *see also id.* at Ex. 2037, Jusko Dep., 66:1-6, 83:16-84:7 (prior art's mention of dose-dependency does not indicate the type of nonlinearity).) Indeed, even in 2001—two years after the priority date of the '196 patent—Petitioners' expert opined:

"Drugs that demonstrate nonlinear pharmacokinetic behavior can prove difficult in terms of designing dosage regimens and determining correlations between drug concentrations and effects (efficacy and toxicity)." (Ex. 2010, Mager & Jusko '01 at 519, 522; *see also* Ex. 2007, Devane & Jusko '82 at 153 (urging caution in adjusting dosing regimens in drugs that exhibit non-linear kinetics because "seemingly small dosage increment changes" can have drastic effects on serum concentration).)

b. Dr. Jusko's selection of a 12-day half-life to model the claimed dose regimens is not supported by the prior art

In addition to incorrectly assuming that the half-life of trastuzumab would remain constant over a three-week interval, Dr. Jusko arbitrarily elected to use a 12-day half-life as the basis of his model. This was error. (Ex. 2039, ¶¶

The prior art reports many different half-lives for trastuzumab, all of which were calculated based on weekly dosing. (Ex. 2039, ¶¶8, 42, 51-53, 55.) Dr. Jusko's decision to select the longest report half-life has no basis in the prior art, and constitutes impermissible cherry-picking. The core assumption of Dr. Jusko's analysis is that trastuzumab's half-life remains constant regardless of the dose amount given, *i.e.*, trastuzumab has linear kinetics. (*See id.* at ¶16.) If that assumption were correct (which Patent Owner disputes), Dr. Jusko could have selected ***any*** of the several mean half-lives reported in the prior art, ranging from

1.7 to 12 days. (*Id.* at ¶44-45.) Instead, Dr. Jusko tries to have it both ways: applying an oversimplified model that assumes half-life remains constant with dose amount while, at the same time, choosing the highest half-life reported in the prior art. (Ex. 2037, Jusko Dep., 71:22-72:6; 63:10-21; 90:15-91:2.) His selection of 12 days, the most favorable to his position, is thus both arbitrary and internally inconsistent.

Dr. Jusko's only attempt at justifying his arbitrary selection of a 12-day half-life in the face of other data is found in paragraph 48 of his declaration where he states, "Because of the 12 day half-life ($t_{1/2}$) at [500 mg], a POSITA would have found it reasonable to begin by analyzing a 500 mg dose…." (Ex. 1003, ¶48; *see also* Ex. 2037, Jusko Dep., 71:22-72:6 ("I used the [half-life] most relevant for the dosage I was simulating."); 63:10-21 (rejecting use of 5.8-day half-life because it was not calculated from the dose amount Dr. Jusko was attempting to simulate); 74:18-21 ("The label states what it does. The bottom line is it gives the value at 500 milligram[s], which is the dosage that I simulated."); *see also id.*, 90:15-91:2.) But if trastuzumab had linear kinetics, which Dr. Jusko assumed, its half-life would be the same at all doses, and there would be no basis for selecting one reported half-life over another. (*See* Ex. 2039, ¶¶44-45.)

Given that Dr. Jusko's core assumption is that the half-life of trastuzumab does not vary with dose amount, Dr. Jusko has no plausible justification for

choosing the 12-day half-life associated with the 500 mg dose instead of the 1.7-day half-life associated with the 10 mg dose reported in the Label. (*Id.*) Under Dr. Jusko's assumed linear kinetics, the 1.7-day half-life would be just as viable because it was based on the same phase I studies that generated the 12-day half-life relied on by Dr. Jusko. (Ex. 1008 at 1.) Critically, a skilled artisan could not have reasonably concluded that the three-week dosing regimen described in the '196 patent claims would have been effective based on a 1.7-day half-life—particularly given that this half-life is less than ***one sixth*** of the half-life used by Dr. Jusko. (Ex. 2039, ¶44-45.)

Moreover, Dr. Jusko concedes that the 12-day half-life was chosen from a Phase I trial. (Ex. 2037, Jusko Dep., 84:21-85:4.) A skilled artisan would have known that phase I trials likely only had a few patients per dose amount and thus while useful to determine pharmacokinetic trends, such studies are less preferable than larger phase III trials which provide data that more accurately reflects an entire patient population. (*See* Ex. 2037, Jusko Dep., 78:12-14 ("[T]he more patients who are studied, the more confidence that would be gained."); *id.* at 78:21-79:8; *see also* Ex. 2038 at 82:1-6; 87:18-88:11; Ex. 2040, ¶¶17, 75.) The need for robust data is particularly acute in the case of trastuzumab where the prior art taught that interpatient variability associated with the presence of shed antigen has severe pharmacokinetic and clinical consequences such as reduced half-life, lower

trough concentration, and absence of clinical response. (*See id.*; Ex. 1008 at 1; Ex. 1013 at 14; Ex. 1014 at 14.)

The dangers of interpatient variability—and the risk of skewed or poor data from small patient populations—is underscored by the wide variety of half-lives reported in the prior art. (*See* Ex. 2039, ¶73.) The Label reports a half-life of 5.8 days for the FDA-approved weekly regiment with a range of 1 to 32 days. (Ex. 1008 at 1.) Baselga '96 reported that the mean serum half-life was 8.3 ± 5.0 days for all 45 patients from which pharmacokinetic information was available. (Ex. 1013, at 11, Table 2.) Pegram '98 reports half-lives of 9.2 ± 5.3 days and 2.9 ± 3.2 days when trastuzumab was administered alone weekly and 11.0 ± 4.4 days and 4.0 ± 2.6 days when trastuzumab was administered together with chemotherapy. (Ex. 1014 at 14.)

Dr. Jusko's arbitrary selection of the data points that are convenient to his analysis—while ignoring others that do not fall within his current understanding of trastuzumab's kinetics—is classic hindsight bias. An obviousness analysis that recreates the steps of the invention through hindsight and ignores the complexities of the prior art when inconvenient for the analysis must be rejected. *See Endo Pharm. Inc. v. Depomed, Inc.*, IPR2014-00654, Paper 69 at 26-27 (Sept. 21, 2015) (finding that Petitioner's obviousness challenge to a dosage form patent reflected impermissible hindsight by picking and choosing certain preferred attributes of the

various references and combining them to yield the claimed invention); *see also Ortho-McNeil Pharm.*., 520 F.3d at 1364 (Fed. Cir. 2008) (An analysis that "simply retrace[s] the path of the inventor with hindsight [and] discount[s] the number and complexity of the alternatives … is always inappropriate for an obviousness test based on the language of Title 35 that requires the analysis to examine 'the subject matter as a whole' to ascertain if it '*would have been obvious at the time the invention was made*.'" (quoting 35 U.S.C. § 103(a) (emphasis in original).)

c. There is insufficient data in the prior art to accurately predict whether a three-week dosing regimen would be clinically effective

Although the prior art disclosed that trastuzumab had dose-dependent kinetics, it did not provide enough information from which a skilled artisan could reliably predict whether a three-week dosing regimen would have been effective. (Ex. 2039, ¶43, 56-60; *id.* at ¶¶23, 48-55, 17-27.) Indeed, Dr. Jusko conceded that there was insufficient data in the prior art to apply a non-linear model for trastuzumab. (Ex. 2037, Jusko Dep., 124:20-125:4 ("Applying a linear model was … the only way possible…. There was no indication of information where one could apply any alternative for my purposes."); *see also id.* at 29:15-19 ("I used … the best information available.").) Moreover, while he conceded that a skilled artisan "needs to appreciate the … mechanism of the nonlinearity and severity of

it" in the context of designing a dosing regimen (Ex. 2037, Jusko Dep., 104:6-16), he admitted that Baselga '96 and the Label's reference to dose-dependency was insufficient to make such a determination. (*Id.* at 66:1-6; 83:16-20.) Here, the only available data in the prior art was isolated, aggregated serum concentration data from weekly administration of different dose amounts. (Ex. 2039, ¶¶56-64, 66; *id.* at ¶¶49-53, 55.) A skilled artisan could not have reliably predicted the results of an alternative dosing regimen based on this data. (*Id.* at ¶¶65-76.)

The lack of sufficient information in the prior art to reliably predict alternative dosing regimens is not a valid reason to apply an oversimplified analysis. (*Id.* at ¶¶66.) A skilled artisan would have known that without the appropriate data, applying linear pharmacokinetics to predict a three-week dosing regimen for trastuzumab could have overestimated the predicted serum trough concentration or could have had other unintended consequences. (*Id.* at ¶¶40-47, 37-39; *see also id.* at ¶¶34-36.)

2. A clinical oncologist would not have used three-week dosing based on Dr. Jusko's pharmacokinetic analysis

Given the flaws in Dr. Jusko's analysis, a clinical oncologist would not have had a reasonable expectation of success that three-week dosing as claimed in the '196 patent would have been clinically effective. (Ex. 2040, ¶8, 65; *cf.* Ex. 1003, ¶¶56, 67.) Under Petitioners' obviousness theory, a clinical oncologist would

make the ultimate decision as to whether to the claims of the '196 patent are obvious based on the opinion of Dr. Jusko that a three-week regimen would be effective. (*See, e.g.*, Ex. 1002, ¶ 50; Ex. 1003, ¶¶43, 67, 11, 13; Ex. 2037, Jusko Dep., at 23:12-24:15.) But that does not mean that a clinical oncologist would unquestioningly adopt the analysis of a pharmacokineticist and abdicate all responsibility in making a decision as to dose interval. (Ex. 2040, ¶¶11, 59-61.) That is precisely what Dr. Lipton has done here. (*See, e.g.*, Ex. 2038 at 86:1-20 ("I'm depending on [Dr. Jusko] to make the pharmacokinetic dose interval decisions."); *id.* at 177:17-178:15.)

A clinical oncologist would not risk the lives of her patients by administering an alternative dosing regimen based on a pharmacokinetic analysis that ignores—without explanation—core teachings in the prior art. (Ex. 2040, ¶¶8, 58-65.)

C. Foreign Proceedings Are Not Relevant

As Petitioners note (Paper 1 at 20-23), the European counterpart to the '196 patent was found obvious in the United Kingdom and invalid for lack of sufficiency before the European Patent Office. However, those foreign proceedings have little relevance here. *See Smith & Nephew v. ConvaTec Techs. Inc*., IPR2013-00097, Paper 76 at 3 (Feb. 24, 2014) (European Patent Office decision "does not involve the U.S. patents at issue in these proceedings, is not

based on U.S. law, and is thus of limited relevance to the instant proceedings"); *see also Medtronic, Inc. v. Daig Corp.*, 789 F.2d 903, 907-08 (Fed. Cir. 1986) (rejecting challenger's position that the court should adopt a decision regarding the validity of a foreign counterpart patent as "specious").

D. These Proceedings are Unconstitutional

The Board should terminate this proceeding because it violates Patent Owner's constitutional rights. Because patents are private property rights and disputes concerning their validity were traditionally decided by courts, patent validity must be litigated in an Article III court, not before an executive branch agency. *McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 609 (1898). Adversarial challenges to an issued patent—like *inter partes reviews*—are also "Suits at common law" for which the Seventh Amendment guarantees a jury trial. U.S. Const. amend. VII; *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 377 (1996). Even if *inter partes* review is constitutional in other circumstances, it is unconstitutional for patents—like the '196 patent—that issued before passage of the America Invents Act.

The Supreme Court has granted certiorari in *Oil States Energy Services, LLC v. Greene's Energy Group*, LLC, No. 16-712, to consider the constitutionality of inter partes reviews. Patent Owner presents this constitutional challenge now to preserve the issue pending the Supreme Court's decision.

VI. CONCLUSION

For the reasons set forth above, Patent Owner asks that the Board confirm the patentability of the challenged claims 1–3, 5, 7, 9–11, and 17–33 of the '196 patent.

Respectfully submitted,

Date: December 22, 2017

/David L. Cavanaugh/
David L. Cavanaugh
Registration No. 36,476

Robert J. Gunther, Jr.
Pro Hac Vice

Counsel for Patent Owner

WILMER CUTLER PICKERING HALE AND DORR LLP
1875 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20006
TEL: 202-663-6000
FAX: 202-663-6363
EMAIL: david.cavanaugh@wilmerhale.com

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Response, contains 13,022 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

Respectfully submitted,

Dated: December 22, 2017

/David L. Cavanaugh/
David L. Cavanaugh
Registration No. 36,476

CERTIFICATE OF SERVICE

I hereby certify that, on December 22, 2017, I caused a true and correct copy of the following materials:

- Patent Owner's Response
- Patent Owner's Exhibit List
- Exhibits 2017-2019, 2021-2052, 2054-2071, 2073, 2075-2079

to be served electronically via File Transfer Protocol (FTP), as previously agreed by the parties, on the following attorneys of record:

Amanda Hollis
KIRKLAND & ELLIS LLP
amanda.hollis@kirkland.com
300 North LaSalle, Chicago, IL 60654

Stefan M. Miller, Ph.D.
stefan.miller@kirkland.com
601 Lexington Avenue, New York, NY 10022

Karen Younkins
karen.younkins@kirkland.com
333 South Hope Street, Los Angeles, CA 90071

Benjamin A. Lasky
benjamin.lasky@kirkland.com
601 Lexington Avenue, New York, NY 10022

Sarah K. Tsou
sarah.tsou@kirkland.com
601 Lexington Avenue, New York, NY 10022

Mark C. McLennan
mark.mclennan@kirkland.com

601 Lexington Avenue, New York, NY 10022

Christopher J. Citro
christopher.citro@kirkland.com
601 Lexington Avenue, New York, NY 10022

Pfizer_Genentech_IPRs@kirkland.com

Dimitrios T. Drivas
White & Case LLP
ddrivas@whitecase.com
1221 Avenues of the Americas, New York, NY 10020

Scott T. Weingaertner
White & Case LLP
scott.weingaertner@whitecase.com
1221 Avenues of the Americas, New York, NY 10020

/Rebecca A. Whitfield/
Rebecca A. Whitfield
Reg. No. 73,756
Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109

PATENT OWNER'S EXHIBIT LIST
IPR2017-00804

Patent Owner's Exhibit Number	Exhibit Name
2001	Marvin M. Goldenberg, *Trastuzumab, a Recombinant DNA-Derived Humanized Monoclonal Antibody, a Novel Agent for the Treatment of Metastatic Breast Cancer*, 21 CLINICAL THERAPEUTICS 309 (1999)
2002	Gert Riethmüller & Judith P. Johnson, *Monoclonal Antibodies in the Detection and Therapy of Micrometastatic Epithelial Cancers*, 4 CURRENT OPINION IN IMMUNOLOGY 647 (1992)
2003	Janice M. Reichert, *Probabilities of Success for Antibody Therapeutics*, 1 MABS 387 (2009)
2004	Arturo Casadevall, *Passive Antibody Therapies: Progress and Continuing Challenges*, 93 CLINICAL IMMUNOLOGY 5 (1999)
2005	Dennis Mungall & William Docktor, *Pharmacokinetics: An Introduction*, *in* APPLIED CLINICAL PHARMACOKINETICS 1 (Dennis R. Mungall ed., 1983)
2006	Sarfaraz Niazi, *Chapter 7: Pharmacokinetic Principles*, *in* TEXTBOOK OF BIOPHARMACEUTICS AND CLINICAL PHARMACOKINETICS 141 (1979)
2007	C. Lindsay DeVane & William J. Jusko, *Dosage Regimen Design*, 17 PHARMACOLOGY & THERAPEUTICS 143 (1982)
2008	Johan Gabrielsson & Daniel Weiner, *Chapter 3: Pharmacokinetic Concepts*, *in* PHARMACOKINETIC AND PHARMACODYNAMIC DATA ANALYSIS 58 (2d ed. 1997)
2009	Sukyung Woo & William J. Jusko, *Interspecies Comparisons of Pharmacokinetics and Pharmacodynamics of Recombinant Human Erythropoietin*, 35 DRUG METABOLISM & DISPOSITION 1672 (2007)
2010	Donald E. Mager & William J. Jusko, *General Pharmacokinetic Model for Drugs Exhibiting Target-Mediated Drug Disposition*, 28 J. PHARMACOKINETICS & PHARMACODYNAMICS 507 (2001)

Patent Owner's Exhibit Number	**Exhibit Name**
2011	William J. Jusko, *Guidelines for Collection and Pharmacokinetic Analysis of Drug Disposition Data*, *in* APPLIED PHARMACOKINETICS 639 (William E. Evans, Jerome J. Schentag, & William J. Jusko eds., 1980)
2012	Declaration of Robert J. Gunther, Jr. in Support of Motion for *Pro Hac Vice*
2013	Declaration of Daralyn J. Durie in Support of Motion for *Pro Hac Vice*
2014	Declaration of Lisa J. Pirozzolo in Support of Motion for *Pro Hac Vice*
2015	Declaration of Kevin S. Prussia in Support of Motion for *Pro Hac Vice*
2016	Declaration of Andrew J. Danford in Support of Motion for *Pro Hac Vice*
2017	Expert Report of William J. Jusko, PhD, In re Ortho Evra® Prods. Liability Litig., No. 1:06-cv-40000 (N.D. Ohio Mar. 31, 2008), ECF No. 241
2018	William J. Jusko, *Guidelines for Collection and Analysis of Pharmacokinetic Data*, *in* APPLIED PHARMACOKINETICS – PRINCIPLES OF THERAPEUTIC DRUG MONITORING 2-1 (William E. Evans et al. eds., 3d ed. 1992)
2019	Yanguang Cao & William J. Jusko, *Incorporating Target-mediated Drug Disposition in a Minimal Physiologically-based Pharmacokinetic Model for Monoclonal Antibodies*, 41 J. PHARMACOKINETICS & PHARMACODYNAMICS 375 (2014)
2020	RESERVED
2021	Patent Owner's Second Amended Notices of Deposition of Allan Lipton, M.D. in IPR2017-00804 and IPR2017-00805
2022	Walter P. Carney et al., *Potential Clinical Utility of Serum HER-2/*neu *Oncoprotein Concentrations in Patients with Breast Cancer*, 49 CLINICAL CHEMISTRY 1579 (2003)
2023	Andrew D. Seidman et al., *Dose-Dense Therapy with Weekly 1-Hour Paclitaxel Infusions in the Treatment of Metastatic Breast Cancer*, 16 J. CLINICAL ONCOLOGY 3353 (1998)

Patent Owner's Exhibit Number	**Exhibit Name**
2024	C Sola et al., *Phase II Study of Weekly Paclitaxel (P) Treatment in Recurrent Breast Cancer After High-Dose Chemotherapy (HDC)*, 18 PROC. AM. SOC'Y CLINICAL ONCOLOGY 65a (Abstract 245) (1999)
2025	S. Breier et al., *Long-Term Weekly Paclitaxel (P) in Metastatic Breast Cancer (MBC): A Phase II Trial in Pretreated Patients (PTS)*, 17 PROC. AM. SOC'Y CLINICAL ONCOLOGY 192a (Abstract 740) (1998)
2026	W. Sikov et al., *Weekly High-Dose Paclitaxel Demonstrates Significant Activity in Advanced Breast Cancer (BC)*, 17 PROC. AM. SOC'Y CLINICAL ONCOLOGY 112a (Abstract 432) (1998)
2027	Andrew D. Seidman et al., *Randomized Phase III Trial of Weekly Compared With Every-3-Weeks Paclitaxel for Metastatic Breast Cancer, With Trastuzumab for All HER-2 Overexpressors and Random Assignment to Trastuzumab or Not in HER-2 Nonoverexpressors: Final Results of Cancer and Leukemia Group B Protocol 9840*, 26 J. CLINICAL ONCOLOGY 1642 (2008)
2028	José Baselga, *Current and Planned Clinical Trials With Trastuzumab (Herceptin)*, 27 (SUPPL. 9) SEMIN. ONCOLOGY 27 (2000)
2029	M Fornier, *Weekly (W) Herceptin (H) + 1 Hour Taxol (T): Phase II Study in HER2 Overexpressing (H2+) and Non-Overexpressing (H2-) Metastatic Breast Cancer (MBC)*, 18 PROC. AM. SOC'Y CLINICAL ONCOLOGY 126a (Abstract 482) (1999)
2030	Edith A. Perez, *Paclitaxel in Breast Cancer*, 3 THE ONCOLOGIST 373 (1998)
2031	E.A. Perez et al., *A Large Phase II Trial of Paclitaxel Administered as a Weekly One Hour Infusion in Patients with Metastatic Breast Cancer*, 18 PROC. AM. SOC'Y CLINICAL ONCOLOGY 126a (Abstract 480) (1999)
2032	Edith A. Perez et al., *Multicenter Phase II Trial of Weekly Paclitaxel in Women With Metastatic Breast Cancer*, 19 J. CLINICAL ONCOLOGY 4216 (2001)

Patent Owner's Exhibit Number	**Exhibit Name**
2033	Neal E. Ready et al., *Phase I Study of the Farnesyltransferase Inhibitor Lonafarnib with Weekly Paclitaxel in Patients with Solid Tumors*, 13 CLINICAL CANCER RES. 576 (2007)
2034	Giuseppe Frasci et al., *Weekly Paclitaxel-Cisplatin Administration with G-CSF Support in Advanced Breast Cancer: A Phase II Study*, 49 BREAST CANCER RES. & TREATMENT 13 (1998)
2035	PierFranco Conte & Valentina Guarneri, *Safety of Intravenous and Oral Bisphosphonates and Compliance with Dosing Regimens*, 9 (Suppl. 4) THE ONCOLOGIST 28 (2004)
2036	David Osoba & Michael Burchmore, *Health-Related Quality of Life in Women with Metastatic Breast Cancer Treated with Trastuzumab (Herceptin)*, 26 SEMIN. ONCOLOGY 84 (1999)
2037	Transcript of Deposition of William Jusko, Ph.D. taken Sept. 27, 2017 in IPR2017-00804 and IPR2017-00805
2038	Transcript of Deposition of Allan Lipton, M.D. taken Dec. 15, 2017 in IPR2017-00804 and IPR2017-00805
2039	Declaration of Dr. George Grass
2040	Declaration of Dr. Karen Gelmon
2041	Michael S. Kopreski et al., *Growth Inhibition of Breast Cancer Cell Lines by Combinations of Anti-P185^{HER2} Monoclonal Antibody and Cytokines*, 16 ANTICANCER RES. 433 (1996)
2042	Steven Lehrer et al., *Tumour HER2 Protein in Breast Cancer and Family History*, 341 THE LANCET 1420 (1993)
2043	Dennis J. Slamon, *Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu *Oncogene*, 235 SCIENCE 177 (1987)
2044	David Holzman, *Gene Therapy for HER-2-Related Cancer*, 2(4) MOLECULAR MED. TODAY 138 (1996)
2045	Russ Hoyle, *Genentech Is Poised for an Anti-cancer Breakthrough*, 16 NATURE BIOTECHNOLOGY 887 (1998)
2046	Steven Shak, *Overview of the Trastuzumab (Herceptin) Anti-HER2 Monoclonal Antibody Clinical Program in HER2-Overexpressing Metastatic Breast Cancer*, 26 (Suppl. 12) SEMIN. ONCOLOGY 71 (1999)

Patent Owner's Exhibit Number	**Exhibit Name**
2047	Cynthia Campbell-Baird et al., *Incidence of Acute Phase Adverse Events Following Denosumab or Intravenous Bisphosphonates: Results from a Randomized, Controlled Phase II Study in Patients with Breast Cancer and Bone Metastases*, 7 COMMUNITY ONCOLOGY 85 (2010)
2048	AM Alvarez et al., *Reinduction of Response with Weekly Taxol(T) in Advanced Breast Cancer (ABC)*, 18 PROC. AM. SOC'Y CLINICAL ONCOLOGY 165a (Abstract 636) (1999)
2049	E. Mickiewicz et al., *A Promising Second Line Treatment with Weekly Taxol (T) in Anthracycline Recurrent, Advanced Breast Cancer (ABC) Patients (PTS)*, 18 PROC. AM. SOC'Y CLINICAL ONCOLOGY 135a (Abstract 515) (1999)
2050	Andrew D. Seidman, *One-Hour Paclitaxel Via Weekly Infusion: Dose-Density with Enhanced Therapeutic Index*, 12 (SUPPL. 1) ONCOLOGY 19 (1998)
2051	Antonius A. Miller, Mark J. Ratain, & Richard L. Schilsky, *Principles of Pharmacology*, *in* THE CHEMOTHERAPY SOURCE BOOK 27 (Michael C. Perry ed., 2d ed. 1996)
2052	Anthe S. Zandvliet et al., *Saturable Binding of Indisulam to Plasma Proteins and Distribution to Human Erythrocytes*, 34 DRUG METABOLISM & DISPOSITION 1041 (2006)
2053	RESERVED
2054	Dennis J. Slamon, *Studies of the HER-2/*neu *Proto-oncogene in Human Breast and Ovarian Cancer*, 244 SCIENCE 707 (1989)
2055	Robert M. Hudziak et al., *p185*^{HER2} *Monoclonal Antibody Has Antiproliferative Effects In Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor*, 9 MOLECULAR & CELLULAR BIOLOGY 1165 (1989)
2056	Richard P. Junghans et al., *Antibody-Based Immunotherapies for Cancer*, *in* CANCER CHEMOTHERAPY & BIOTHERAPY: PRINCIPLES AND PRACTICE 655 (1996)
2057	Paul Carter et al., *Humanization of an Anti-p185*^{HER2} *Antibody for Human Cancer Therapy*, 89 PROC. NAT'L ACAD. SCI. 4285 (1992)

Patent Owner's Exhibit Number	Exhibit Name
2058	Melody A. Cobleigh et al., *Multinational Study of the Efficacy and Safety of Humanized Anti-HER2 Monoclonal Antibody in Women Who Have HER2-Overexpressing Metastatic Breast Cancer That Has Progressed After Chemotherapy for Metastatic Disease*, 17 J. CLINICAL ONCOLOGY 2639 (1999)
2059	Dennis J. Slamon et al., *Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer That Overexpresses HER2*, 344 NEW ENG. J. MED. 783 (2001)
2060	Walter M. Stadler & Mark J. Ratain, *Development of Target-based Antineoplastic Agents*, 18 INVESTIGATIONAL NEW DRUGS 7 (2000)
2061	Robert B. Livingston, *Dose Intensity & High Dose Therapy*, 74 CANCER SUPPL. 1177 (1994)
2062	Gabriel N. Hortobagyi, Mien-Chie Hung, & Aman U. Buzdar, *Recent Developments in Breast Cancer Therapy*, 26 (SUPPL. 12) SEMIN. ONCOLOGY 11 (1999)
2063	McGuire, William P., *High-Dose Chemotherapy and Autologous Bone Marrow or Stem Cell Reconstitution for Solid Tumors*, CURRENT PROBS. IN CANCER, May/June 1998, at 138
2064	William P. Peters et al., *High-Dose Chemotherapy and Autologous Bone Marrow Support as Consolidation After Standard-Dose Adjuvant Therapy for High-Risk Primary Breast Cancer*, 11 J. CLINICAL ONCOLOGY 1132 (1993)
2065	Larry Norton, *Evolving Concepts in the Systemic Drug Therapy of Breast Cancer*, 24 (SUPPL. 10) SEMIN. ONCOLOGY S10-3 (1997)
2066	John Crown et al., *High-Intensity Chemotherapy with Hematopoietic Support In Breast Cancer*, 698 ANNALS N.Y. ACAD. SCI. 378 (1993)
2067	Charles L. Vogel & Jean-Marc Nabholtz, *Monotherapy of Metastatic Breast Cancer: A Review of Newer Agents*, 4 THE ONCOLOGIST 17 (1999)
2068	H.A. Burris et al., *Phase II Trial of Docetaxel and Herceptin (R) as First- or Second-Line Chemotherapy for Women with Metastatic Breast Cancer Whose Tumours Overexpress HER2*, 35 (SUPPL. 4) EUR. J. CANCER S322 (Abstract 1293) (1999)

Patent Owner's Exhibit Number	**Exhibit Name**
2069	Wallace Akerley et al., *Weekly Paclitaxel in Patients with Advanced Lung Cancer: Preliminary Data from a Phase II Trial*, 24 (SUPPL. 12) SEMIN. ONCOLOGY S12-10 (1997)
2070	Hak Choy et al., *Multiinstitutional Phase II Trial of Paclitaxel, Carboplatin, and Concurrent Radiation Therapy for Locally Advanced Non-Small-Cell Lung Cancer*, 16 J. CLINICAL ONCOLOGY 3316 (1998)
2071	Hak Choy et al., Phase II Trial of Weekly Paclitaxel and Concurrent Radiation Therapy for Locally Advanced Non-Small Cell Lung Cancer, 4 Clinical Cancer Res. 1931 (1998)
2072	RESERVED
2073	David Spiegel, *Psychosocial Aspects of Breast Cancer Treatment*, 24 (SUPPL. 1) SEMIN. ONCOLOGY S1-S36 (1997)
2074	RESERVED
2075	CTR. FOR DRUGS & BIOLOGICS, FOOD & DRUG ADMIN., GUIDELINE FOR THE FORMAT AND CONTENT OF THE HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION OF AN APPLICATION, FDA GUIDANCE (1987) 18 pages
2076	FDA Approved Label for Ativan® (lorazepam) (Mar. 2007) 8 pages
2077	David J. Greenblatt et al., *Pharmacokinetics and Bioavailability of Intravenous, Intramuscular, and Oral Lorazepam in Humans*, 68 J. PHARMACEUTICAL SCIS. 57 (1979)
2078	FDA Approved Label for Onfi® (clobazam) (Oct. 2011) 28 pages
2079	S. Jawad & A. Richens, *Single Dose Pharmacokinetic Study of Clobazam in Normal Volunteers and Epileptic Patients*, 18 BRIT. J. CLINICAL PHARMACOLOGY 873 (1984)