Filed on behalf of Patent Owner Genentech, Inc. by

David L. Cavanaugh (Reg. No. 36,476)
Owen K. Allen (Reg. No. 71,118)
Robert J. Gunther, Jr. (*Pro Hac Vice to be filed)*
Lisa J. Pirozzolo (*Pro Hac Vice to be filed*)
Kevin S. Prussia (*Pro Hac Vice to be filed*)
Andrew J. Danford (*Pro Hac Vice to be filed*)
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 to be filed*)
DURIE TANGRI LLP
217 Leidesdorff Street
San Francisco, CA 94111

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01140
U.S. Patent 7,371,379

PATENT OWNER'S PRELIMINARY RESPONSE

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I. INTRODUCTION

Herceptin® dramatically improved the prognosis for patients with HER2-positive breast cancer, a particularly aggressive form of cancer that afflicts tens of thousands of women in the U.S. each year. One of the first monoclonal antibodies shown to treat cancer, Herceptin® was approved by the Food and Drug Administration in September 1998 following extensive clinical trials. Based on the data from these clinical trials, some of which is reported in the prior art references cited by Petitioner, Genentech scientists and other skilled artisans focused on a weekly dosing regimen—a "loading dose" of 4 mg/kg of trastuzumab[1] followed by weekly "maintenance doses" of 2 mg/kg. The invention claimed in U.S. Patent No. 7,371,379 ("the '379 patent"), which is based on knowledge and information obtained as a result of Phase III clinical trials with the weekly regimen, is a different, extended-interval dosing regimen, pursuant to which anti-ErbB2 antibodies such as trastuzumab can be administered as infrequently as every three weeks without compromising efficacy.

Petitioner now asserts that the extended-interval dosing schedule was nothing more than an "obvious variation" of the weekly regimen. But Petitioner's

[1] Trastuzumab is the antibody molecule in Herceptin®. Trastuzumab is also known as "rhuMAb HER2" or "rhuMAb4D5-8."

obviousness claim is not supported by the prior art. Not one of Petitioner's references suggests a dosing interval longer than a week. To the contrary, all the cited prior art focuses on weekly dosing. Accordingly, Petitioner has not established that the prior art teaches or suggests the limitations of the challenged claims. Moreover, as demonstrated by the cited prior art references, Petitioner has failed to establish the requisite motivation to pursue an extended dosing interval, let alone a reasonable expectation of success.

First, all four of the prior art references upon which Petitioner relies—the Watanabe Abstract (Ex. 1006), the Slamon Abstract (Ex. 1005), Baselga '96 (Ex. 1007), and Pegram '98 (Ex. 1009)—describe and recommend ***weekly dosing*** of trastuzumab. Although Petitioner makes much of the statement in the Watanabe Abstract that the second dose in the reported Phase I study was given three weeks after the first dose, Petitioner ignores the fact that each of the subsequent nine dosing intervals was weekly. Moreover, the Abstract concludes with the recommendation that a ***weekly*** regimen should be further studied. Accordingly, Petitioner has not established that the prior art including the Watanabe Abstract teaches or suggests the claimed dosing regimens.

Second, Petitioner has failed to establish any motivation to modify the prior art to achieve the claimed dosing regimens. For example, the prior art does not articulate (or even hint at) an alleged desire for convenience. To the contrary, the

prior art references focus on effectively treating a deadly cancer in patients for whom there had previously been little hope. A vague and conclusory sentence about convenience in Petitioner's expert declaration, with no basis in the prior art, is insufficient to support Petitioner's obviousness claim. *See, e.g.*, *Novartis Pharm. Corp. v. Breckenridge Pharm., Inc.*, --- F. Supp. 3d ----, No. 1:14-CV-1043-RGA, 2017 WL 1278672, at *10 (D. Del. Apr. 3, 2017) (rejecting the argument that "patient compliance" would be sufficient motivation for a physician to co-administer two drugs in the absence of evidence that co-administration would be safe).

Third, Petitioner fails to identify any reasonable expectation of success in achieving the claimed dosing regimens based on the prior art. Petitioner's assertions based on the alleged predictability of the pharmacokinetics of trastuzumab are unfounded. In August 1999, the pharmacokinetics of antibodies in general, and anti-ErbB2 antibodies in particular, were known to be unpredictable. Notably, the prior art explicitly taught that trastuzumab is "dose dependent." This means that the rate at which the drug is cleared from the body depends on its concentration in the body, a phenomenon also described as "non-linear kinetics." As Petitioner's expert has acknowledged outside of these proceedings, drugs with non-linear kinetics are more unpredictable than drugs with linear kinetics. (Ex. 2001 at 130.) This is because a drug with non-linear kinetics has pharmacokinetic

parameters that vary depending on the concentration of the drug in the bloodstream. (*See infra* pp. 11-13.) Indeed, Petitioner's expert has warned that in contrast to drugs with linear pharmacokinetics, alteration of the schedule of drugs that display non-linear kinetics may unpredictably alter clinical effects. (Ex. 1025 at 15.) Petitioner's assertion that the pharmacokinetics were predictable beyond known dose amounts and dosing intervals stands in direct contradiction with the prior teachings of its expert and cannot support any reasonable expectation of success in dosing trastuzumab as claimed.

Finally, the Petition repeats arguments that were made and overcome during prosecution of the '379 patent and its parent, U.S. Patent No. 6,627,196 ("the '196 patent"). Although Petitioner purports to anchor its arguments in a "new" reference—the Slamon Abstract—the very same Phase III results discussed therein were before the Examiner during prosecution of the '379 patent's parent in the Goldenberg '99 reference, which expressly cites to the Slamon Abstract. (*See infra* pp. 20-21.) Indeed, in allowing the '196 patent claims to issue, the Examiner concluded that much of the same prior art as that advanced in the Petition, including the Watanabe Abstract and Baselga '96, "fails to teach or fairly suggest the recited minimum dosages and dosing schedules where the subsequent doses are separated from each other by at least 2 weeks." (Ex. 1011 at 246.) The Examiner also considered and rejected the argument that a skilled artisan would have been

motivated to dose trastuzumab over the same three-week schedule as chemotherapy. The Examiner of the '379 patent—the same examiner who concluded that the '196 patent claims were allowable—reviewed these same references and chose not to reject claims directed to two- or three-week dosing intervals of trastuzumab. Because the Examiner already twice considered substantially the same prior art, the Board should exercise its discretion under Section 325(d) and deny the Petition.

In sum, Petitioner has failed to establish that the claimed dosing intervals of at least two and three weeks are disclosed in the cited prior art, let alone that the prior art provides any motivation to pursue the claimed dosing regimens or reasonable expectation of success in doing so. If it did, the skilled clinicians pursuing the studies upon which Petitioner relies would not have focused exclusively on the weekly dosing interval that was first approved. Indeed, this is not a case where the Board needs to hypothesize as to what a person of ordinary skill in the art might have done in devising a dosing regimen for trastuzumab based on the information disclosed in Petitioner's references. We already know. Faced with the same information upon which Petitioner relies, the authors of the prior art references recommended and pursued ***weekly*** dosing of Herceptin®. If three-week dosing were as obvious as Petitioner claims, that regimen would have been pursued earlier. That skilled artisans did not do so, when under Petitioner's rationale the

more convenient regimen was supposedly obvious, underscores the nonobviousness of the invention claimed in the '379 patent.

The conclusory opinion of Petitioner's expert that the invention was an obvious variation of weekly dosing lacks any basis in the prior art and reflects the impermissible use of hindsight to arrive at the teachings set forth in the '379 patent. The Examiner found that the prior art on which Petitioner relies did not render the two- or three-week interval claims in the '196 patent obvious, and did not revisit those arguments again in the subsequent prosecution of the '379 patent. Petitioner has not presented any evidence to suggest that the Examiner's conclusion regarding patentability was wrong and therefore its Petition should be denied.

II. TECHNOLOGY BACKGROUND

A. Herceptin® Was The First FDA-Approved Antibody For Treatment Of Breast Cancer And Solid Tumors.

Certain types of breast cancers are caused by overexpression of human epidermal growth factor receptor 2 (HER2 or ErbB2). (Ex. 1013 at 2-3.) The humanized monoclonal antibodies claimed in the '379 patent are large, complex molecules that bind to HER2 receptors on the surface of breast cancer tumor cells. (*Id.* at 3.) Although trastuzumab's mechanisms of action are still being researched today, it was understood in August 1999 that the binding of trastuzumab to HER2 receptors inhibits tumor cell proliferation and induces a process known as

antibody-dependent cellular cytotoxicity, during which trastuzumab flags HER2 overexpressing tumor cells for destruction by the body's immune system. (*See, e.g.*, Ex. 1001, 35:63-36:10; Ex. 1008 at 1.)

At the time of the invention, the use of antibodies to treat cancer was relatively new. 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 gastrointestinal tumors; breast, colon, ovarian, and lung cancer; pancreatic adenocarcinoma; neuroblastoma; and melanoma).) As one reviewer observed, "antibody therapy of cancer has become a story of unending failures." (Ex. 2009 at 732.) Indeed, prior to August 1999, the FDA had approved only one other monoclonal antibody for use in treating cancer—Genentech's rituximab product, which was approved for the treatment of non-Hodgkin's lymphoma in 1997. (Ex. 2003 at 388.) Trastuzumab was the first antibody approved to target solid tumors and the first approved to treat breast cancer. (*Id.*)

B. Designing Dosing Regimens For Anti-ErbB2 Antibodies Was No Simple Task.

Developing dosing regimens for therapeutic antibodies like trastuzumab remains a complex undertaking today, and was even more difficult and unpredictable in August 1999. As one author explained, "Unfortunately, the

selection of antibody dose for clinical use is a ***complicated task*** that is dependent on the type of antibody preparation, the amount of antigen present, the pharmacokinetics of the antibody, and the intended use." (Ex. 2004 at 11 (emphasis added).)[2] Accordingly, a skilled person would have considered many factors, including pharmacokinetics, when designing an alternative dosing regimen for trastuzumab.

1. Therapeutic trough concentrations of the antibody must be maintained throughout treatment to treat cancer effectively.

A dosing regimen should result in drug levels that are both safe and effective, *i.e.*, that fall within the drug's therapeutic window. The boundaries of the therapeutic window are often defined with reference to the concentration of the drug in the bloodstream, also referred to as "serum concentration." (*See, e.g.*, Ex. 1003, Ratain Decl. ¶¶48, 58; Ex. 2005 at 171.) "Peak serum concentration" refers to the highest concentration, which typically occurs immediately after the drug is administered; "trough serum concentration" refers to the lowest concentration,

[2] Although Casadevall was published in October 1999, the state of the art was no less complicated two months earlier in August 1999.

which typically occurs before the next dose is administered.[3] (*See, e.g.*, Ex. 1001, 18:27-37.) In designing a dosing regimen, the skilled artisan typically seeks to avoid causing serum concentration levels to climb above a certain peak, at which toxicity can occur, or to fall below a certain trough, at which efficacy is no longer maintained. (*See* Ex. 1003, Ratain Decl. ¶58; Ex. 2005 at 171.)

With respect to anti-ErbB2 antibodies, the prior art teaches that maintaining certain trough serum concentration levels is associated with efficacy in treating cancer. Based on preclinical models, early studies evaluating the clinical efficacy of trastuzumab targeted maintaining a trough concentration of greater than 10-20 µg/mL. (*See, e.g.*, Ex. 1007 at 4 (targeting 10 µg/mL based on preclinical models); Ex. 1006 at 5 (same); Ex. 1009 at 3 (targeting 10-20 µg/mL based on

[3] As defined in the '379 patent, "'peak serum concentration' refers to the maximal serum drug concentration shortly after delivery of the drug into the animal or human patient, after the drug has been distributed through the blood system, but before significant tissue distribution, metabolism or excretion of drug by the body has occurred." (Ex. 1001, 18:27-32.) The term "'trough serum concentration' refers to the serum drug concentration at a time after delivery of a previous dose and immediately prior to delivery of the next subsequent dose of drug in a series of doses." (*Id.* at 18:33-37.)

preclinical models).) For example, one preclinical model showed reduced cell proliferation in HER2-overexpressing cells that were suspended in 1 mL of solution and incubated with 10 µg trastuzumab. (*See, e.g.*, Ex. 1013 at 3-4 (summarizing preclinical studies).) Based on these *in vitro* studies, early clinical trials focused on maintaining patient serum trough concentrations above the 10 µg/mL target. For example, Baselga '96 reports that more than 90% of patients receiving trastuzumab achieved trough serum concentrations over 10 µg/mL and notes that those individuals with subtherapeutic serum levels failed to achieve an anticancer response. (Ex. 1007 at 5, 7-8.)

The average trough concentration across all patients receiving trastuzumab in these prior art clinical studies was significantly higher than the 10-20 µg/mL preclinical target. For example, the regimen administered in Baselga '96 resulted in a mean maximum trough concentration of 54 µg/mL. (Ex. 1009 at 8, Table 6.) Similarly, the 1998 Herceptin® Label reports that the approved weekly dosing regimen resulted in mean trough serum concentration levels of approximately 79 µg/mL. (Ex. 1008 at 1.) A skilled person would thus have understood that maintaining therapeutic trough concentration levels for as many patients as possible was important to achieve efficacy.

2. Drugs with non-linear kinetics like trastuzumab were known to be unpredictable.

As discussed above, one of ordinary skill in the art would have recognized that keeping serum trough concentrations above a certain level is necessary to maintain the efficacy of a drug. To determine whether a particular dosing regimen will sustain therapeutic trough concentrations, a pharmacokineticist must understand how quickly the drug is eliminated from the body after administration. The elimination rate directly impacts serum concentrations over time and can be used to determine how changes in dose amount or interval are likely to impact serum trough concentrations and thus efficacy. For example, a skilled person could use the elimination rate to determine that extending a dosing interval without increasing the dose amount would cause serum trough concentration to be lower, potentially dropping below the desired level, and thus compromising efficacy. Similarly, a skilled person could use the elimination rate to determine how much to raise the dose amount to maintain the desired trough concentration over a given interval.

Drugs are eliminated from the body in either a dose-independent or dose-dependent fashion. Dose-independent drugs are eliminated from the body at the same rate regardless of the concentration of the drug in the body. (*See* Ex. 1025 at 14, Table 3.2; Ex. 2005 at 179, 143.) For example, an 8 mg/kg dose will be

eliminated at the same rate as a 4 mg/kg dose. As a result, these dose-independent drugs are said to exhibit "linear kinetics" because the elimination rate and half-life,[4] among other parameters, remain constant regardless of the concentration of drug in the body. (Ex. 1025 at 14, Table 3.2; Ex. 2005 at 179, 143.)

In contrast, dose-dependent drugs exhibit non-linear kinetics, meaning that the elimination rate (and thus half-life) changes depending on the concentration of the drug in the body. (Ex. 2006 at 119-20; Ex. 2005 at 181-82.) Because the elimination rate changes with the concentration of drug in the body, the elimination rate of dose-dependent drugs can be different for different doses. (Ex. 2006 at 120-21; Ex. 2005 at 181-82.) For example, an 8 mg/kg dose will be eliminated from the body at a different rate than a 4 mg/kg dose. Therefore, dose-dependent drugs are said to exhibit "non-linear kinetics." (Ex. 2005 at 181.) The variability of the elimination rate also means that for any given dose, the elimination rate will change over time. For dose-dependent drugs, because the elimination rate changes

[4] The elimination half-life (referred to throughout as "half-life") of a drug is the time it takes for its concentration within the body to decrease by half. (Ex. 2005 at 145-46.) The faster a drug is eliminated from the body, the shorter the half-life. (*See, e.g.*, *id.* at 143-44.)

as the concentration of the drug changes, other parameters such as the half-life will also change with dose amount and over time. (*See* Ex. 2006 at 123-24.)

When considering dose modifications, linear analysis can be used to predict kinetics for a dose-independent drug because key pharmacokinetic parameters, such as elimination rate and half-life, usually do not systematically change with dose. (*See, e.g.*, Ex. 2001 at 130 ("Drugs with linear pharmacokinetics have relatively predictable behavior …, particularly in making dose modifications …."); Ex. 1025 at 14 (with linear kinetics, "the half-life will remain constant, no matter how high the concentration;" drug exposure is not affected by changes in drug schedule).) However, as Petitioner's expert has explained, "pharmacokinetic parameters are unpredictable" for non-linear, dose-dependent drugs. (Ex. 2001 at 130.) That is because for drugs with dose-dependent kinetics, pharmacokinetic parameters such as elimination rate change with the size of the dose administered or the dosing interval. (Ex. 2007 at 394; *see also* Ex. 2001 at 130.) As a consequence, with "*dose-dependent kinetics*, ***any one or a combination of these parameters appears to change with administration of different doses***." (Ex. 2007 at 395 (emphasis added).)

Developing dosing regimens for dose-dependent drugs is therefore more complex than developing dosing regimens for more predictable linear or dose-independent drugs. Indeed, Petitioner's expert has urged caution in adjusting

dosing regimens in drugs that exhibit non-linear kinetics because "small dose changes may lead to large changes in concentrations …." (Ex. 2001 at 130.) As a result, for drugs exhibiting non-linear kinetics, "when the dose or schedule is changed, a different clinical effect than that predicted may occur." (Ex. 2008 at 8.)

Petitioner concedes, as it must, that the prior-art disclosed trastuzumab exhibited non-linear kinetics. (*See, e.g.*, Paper 1 at 34-35; Ex. 1003, Ratain Decl. ¶102.) Indeed, the prior art upon which Petitioner relies explicitly discloses that trastuzumab is dose dependent and exhibited non-linear kinetics. For example, Baselga '96 reports: "The resulting recombinant humanized anti-p185^{HER2} monoclonal antibody (rhuMAb HER2) was found to be safe and to have ***dose-dependent pharmacokinetics*** in two prior phase I clinical trials." (Ex. 1007 at 3 (emphasis added).) Likewise, the Watanabe Abstract shows that increases in dose amount of trastuzumab from 1 mg/kg to 8 mg/kg did not result in proportionate increases to trough serum concentration. (Ex. 1006 at 5.) Petitioner concedes that this is indicative of non-linear kinetics. (*See, e.g.*, Paper 1 at 36 n.8; Ex. 1003, Ratain Decl. ¶ 102; *see also* Ex. 2005 at 181 ("Nonlinear pharmacokinetics are also called DOSE-DEPENDENT pharmacokinetics."); Ex. 1008 at 1 ("Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated ***dose-dependent pharmacokinetics***.") (emphasis added).) Given this information, a skilled person would expect trastuzumab to have non-linear kinetics and would therefore

anticipate challenges in predicting how changes in dose amount and dosing interval would impact trough serum concentrations, and thus, efficacy.

III. THE CLAIMED INVENTION

A. The '379 Patent.

The '379 patent issued from a divisional of the application that matured into the '196 patent and thus shares the same specification. The '379 patent discloses and claims new regimens for treating cancer with anti-ErbB2 antibodies. The new dosing regimens described in the patent feature infrequent dosing of anti-ErbB2 antibodies as well as higher initial loading doses and higher maintenance doses in conjunction with the administration of a chemotherapy agent. (Ex. 1001, 1:36-37, 6:23-24, 45:19-27; *id.* at 57:31-46.) Before the invention, persons of ordinary skill in the art had concluded that the "optimal" dose schedule of trastuzumab was weekly. (*See, e.g.*, Ex. 1007 at 4.) The '379 patent revealed that the time between trastuzumab doses could be longer, even two to three times longer. For example, the patent explicitly describes a dosing regimen with an initial dose of 8 mg/kg followed by subsequent maintenance doses of 6 mg/kg every three weeks.[5] (Ex. 1001, 5:37-39; 34:34-36; 45:19-27.)

[5] Petitioner incorrectly questions the legitimacy of the invention because the patent specification does not contain clinical trial data specific to the claimed

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, 38:63-39:38, 39:40-59 (Table 2), 39:60-40:45, Fig. 3.) For example, Table 2 of the specification discloses weekly mean trough serum concentrations over seven weekly infusions. (Ex. 1001, 39:40-59.) 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.

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regimens. (*See* Paper 1 at 1-2, 12-13.) Clinical trial data for the precise regimen claimed is not required. *See, e.g.*, *Avanir Pharm., Inc. v. Actavis S. Atl. LLC*, 36 F. Supp. 3d 475, 509 (D. Del. 2014), *aff'd sub nom. Avanir Pharm. Inc. v. Par Pharm. Inc.*, 612 F. App'x 613 (Fed. Cir. 2015) (although the clinical study in the specification tested a different dose range than the claimed method, the specification expressly disclosed the claimed dose range as "particularly preferred"); *see also Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (en banc) (actual reduction to practice is not required; constructive reduction to practice is sufficient).

B. The Challenged Claims.

The Petition challenges claims 1-3, 5, 7, 9-11, 13-28, and 30-40. Genentech opposes Petitioner's arguments with respect to all of the challenged claims, but will refer to claims 11, 17, and 21 as exemplary for purposes of this preliminary response. Unless otherwise noted, the arguments made in this preliminary response apply equally to the other challenged claims. Claim 1 is independent; claims 11, 17, and 21 depend indirectly from claim 1.

Claim 1 is directed to a method for the 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 and subsequent maintenance doses, comparable to or smaller than the loading dose, are separated in time from each other "by at least two weeks." Claim 1 also requires the administration of an effective amount of a chemotherapeutic agent to the patient. The dependent claims narrow claim 1, specifying the type of cancer, the amount of the initial dose, the amount of the maintenance doses, the time interval between the maintenance doses, and the type of chemotherapy agent to be administered.

For example, claim 11 depends from claim 10, and further requires the loading dose to be 8 mg/kg and at least one subsequent maintenance dose to be 6

mg/kg, and for the interval between doses to be three weeks.[6] 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***.
>
> further comprising administering an effective amount of a chemotherapeutic agent to the patient.

Claim 17 limits the "at least two weeks" dosing regimen of claim 1 to breast cancer. Claim 21 limits the "at least two weeks" dosing regimen of claim 1 to a humanized 4D5 anti-ErbB2 antibody.

[6] Challenged claims 5, 10, 11, and 36 are directed to maintenance dose intervals of at least three weeks. The remaining challenged claims (1-3, 7, 9, 13-28, 30-35, 37-40) require maintenance dose intervals of at least two weeks.

IV. PETITIONER'S ASSERTED REFERENCES

The references upon which Petitioner relies to support its obviousness claim focus exclusively on weekly dosing of trastuzumab. None of the references mention convenience or suggest treating patients with less frequent dosing, notwithstanding the awareness of the data upon which Petitioner relies to support an obviousness claim. The cited prior art also does not contain sufficient pharmacokinetic data to permit a skilled person to reasonably predict that extended intervals of two to three weeks would be effective, even if that were a goal. To the contrary, the limited pharmacokinetic data reported in the prior art would have discouraged efforts to dose at the claimed two- or three-week intervals. Moreover, the teaching that trastuzumab was dose dependent would have led a skilled person to conclude that changes in dose amounts and intervals could cause unpredictable changes in trough serum concentrations and therefore efficacy.

A. The Substance Of The Slamon Abstract Was Considered By The Patent Office And Does Not Lead To The Claimed Invention.

1. The Slamon Abstract does not suggest or support the claimed regimen.

The Slamon Abstract (Ex. 1005) consists of two brief paragraphs reporting the preliminary results of a Phase III clinical trial of trastuzumab administered in conjunction with either doxorubicin-cyclophosphamide or paclitaxel, both chemotherapy agents. Trastuzumab was administered as a 4 mg/kg loading dose

followed by ***weekly*** 2 mg/kg maintenance doses. (Ex. 1005 at 5.) The Abstract includes data indicating that adding weekly trastuzumab to chemotherapy increases clinical benefit. (*Id.*) In the study, chemotherapy agents were administered every three weeks, but trastuzumab was not. (*Id.*) The Abstract does not suggest extending the trastuzumab dosing interval to match the chemotherapy schedule. Nor does the Slamon Abstract contain any pharmacokinetic data that a skilled artisan could use to evaluate alternative dosing regimens, such as those claimed.

2. The information in the Slamon Abstract was considered during prosecution of the '379 patent and its parent.

Petitioner's allegation that the Examiner was not presented with information disclosing the "beneficial effects from a combination of trastuzumab and chemotherapy" (Paper 1 at 40), is incorrect. Goldenberg '99—which cites the Slamon Abstract and discusses the same Phase III trial results in more detail—was considered during prosecution of the '379 patent's parent, and again considered during the prosecution of the '379 patent. (*See, e.g.*, Ex. 1011 at 185, 189-90 (relying on Goldenberg '99 to issue a rejection of the '196 patent claims); Ex. 1002 at 243 (considering Goldenberg '99 during prosecution of the '379 patent); Ex. 1013 at 6, 7, 10 (citing the Slamon Abstract); *see also infra* pp. 28-32.)

During the Phase III trial described in both Goldenberg '99 and the Slamon Abstract, patients were administered a 4 mg/kg loading dose of trastuzumab,

followed by 2 mg/kg weekly maintenance doses. (*Compare* Ex. 1013 at 6-7, *with* Ex. 1005 at 5.) As described in both Goldenberg '99 and the Slamon Abstract, patients also received doses of chemotherapy agents every three weeks. (*Compare* Ex. 1013 at 6-7, *with* Ex. 1005 at 5.) And like the Slamon Abstract, Goldenberg '99 reports that patients who received trastuzumab plus chemotherapy "benefited measurably in terms of time to disease progression, overall response rate, median duration of response, and 1-year survival compared with patients treated with chemotherapy alone." (Ex. 2013 at 7. *Compare id.*, *with* Ex. 1005 at 5.)

Also before the Examiner was Pegram '98, which (as discussed more fully below) discloses the benefit of combining trastuzumab and chemotherapy. (Ex. 1009 at 2 ("The use of [trastuzumab] in combination with [cisplatin] … results in objective clinical response rates higher than those previously reported from [cisplatin] alone, or [trastuzumab] alone."); Ex. 1011 at 159, 198 (considering Pegram '98 during '196 patent prosecution); Ex. 1002 at 244 (considering Pegram '98 during '379 patent prosecution).)

Notably, none of these references, *i.e.*, the Slamon Abstract, Pegram '98 or Goldenberg '99, teach or even suggest extending trastuzumab's dosing schedule to match the every-three-week chemotherapy regimens administered. (*See supra* pp. 19-20; *infra* pp. 24-25.)

B. The Watanabe Abstract Does Not Suggest Or Support The Claimed Dosing Regimen.

The Watanabe Abstract, which was previously considered by the Patent Office, consists of two brief paragraphs reporting results of a Phase I dose-escalation study of trastuzumab and recommending that ***weekly*** administration of 2 mg/kg or 4 mg/kg of trastuzumab should be investigated further. (Ex. 1006 at 5.) In the study, 18 patients received a first trastuzumab dose of 1, 2, 4, or 8 mg/kg and then, after three weeks, received nine weekly doses. (*Id.*) The Abstract reports that the "trough level" of each tested dose ranged from 9 μg/mL for the 1 mg/kg dose amount to 248 μg/mL for the 8 mg/kg dose amount, but does not indicate when trough levels were measured or whether the reported values are individual or mean levels. (*Id.*) The Watanabe Abstract demonstrates that the effect of increased dose amount on trough levels is not linear, a phenomenon associated with dose-dependent kinetics. But the Abstract does not report any other pharmacokinetic information, such as half-life.

Based on the data collected, the authors concluded that 2-4 mg/kg ***weekly*** doses of trastuzumab should be investigated in further clinical trials. (*Id.*)

C. Baselga '96 Does Not Suggest Or Support The Claimed Dosing Regimen.

Baselga '96, which was considered by the Patent Office, reports results of a Phase II clinical study designed to "evaluate[] the efficacy and toxicity of ***weekly***

intravenous administration of rhuMAb HER2 in patients with HER2-overexpressing metastatic breast cancer." (Ex. 1007 at 3 (emphasis added).) Patients received a loading dose of 250 mg of trastuzumab followed by weekly doses of 100 mg. (*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 4 (emphasis added).) Baselga '96 notes that trastuzumab has "documented dose dependent pharmacokinetics" (*id.*) and reports, for the weekly regimen tested, a mean serum half-life of 8.3 +/- 5.0 days (*id.* at 5).

Baselga '96 sought to achieve trough concentrations of at least 10 µg/mL based on preclinical studies. (*Id.* at 4.) Baselga '96 reported that over 90% of patients had trough serum concentrations above the 10 µg/mL target, and that patients with trough concentrations below 10 µg/mL did not demonstrate a therapeutic response. (*Id.* at 5, 7-8.)

Baselga '96 does not reference or suggest administering trastuzumab at any dosing interval other than weekly. Nor does Baselga '96 discuss patient convenience or the possibility of administering trastuzumab on a less frequent regimen. Although Baselga '96 refers generally to preclinical studies administering trastuzumab with a chemotherapy agent such as paclitaxel (*id.* at 9),

there is no mention or hint as to the desirability of administering trastuzumab on the same schedule as chemotherapy.

D. Pegram '98 Does Not Suggest Or Support The Claimed Dosing Regimen.

Pegram '98, which was before the Patent Office, 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. 1009 at 2.) Patients were treated with a loading dose of 250 mg of trastuzumab followed by weekly doses of 100 mg for nine weeks. Patients also received 75 mg/m^2 doses of cisplatin about every four weeks, but the cisplatin doses ***were not*** administered on the same day as trastuzumab. (*Id.* at 2, 3-4.) Rather, cisplatin was administered on the second day of treatment and on days 29 and 57 of the study (about every four weeks), whereas trastuzumab was administered once weekly on days 0, 7, 14, 21, 28, and so forth. (*Id.*) In studying administration of both trastuzumab and cisplatin, Pegram '98 does not mention convenience or suggest aligning the treatments such that both therapies are given on the same day.

Pegram '98 provides only limited pharmacokinetic information on trastuzumab. Specifically, Table 6 of Pegram '98 reports a half-life of 11.0 ± 4.0 days for patients treated with trastuzumab and cisplatin. (*Id.* at 8, Table 6.) 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. 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.*)

V. PERSON OF ORDINARY SKILL

Petitioner argues that a skilled artisan would have expertise in both oncology and pharmacokinetics. (Paper 1 at 15 (citing Ex. 1003, Ratain Decl. ¶44).) For the purposes of these proceedings, Patent Owner does not dispute the areas of substantive expertise, but disagrees with Petitioner's characterization of a skilled artisan insofar as it could be construed to exclude a clinical oncologist working ***in consultation with*** a pharmacokineticist. In any event, the challenged claims would not have been obvious under either definition.

VI. CLAIM CONSTRUCTION

Patent Owner requests that the Board construe "effective amount" in claims 1-3, 5, 7, 9-11, and 13-28 as "an amount having antiproliferative effect or an amount yielding a target serum concentration, such as a trough serum concentration, that has been shown to be effective in suppressing disease symptoms when maintained for a period of time." This is consistent with the definition at column 15 of the '379 patent, which defines the term "therapeutically effective amount" in two ways: "an amount having antiproliferative effect" (Ex.

1001, 15:17-18) and "a target serum concentration, such as a trough serum concentration, that has been shown to be effective in suppressing disease symptoms when maintained for a period of time." (*Id.* at 15:26-30.) *See, e.g.*, *SAS Inst., Inc. v. ComplementSoft, LLC.*, 825 F.3d 1341, 1348 (Fed. Cir. 2016) (construing term according to specification's definition under broadest reasonable interpretation); *see also In re Bass*, 314 F.3d 575, 577 (Fed. Cir. 2002) ("[T]he PTO must apply the broadest reasonable meaning to the claim language, taking into account any definitions presented in the specification."); *Roxane Labs., Inc. v. Novartis AG*, IPR2016-01461, Paper 9 at 5 (Feb. 13, 2017) (under the broadest reasonable interpretation, "[a]ny special definitions for claim terms or phrases must be set forth with reasonable clarity, deliberateness, and precision." (citing *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994))).

For the purposes of these proceedings, Patent Owner does not contest Petitioner's proposed constructions.

VII. ARGUMENT

A. Petitioner's Arguments Were Considered And Rejected During Prosecution.

The Board has authority to reject an *inter partes* review petition if "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). The Board has exercised this authority and denied institution of *inter partes* review on numerous occasions. *See, e.g.*, *Lower Drug*

Prices for Consumers, LLC v. Forest Labs. Holdings Ltd., IPR2016-00379, Paper 14 at 9-12 (July 1, 2016) (denying institution under § 325(d) where the petitioner's obviousness challenge was based on the same primary reference considered during prosecution and the same arguments regarding how that primary reference would have been modified); *Fustibal LLC v. Bayer Healthcare LLC*, IPR2016-01490, Paper 9 at 11, 15-16 (Feb. 8, 2017) (denying institution under § 325(d) where the petitioner's anticipation and obviousness challenges were based on the same primary reference considered during prosecution); *Prism Pharma Co., Ltd. v. Choongwae Pharma Corp.*, IPR2014-00315, Paper 14 at 12-13 (July 8, 2014) (denying institution under § 325(d) where the Examiner considered the same priority issue with respect to the same reference during prosecution).

Here, Petitioner's obviousness challenge rests on the same prior art disclosures and arguments that the Patent Office considered and rejected during prosecution of the '379 patent's parent—very same arguments that the Patent Office chose not to raise a second time during the prosecution of the '379 patent.[7]

[7] In the pending prosecution of U.S. Patent Application No. 14/073,659, a continuation application in a chain of applications in the '379 patent family, the Patent Office has issued a non-final rejection on similar grounds to those raised during prosecution of the '196 patent and proposed by Petitioner. In addition,

First, the Patent Office already twice-considered the substance of Petitioner's references. During prosecution of the '379 patent's parent, the applicants successfully overcame obviousness rejections based on Baselga '96 and the Watanabe Abstract, and did not receive a rejection based on Pegram '98, though the reference was of record and considered. (*See, e.g.*, Ex. 1011 at 189-90, 218-19, 223-25, 246.) These references were again considered during prosecution of the '379 patent. (Ex. 1002 at 242, 244, 246.) Although, Petitioner alleges that the Examiner was not presented with information in the Slamon Abstract disclosing "the beneficial effects from a combination of trastuzumab and chemotherapy" (Paper 1 at 40), that is not true. Goldenberg '99, which formed the basis of an obviousness rejection that was overcome during prosecution of the '196 patent, cites the Slamon Abstract and discloses the very same information upon which Petitioner relies. (*See supra* pp. 20-21.) Moreover, Pegram '98, also considered during prosecution of both the '379 patent and its parent (Ex. 1011 at 198; Ex. 1002 at 244), discloses that chemotherapy in addition to trastuzumab

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Hospira, Inc. has filed a separate petition (IPR2017-00805) challenging the '379 patent, which involves many of the same references asserted here. Genentech is disputing the Patent Office's rejection and Hospira's petition on substantially the same grounds set forth in this preliminary response.

produced beneficial effects. (Ex. 1009 at 2.) Under such circumstances, the fact that the Slamon Abstract itself was not considered is of no moment. *Apple Inc. v. Papst Licensing GmbH & Co., KG*, IPR2016-01841, Paper 10 at 8 n.2, 13 (Apr. 17, 2017) (denying institution under § 325(d) where "there [was] no significant, substantive difference" between the reference considered during prosecution and the reference cited in the petition).

The Examiner's decision not to issue a rejection of the '379 patent claims based on these references is not surprising. The application that matured into the '379 patent was filed June 20, 2003, shortly after the Examiner issued a notice of allowance for the '196 patent. (Ex. 1001 at 1; Ex. 1011 at 248.) The '379 patent was filed with the same specification as the '196 patent and the same references were considered by the same Examiner who examined the '196 patent. (*Compare* Ex. 1002 at 10-70, *and id.* at 75-85, 239-246, *with* Ex. 1011 at 51-97, 108-14, *and id.* at 154-60, 198, *and* Ex. 1010 at 1-4.) Having already concluded that claims to two- or three-week dosing intervals were patentable over Baselga '96, the Watanabe Abstract, and Goldenberg '99, the Examiner allowed the claims that included such limitations. (Ex. 1002 at 392, 395.)

Second, the Petition simply repeats arguments the Patent Office has already considered and rejected. For example, Petitioner makes the same argument the Examiner raised during prosecution of the '196 patent—that the extended dosing

schedule of chemotherapy agents used in combination with trastuzumab would have motivated a skilled artisan to find a less frequent dosing schedule for trastuzumab. (*Compare, e.g.*, Paper 1 at 28-29, *with* Ex. 1011 at 218-19.) In addition, much as Petitioner argues here, the Examiner posited the claims were obvious over the Watanabe Abstract, Baselga '96, and Goldenberg '99. (*See, e.g.*, Ex. 1011 at 189-90.) In response, the applicants argued that (1) the prior art disclosed only weekly dosing and did not teach or suggest the claimed extended dosing intervals; and (2) Goldenberg '99's and Baselga '96's reported half-life of 5.8 and 9.1 days would not have led a person of skill to dose every two weeks for fear that trough serum concentrations would be insufficient to treat cancer. (*Id.* at 209-10, 223.) The Examiner agreed, stating in the Reasons for Allowance: "The prior art fails to teach or fairly suggest the recited minimum dosages and dosing schedules where the subsequent doses are separated from each other by at least 2 weeks." (*Id.* at 246.)

The Examiner also considered the argument that the extended-interval dosing schedule was an obvious variation of the weekly regimen in view of the higher dose amounts and the half-lives taught in the prior art. The Examiner asserted (as Petitioner does here) that the Watanabe Abstract supported an obviousness finding because it "teaches that higher doses than 4 mg/kg are tolerated and that the higher the initial dose the higher the trough level." (Ex. 1011

at 218.) But the applicants overcame that argument by pointing out that "[b]ased on the dose escalation study, Watanabe proposes further clinical trials examining the efficacy of [trastuzumab] 'with 2-4 mg/kg weekly intravenous infusions.'" (*Id.* at 224.) The Examiner then allowed the claims. (*Id.* at 246.)

The addition of an expert opinion repeating arguments previously rejected by the Patent Office is not a sufficient reason to second guess the Examiner's decision. *See Lower Drug Prices for Consumers, LLC v. Forest Labs. Holdings Ltd.*, IPR2016-00379, Paper 16 at 2-3 (Oct. 19, 2016) (confirming on reconsideration denial of institution under § 325(d) and rejecting argument that petition differed from arguments made during prosecution due to the inclusion of expert opinion not previously before the Patent Office); *see also id.* at 3 (Section 325(d) only requires that the arguments be substantially the same, not identical.) Petitioner's expert relies on the very same prior art disclosures that were considered by the Examiner. (*Compare* Ex. 1003, Ratain Decl. ¶¶63-84, *with* Ex. 1011 at 189-190, 218-19; *see also supra* pp. 28-30.) Moreover, Petitioner's expert makes the very same argument that a skilled artisan would have been motivated to dose trastuzumab on the same schedule with an every-three-week chemotherapy regimen. (*Compare* Ex. 1003, Ratain Decl. ¶¶89-90, *with* Ex. 1011 at 218-19.) And also like the Examiner, Petitioner's expert argues that the pharmacokinetic data in the prior art—such as the half-life data reported in Baselga '96 and trough

serum concentrations reported in the Watanabe Abstract—would have rendered the claimed regimen obvious. (*Compare, e.g.*, Ex. 1003, Ratain Decl. ¶¶136, 89-112 *with* Ex. 1011 at 218.) This repetition of arguments in an expert declaration does not make them "new" or justify revisiting the Examiner's decision to allow the claims.

In sum, Petitioner's sole ground for institution is precisely the same as that previously considered by the Patent Office prior to issuing the '379 patent's parent. Petitioner has provided no basis for the Board to reach a different conclusion here. Accordingly, the Board in its discretion should deny institution under 35 U.S.C. § 325(d).

B. Petitioner Has Failed To Show A Reasonable Likelihood That The Challenged Claims Are Obvious Over The Watanabe Abstract And The Slamon Abstract In View Of Baselga '96 And Pegram '98.

The Petition fails to establish the requisite teaching or suggestion of the claimed extended dosing regimens, motivation to modify the accepted weekly dosing interval for trastuzumab, or reasonable expectation of success in doing so. Indeed, Petitioner's obviousness argument is a textbook case of hindsight-driven analysis. At every turn, Petitioner chooses the path leading to the claimed invention while ignoring the prior art pointing in a different direction. First, the cited prior art does not suggest dosing intervals of more than one week; on the

contrary, the cited prior art shows that skilled artisans considering the same information upon which Petitioner relies recommended and pursed weekly dosing. Second, the utter absence of any reference to convenience in the prior art shows that Petitioner's motivation argument is completely unfounded, a shortcoming that cannot be overcome with a single conclusory sentence in an expert declaration. Third, Petitioner's argument that a skilled artisan would have expected extended dosing of trastuzumab to be effective has no basis in the prior art, and is untenable in view of the acknowledged unpredictability associated with altering dosing regimens of drugs with non-linear kinetics. In sum, the prior art provides no basis upon which to conclude that skilled artisans would have been motivated to develop an alternative dosing regimen to treat a life-threatening disease condition, let alone have followed Petitioner's course.

The Federal Circuit has consistently criticized Petitioner's type of hindsight-driven analysis. For example, in *Zoltek Corp. v. United States*, 815 F.3d 1302 (Fed. Cir. 2016), the Federal Circuit rejected an obviousness analysis where defendant's expert cherry picked data from the prior art and plugged that data into an equation derived by the expert to reconstruct the claimed invention. *Id.* at 1311-13; *see also W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or

suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.").

That is precisely what Petitioner's expert has done here in selecting a three-week dosing interval based on an alleged motivation that appears nowhere in the prior art. Petitioner's expert also falls victim to hindsight in glossing over the lack of information in the prior art regarding the pharmacokinetics of one of the first antibodies used to treat cancer with the conclusory assertion that trastuzumab pharmacokinetics were "predictable." Indeed, the Federal Circuit has cautioned that expert testimony 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*.'" *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc*., 520 F.3d 1358, 1364 (Fed. Cir. 2008) (quoting 35 U.S.C. § 103(a)).

1. The cited prior art does not suggest administration of subsequent doses separated in time from each other by at least two weeks or at least three weeks.

At the time of the claimed invention in August 1999, the only approved dosing of trastuzumab was weekly. Each and every one of the references that Petitioner cites teaches weekly dosing intervals of trastuzumab. Indeed, weekly

dosing was not only recommended, (Ex. 1006 at 5) but described as "optimal" (Ex. 1007 at 4). Nor do any of the cited prior art references refer in any way to the possibility—let alone the likely success—of the extended intervals in the claims. The Federal Circuit and the Board have repeatedly rejected obviousness challenges that lack a basis in the prior art. *See, e.g.*, *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1374-75 (Fed. Cir. 2017) (declining to find claim to dosing regimen obvious where prior art did not disclose the dosing schedule for the claimed drug in the relevant field of treatment); *Endo Pharm. Inc. v. Depomed, Inc.*, IPR2014-00654, Paper 69 at 26-27 (Sept. 21, 2015) (Board 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).

As recognized by the Patent Office during prosecution, a key element of the claimed invention is the extended dosing interval of "at least two weeks" and up to "at least three weeks" between maintenance doses. (*See, e.g.*, Ex. 1002 at 367-68; Ex. 1011 at 246.) ***All*** of the challenged claims require an interval of "at least two weeks;" and claims 5, 10, 11, and 36 require an interval of "at least three weeks" between maintenance doses. But the asserted obviousness ground in the Petition is based entirely upon references that teach ***weekly*** dosing. (Ex. 1005 at 5; Ex. 1006 at 5; Ex. 1007 at 3; Ex. 1009 at 2.)

Faced with unanimity in the cited prior art, Petitioner focuses on one aspect of the Phase I study reported in the Watanabe Abstract: the second dose was administered three weeks after the first dose. But this fact does not support Petitioner's obviousness argument. Although the Watanabe Abstract did include a three-week gap between the first and second doses, each of the subsequent doses are separated in time by only one week. (*Compare* Ex. 1006 at 5, *with* Ex. 1001 at Claim 11 ("the plurality of subsequent doses are separated in time from each other by at least three weeks").) Moreover, based on the study results, the authors concluded that ***weekly*** administration of trastuzumab should be pursued in the next round of studies. (Ex. 1006 at 5.) The ultimate teaching of the reference—to focus future work on weekly dosing—cannot be disregarded as Petitioner suggests.[8] *See,*

[8] Petitioner also implies that a skilled artisan would disregard the Watanabe Abstract's recommendation for further study of weekly dosing because the Slamon Abstract, presented at the same ASCO meeting, shows that weekly dosing had already been studied. (Paper 1 at 30-31.) Even if that were the case, the Slamon Abstract's report of initial Phase III results is entirely consistent with Watanabe's focus on weekly dosing. Moreover, there is no basis upon which to accept as relevant some portions of Watanabe while disregarding others. *See, e.g.*, M.P.E.P.

e.g., M.P.E.P. § 2141.02(VI) (instructing examiners that, in evaluating obviousness, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention"); *see also W.L. Gore & Assocs.*, 721 F.2d at 1550 (prior art reference must be considered in its entirety).

The Watanabe Abstract's recommendation that weekly administration be pursued even after conducting a Phase I study with a three-week gap between the first and second doses, combined with the uniform focus on weekly dosing in concurrent and subsequent clinical trials (Baselga '96, Pegram '98, the Slamon Abstract, and the 1998 Herceptin® Label) is "strong evidence" of non-obviousness. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082 (Fed. Cir. 2012) ("Evidence that others were 'going in different ways' is strong evidence that the [inventor's] way would not have been obvious." (citations omitted)).

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§ 2141.02(VI) (a prior art reference must be considered in its entirety); *see also W.L. Gore & Assocs.*, 721 F.2d at 1550 (same).

2. Petitioner has failed to establish any motivation in the prior art.

a. The prior art does not support Petitioner's claim that convenience would have motivated skilled persons to administer trastuzumab at three-week dosing intervals.

i. No cited reference mentions convenience or suggests a need to develop a dosing regimen based on convenience.

There is no reference to convenience (or lack thereof) in any of the prior art identified by Petitioner, let alone a suggestion that less frequent administration would be more convenient. Baselga '96 and the Watanabe Abstract expressly conclude that weekly administration is either "optimal" (Baselga) or should be pursued in further trials (Watanabe). And while the Slamon Abstract and Pegram '98 both report studies where trastuzumab was administered in conjunction with a multi-week chemotherapy dosing regimen (Ex. 1005 at 1; Ex. 1009 at 2), neither reference mentions convenience or suggests that the therapies should be administered on the same schedule or even on the same day. Pegram '98 suggests the exact opposite insofar as it only describes a study in which trastuzumab was dosed on ***different*** days than when the chemotherapy agent was administered. (*See*

Ex. 1009 at 2, 4 (describing administration of cisplatin the day after trastuzumab, even when the two drugs were administered during the same week).)

ii. A conclusory expert declaration cannot provide the requisite evidentiary support.

The sole support for Petitioner's assertion that skilled artisans would have been motivated to align trastuzumab therapy with a chemotherapy regimen to "improve patient convenience" is a single, conclusory sentence in the declaration of its expert. (*See*, *e.g.*, Paper 1 at 43-44; Ex. 1003, Ratain Decl. ¶¶90, 136.) After noting that the Slamon Abstract's trastuzumab regimen would have required three times as many infusion visits as chemotherapy alone, (Ex. 1003, Ratain Decl. ¶89), Petitioner's expert states as follows:

> For the convenience of both patient and clinician, a POSA therefore would have been motivated to administer trastuzumab for the treatment of metastatic breast cancer characterized by overexpression of ErbB2, as disclosed by Slamon, but on the same schedule—once every three weeks—as chemotherapy.

(*Id.* at ¶90.) This conclusory sentence lacks any basis in the cited prior art (which is exclusively focused on safety and efficacy) and is pure hindsight.

Motivation absent in the prior art cannot be provided by a conclusory after-the-fact expert opinion of the sort proffered here. Courts and the Board have

repeatedly rejected expert opinions that are not based in the prior art. *See Roxane Labs.*, IPR2016-01461, Paper 9 at 10 ("Where … conclusory testimony is the sole basis for establishing that a claim limitation is taught or suggested by the prior art, we find it insufficient to establish a reasonable likelihood of prevailing regarding that claim."); *Phigenix, Inc. v. Genentech, Inc.*, IPR2014-00842, Paper 10 at 16-17 (Dec. 9, 2014) (finding conclusory a clinical expert's unsupported testimony that the Herceptin® Label, which taught that certain patients failed to respond to Herceptin®, would have motivated a skilled artisan to treat such patients using a Herceptin® conjugate). Petitioner's failure to provide any justification for the purported motivation to combine beyond a sentence in a post-hoc expert opinion fails to provide the kind of "reasoned analysis" necessary to supply a motivation not found in the prior art. *See, e.g.*, *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1362 (Fed. Cir. 2016) ("[O]ur cases repeatedly warn that references to 'common sense'—whether to supply a motivation to combine or a missing limitation—cannot be used as a wholesale substitute for reasoned analysis and evidentiary support, especially when dealing with a limitation missing from the prior art references specified.").

Generic assertions of "convenience" cannot substitute for evidence that a skilled artisan would have known the extended dosing regimens to be safe and effective. *See Novartis*, 2017 WL 1278672, at *10-11. This is especially true here,

where Petitioner's clinical expert acknowledges the importance of safety and efficacy, and where his statements as to convenience are contradicted by the cited prior art, which not only focused on weekly dosing but taught administering chemotherapy the day after trastuzumab treatment. (*Compare* Ex. 1003, Ratain Decl. ¶¶ 89-90, *with* Ex. 1009 at 4.)

In a case involving similar issues, a party argued that a patent claiming the co-administration of rapamycin and cyclosporin A would have been obvious to a skilled artisan. *Novartis*, 2017 WL 1278672, at *9-11. In particular, defendants argued that the prior art taught co-administration of the drugs in mice, and that "co-administration of the two drugs would be important for ensuring patient compliance." *Id.* at 10. However, in that case as here, there was no teaching in the prior art that the administered dosing regimen would be safe and effective. *Id.* at *11. The district court rejected Petitioner's argument, holding that "patient compliance" would not have been a sufficient motivation to co-administer the two drugs absent evidence in the prior art that the combination would have been safe and effective in humans. *Id.* Here too Petitioner asks the Board to gloss over the gaps in the prior art and conclude that patient "convenience" would have motivated a skilled artisan to administer trastuzumab at an extended dosing regimen.

In sum, Petitioner's alleged motivation, untethered to the asserted prior art and devoid of any "reasoned analysis," presents exactly the type of hindsight the

obviousness inquiry is designed to avoid. "[T]he Board cannot accept general conclusions about what is 'basic knowledge' or 'common sense' as a replacement for documentary evidence for core factual findings in a determination of patentability." *K/S HIMPP v. Hear-Wear Techs.*, *LLC*, 751 F.3d 1362, 1366 (Fed. Cir. 2014). Petitioner's expert's after-the-fact say so is simply not enough to carry the day in an obviousness challenge. *See, e.g.*, *Nuvasive*, 842 F.3d at 383 ("'conclusory statements' alone are insufficient" articulations of motivation to combine) (quoting *In re Sang Su Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2002)).

iii. Petitioner's contention that convenience would have motivated a skilled person to use three-week dosing is contradicted by what skilled persons actually did at the time.

Petitioner's theory that skilled artisans would have been motivated to pursue three-week dosing is directly contradicted by what skilled artisans actually concluded at the time: ***weekly*** dosing was the optimal schedule.

First, the same "convenience" that allegedly would have motivated skilled persons in August 1999 (Ex. 1003, Ratain Decl. ¶¶ 89-90) existed well before the priority date, when the studies reported in Baselga '96, the Watanabe Abstract, Pegram '98, and the 1998 Herceptin® Label were conducted. The Watanabe Abstract does not discuss chemotherapy at all, and the other references teach administering trastuzumab every week without regard to any schedule for

chemotherapy. Petitioner provides no argument or explanation for why, "[f]or the convenience of both patient and clinician," (Ex. 1003 at ¶ 90), the authors of these studies did not dose trastuzumab on the same schedule as the chemotherapy agents tested. The uniform pursuit of a *weekly* dosing regimen, even when trastuzumab was administered with chemotherapy, points away from the claimed extended dosing interval.

Second, the Phase I dose-rising studies relied on by Petitioner's expert to support his opinion that extended dosing would be effective were already known to the extraordinarily skilled individuals who conducted the early clinical trials of trastuzumab that are reported in Baselga '96, Pegram '98, and on the 1998 Herceptin® Label. None of these skilled individuals, working prior to the invention of the '379 patent, pursued a three-week dosing interval for trastuzumab. As set forth more fully below, given the unpredictability associated with dose-dependent kinetics, it is not surprising that in the studies reported in Baselga '96—like those reported in Pegram '98, the Watanabe Abstract, and ultimately the 1998 Herceptin® Label—clinicians opted for a weekly dosing regimen for trastuzumab based on the available pharmacokinetic data.

b. The prior art does not suggest the claimed loading and maintenance doses.

None of the prior art referenced in the asserted ground for institution would have led to the claimed combination of loading and maintenance doses in a two- or three-week regimen. Instead, to arrive at the claimed invention, Petitioner extrapolates an 8 mg/kg loading dose and a 6 mg/kg maintenance dose with the benefit of hindsight, and attempts to justify the selection. (Paper 1 at 29-30, Ex. 1003, Ratain Decl. ¶91.) To arrive at the claimed dose amounts, Petitioner asserts that a skilled artisan would apply the concept of "dose intensity" to triple the Slamon Abstract's weekly dose amount to match the every-three-week administration of a chemotherapy agent. (Paper 1 at 29-30.) Likewise, Petitioner argues a skilled artisan would have selected an 8 mg/kg loading dose to correspond to the aggregate quantity of trastuzumab administered over the first three weeks of the Slamon Abstract's regimen. (*Id.*) But Petitioner provides no explanation for why a skilled artisan would apply the concept of "dose intensity," which is a chemotherapy dosing strategy, to trastuzumab. (*See id.* at 29 (citing Exs. 1024, 1029); Ex. 1024 at 1 (describing dosing of doxorubicin, a chemotherapy agent); Ex. 1029 at 6 (same).) The approach is flawed for the following two reasons.

First, a skilled artisan would not use a chemotherapy dosing strategy because the prior art teaches that "the biologic action of [trastuzumab] … differs

markedly from conventional anticancer agents" like chemotherapy. (Ex. 1007 at 7.) Trastuzumab and chemotherapy agents are dosed according to very different principles. The goal of most chemotherapy dosing in 1999 was to deliver the largest tolerable dose that would kill the greatest number of tumor cells without causing severe toxicity effects like white blood cell destruction or suppression. (*See, e.g.*, Ex. 1021 at 51 (contrasting "most fields of medicine" with chemotherapy dosing because chemotherapy targets the maximum tolerated dose).) As a result, chemotherapy dosing intervals are generally designed to kill tumor cells and then allow a patient's body time to recover. (*See, e.g.*, Ex. 1029 at 7 (only administering next dose of chemotherapy if white blood cell and platelet levels recovered above a certain threshold).) By comparison, the aim of trastuzumab dosing is to maintain therapeutic trough, *i.e.*, minimum, serum levels throughout treatment. (*Supra* pp. 8-11.) Thus, while chemotherapy is concerned with maximum tolerated concentration and recovery time, a skilled artisan developing a trastuzumab regimen would have been concerned with maintaining a minimum trough concentration throughout treatment.

Second, increasing the dose amount and extending the dosing interval was known to cause higher peak and lower trough concentrations as compared to smaller dose amounts administered more frequently. (Ex. 2005 at 171 (greater dosing interval corresponds to greater percent fluctuation in plasma

concentration).) As Petitioner's expert explains, "as the intervals between doses increase, the fluctuation increases, with higher peaks and lower trough concentrations." (Ex. 1003, Ratain Decl. ¶57.) Given this, a skilled artisan would not apply dose-intensity principles from chemotherapy agents (which focused on maximum tolerated dose for therapeutic effect) to designing a dosing regimen for trastuzumab (which focused on trough concentrations for therapeutic effect).

Petitioner's failure to identify a reason to select the claimed dose amounts is fatal. *See Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d at 1072 ("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.*, 520 F.3d at 1364)). Indeed, the Federal Circuit and the Board have repeatedly rejected obviousness challenges that lack a basis in the prior art. *See, e.g.*, *Eli Lilly & Co.*, 845 F.3d at 1374-75; *Endo Pharm. Inc.*, IPR2014-00654, Paper 69 at 26-27.

3. Petitioner has failed to establish a "reasonable expectation of success."

Petitioner's obviousness case depends on its further assertion that trastuzumab exhibits predictable kinetics, such that a skilled artisan would have had a reasonable expectation of success in treating cancer with the more

convenient dosing regimen. This assertion is not plausible in view of the prior art's teaching that trastuzumab has non-linear kinetics. The prior art—including prior art authored by Petitioner's own expert—is replete with warnings about modifying dosing regimens of drugs with non-linear kinetics. Without sufficient data, extrapolations beyond known dosing intervals risk unpredictable changes in drug concentration. This failure to acknowledge the unpredictability of altering the known dosing regimens for trastuzumab is critically important because Petitioner's predicted trough serum concentrations of 10.9 to 21.1 μg/mL leave no margin for error; they are just barely above the targets of 10-20 μg/mL established by the preclinical studies, and far below the levels reached in clinical studies like Baselga '96 and Pegram '98. (*See, e.g.*, Ex. 1009 at 8, Table 6; *supra* pp. 9-10.)

Despite recognizing that the prior art taught that trastuzumab had documented non-linear kinetics, the foundation of Petitioner's analysis is the application of simple equations that apply only to drugs that exhibit linear kinetics. (*See* Ex. 1003, Ratain Decl. ¶¶51-55.) This is erroneous. Drugs with dose-dependent, non-linear pharmacokinetics, unlike drugs with linear pharmacokinetics, have pharmacokinetic parameters such as half-life and elimination rate that change as the concentration of the drug changes in the bloodstream. (*See* Ex. 2005 at 179, 181-82; Ex. 2006 at 120-21; *see also supra* pp. 12-13.) As a result, pharmacokinetic data from one dose amount—for example,

the half-life for a 250 mg loading dose, followed by weekly 100 mg doses, reported in Pegram '98 and Baselga '96 and selected by Petitioner's expert for his calculation—will not be the same for the half-life of a different dose amount, *e.g.*, 4 mg/kg or 6 mg/kg. (*See, e.g.*, Ex. 2006 at 123 ("The half-life is a function of plasma concentration for the non-linear system.").)

Similarly, one cannot reasonably assume that the half-life of a 4 mg/kg dose of trastuzumab measured after weekly administration could be extrapolated out to three weeks because the concentration of drug in the blood is continually changing as the drug is eliminated. (*See id.*) As a consequence, the half-life measured from between days 1 to 7 will be different from the half-life from days 8 to 14, which will be different from the half-life from days 15 to 21. (*See id.*)

Petitioner's pharmacokinetic analysis nevertheless assumes that the half-life for the ***weekly*** regimen reported in Baselga '96 will remain constant when extrapolated to two or three weeks. (Paper 1 at 34-36; Ex. 1003, Ratain Decl. ¶¶103-04; *id.* at ¶¶51-55.) Yet Petitioner points to nothing in the prior art that would enable a skilled artisan to determine how trastuzumab would be cleared from the body over a two- or three-week period.

Petitioner's reliance on a statement in Pegram '98 that trastuzumab showed "predictable" kinetics is misplaced. (*See, e.g.*, Paper 1 at 18, Ex. 1003, Dr. Ratain Decl., ¶¶26, 84.) Pegram '98 reports that the pharmacokinetics of trastuzumab

were predictable in prior Phase I clinical trials, but provides no context for that observation and nevertheless proceeds with a weekly regimen. (Ex. 1009 at 3.) Neither Pegram '98 nor Petitioner's expert provides a basis for predicting the impact of an extended dose interval on the pharmacokinetics of trastuzumab.

Petitioner's expert has warned that "[e]xtrapolation of models outside the known time points must be done with great caution," (Ex. 1025 at 15), but here Petitioner proceeds with anything but caution. Petitioner applies linear equations based only on isolated data points to a drug it concedes exhibits non-linear kinetics. Petitioner also modifies the prior art's dose amount and dose schedule without addressing the teaching of its own expert that, for drugs with non-linear kinetics, "when the dose or schedule is changed, a different clinical effect than that predicted may occur," (Ex. 2008 at 8). (*See also* Ex. 1025 at 15 ("In contrast to drugs with linear pharmacokinetics, alteration of the schedule of drugs that display nonlinear kinetics may markedly affect [drug exposure] and potentially alter clinical effects.").)

The resulting uncertainty of extrapolating from the prior art a dosing regimen involving a different dose amount and a different dosing interval is particularly important here, where Petitioner's predicted trough serum

concentrations of 10.9 to 21.1 µg/mL leave little margin for error.[9] (*See* Ex. 1021 at 49 ("Variability in half-life will influence variability in time above any specific plasma concentration. This is becoming increasingly well-recognized as an important factor in both toxicity and response."); *cf.* Ex. 1007 at 7-8 (reporting no anticancer effects for patients with subtherapeutic trough levels).) Petitioner provides no explanation for why a skilled artisan would ignore the prior art's warnings, including warnings from Petitioner's own expert, and administer a speculative dosing regimen based on oversimplified calculations that ignore the complexities of the prior art.

* * *

In sum, Petitioner has failed to show a reasonable likelihood that the challenged claims are obvious. The prior art references relied on by Petitioner describe and recommend ***weekly*** dosing, even when trastuzumab is administered as

[9] Even putting aside the non-linear kinetics of trastuzumab, the flaws in Petitioner's analysis are self-evident. Depending on which cherry-picked data points are used, Petitioner's expert predicts a widely different result. For example, Petitioner predicts a trough of 21.1 µg/mL based on selected data from Pegram '98 and Baselga '96 (Paper 1 at 36; Ex. 1003, Ratain Decl. ¶104) and 10.9 µg/mL based on the 1998 Herceptin® Label (Paper 1 at 39; Ex. 1003, Ratain Decl. ¶109).

part of a treatment that includes chemotherapy. Petitioner has thus failed to establish that the prior art teaches or suggests the limitations of the challenged claims. Petitioner has also failed to establish that a skilled artisan would have been motivated to pursue extended dosing regimens or would have reasonably expected success in doing so given the prior art's teaching that trastuzumab demonstrated non-linear kinetics.

C. This *Inter Partes* Review Proceeding Is Unconstitutional.

The Board should deny institution because this proceeding would violate Patent Owner's constitutional rights. Adversarial challenges to an issued patent—like inter partes reviews—are "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). Moreover, because patents are private property rights, disputes concerning their 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) ("The only authority competent to set a patent aside, or to annul it, or to correct it for any reason whatever, is vested in the courts of the United States, and not in the department which issued the patent."). 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. *Oil States Energy Servs., LLC v.*

Greene's Energy Grp., LLC, No. 16-712, 2017 WL 2507340, at *1 (U.S. June 12, 2017). Patent Owner presents this constitutional challenge now to preserve the issue pending the Supreme Court's decision.

VIII. CONCLUSION

For the reasons set forth above, the Board should decline to institute *inter partes* review of the challenged claims 1-3, 5, 7, 9-11, 13-28, and 30-40 of the '379 patent.

Respectfully submitted,

Date: July 6, 2017

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

Robert J. Gunther, Jr.
Pro Hac Vice Motion To Be Filed

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 Preliminary Response, contains 11,435 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: July 6, 2017

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

CERTIFICATE OF SERVICE

I hereby certify that, on July 6, 2017, I caused a true and correct copy of the following materials:

- Patent Owner's Preliminary Response
- Patent Owner's Exhibit List
- Exhibits 2001-2009

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

Cynthia Lambert Hardman
chardman@goodwinlaw.com
620 Eighth Avenue New York, NY 10018

Robert V. Cerwinski
rcerwinski@goodwinlaw.com
620 Eighth Avenue New York, NY 10018

Elaine Herrmann Blais
eblais@goodwinlaw.com
100 Northern Avenue Boston, MA 02210

/Rebecca 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
IPR2017-01140

Patent Owner's Exhibit Number	Exhibit Name
2001	Mark J. Ratain & Rosemarie Mick, *Chapter 7: Principles of Pharmacokinetics and Pharmacodynamics*, *in* PRINCIPLES OF ANTINEOPLASTIC DRUG DEVELOPMENT AND PHARMACOLOGY 123 (1996)
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	Sarfaraz Niazi, *Chapter 7: Pharmacokinetic Principles*, *in* TEXTBOOK OF BIOPHARMACEUTICS AND CLINICAL PHARMACOKINETICS 141 (1979)
2006	Johan Gabrielsson & Daniel Weiner, *Chapter 3: Pharmacokinetic Concepts, in* PHARMACOKINETIC AND PHARMACODYNAMIC DATA ANALYSIS 58 (2d ed. 1997)
2007	Malcolm Rowland & Thomas N. Tozer, *Chapter 22: Dose and Time Dependencies*, *in* CLINICAL PHARMACOKINETICS: CONCEPTS AND APPLICATIONS 394 (3d ed. 1995)
2008	Mark J. Ratain, *Therapeutic Relevance of Pharmacokinetics and Pharmacodynamics*, 19 (SUPPL. 11) SEMIN. ONCOL. 8 (1992)
2009	Gert Riethmüller, et al., *Monoclonal Antibodies in Cancer Therapy*, 5 CURRENT OPINION IN IMMUNOLOGY 732 (1993)