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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,
v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00805
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 the disease that afflicts tens of thousands of women in the U.S. each year. One of the first monoclonal antibodies shown to treat cancer, Herceptin's September 1998 approval by the Food and Drug Administration (FDA) followed extensive clinical trials. Based on the data from these clinical trials, some of which is reported in the prior art references cited by Petitioner (and co-authored by Genentech scientists), Genentech initially focused on and pursued approval of a weekly dosing regimen—a "loading dose" of 4 mg/kg of trastuzumab[1] followed by "maintenance doses" of 2 mg/kg administered weekly. The invention claimed in U.S. Patent No. 7,371,379 ("the '379 patent") 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 cited prior art would have rendered the extended-interval dosing schedule obvious because a skilled person would have been motivated to develop a more convenient regimen and could have done so with

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

routine calculation and optimization. But the flaw in Petitioner's argument is that it cannot be squared with the prior art or what really happened.

This is not a case where the Board needs to hypothetically inquire as to what a person of ordinarily skill in the art might have done in devising a dosing regimen for trastuzumab. We already know. Petitioner's obviousness challenge rests on two scientific publications reporting on clinical trials leading up to the initially approved weekly dosing regimen as well as the first FDA-approved label for Herceptin. All of the prior art information on which Petitioner relies was already known to the scientists and clinicians who were conducting clinical trials for Herceptin. Faced with the same information upon which Petitioner relies, these individuals pursued weekly dosing of Herceptin. If three-week dosing were as obvious as Petitioner claims it was, that regimen would have been pursued by Genentech at the outset. The fact that Genentech did not, when under Petitioner's rationale it had every incentive to do so, underscores the nonobviousness of the invention claimed in the '379 patent.

The reason that skilled artisans initially selected weekly dosing with Herceptin is clear—it was what the data supported. Taken together, the prior art references fail to provide the requisite motivation and expectation of success, and affirmatively contradict many assumptions upon which Petitioner's obviousness argument is based.

First, all three of the prior art references upon which Petitioner relies—the 1998 Herceptin Label (Ex. 1008), Baselga '96 (Ex. 1013), and Pegram '98 (Ex. 1014)—only describe ***weekly dosing*** of trastuzumab. None of these references suggests administering trastuzumab less frequently, let alone at intervals as long as the two to three weeks claimed in the '379 patent. This is hardly surprising given that the reported half-life of trastuzumab in these references ranged from 1.7 days at the lowest dose (10 mg) to 12 days at the highest dose (500 mg). Given that one approach to estimating dose interval is administering a drug once every half-life, these reported half-lives would have discouraged skilled persons from dosing trastuzumab every three weeks. Indeed, the Phase I dose-rising studies analyzed by Petitioner's pharmacokinetics expert were known to the extraordinarily skilled persons researching trastuzumab, who nevertheless determined that weekly dosing was "optimal." (*See, e.g.*, Ex. 1013 at 10.)

Second, the prior art does not articulate (or even hint at) the alleged desire for convenience upon which Petitioner's obviousness case rests. To the contrary, the prior art references focus on effectively treating a deadly cancer in patients for whom there had previously been little hope. Indeed, the absence of any reference to convenience in the prior art strongly suggests that, if considered by a skilled person at all in August 1999, it would have been secondary to efficacy. In any event, vague and conclusory observations about convenience untethered to the

prior art are insufficient to support Petitioner's claim. *See, e.g.*, *Novartis Pharm. Corp. v. Breckenridge Pharm., Inc.*, 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's argument that a more convenient dosing regimen could have been developed through "routine calculation and optimization" (Paper 1 at 27) is made possible only with the benefit of hindsight and contradicts the contemporaneous prior art. In August 1999, the pharmacokinetics of antibodies in general, and anti-ErbB2 antibodies in particular, were known to be unpredictable. For example, the prior art explicitly taught that trastuzumab is "dose dependent," which means that the rate at which the drug is cleared from the body depends on its concentration in the body. Such drugs are said to demonstrate non-linear kinetics, and as Petitioner's expert has acknowledged, it is more challenging to develop a dosing regimen for a drug with non-linear kinetics than for one with linear kinetics. This is because, for a drug with non-linear kinetics, several pharmacokinetic parameters commonly used to develop dosing regimens vary depending on the concentration of the drug in the bloodstream. Indeed, the primary textbook on which Petitioner's pharmacokinetics expert relies explains that such drugs "defy easy quantitative description and prediction." (Ex. 1022 at 3:109.) Yet Petitioner's

obviousness argument rests on the incorrect assumption that trastuzumab exhibits predictable, linear kinetics.

Finally, the Petition largely repeats arguments that were made and overcome during prosecution of the '379 patent and its parent, U.S. Pat. No. 6,627,196 ("the '196 patent"). Although Petitioner purports to anchor its arguments in a "new" reference—the 1998 Herceptin Label ("the Label")—the pharmacokinetic information upon which Petitioner relies was already before the Examiner during the prosecution of the '379 patent's parent in the form of the Goldenberg '99 reference. (*See infra* pp. 21-23 (comparing the Label with Goldenberg '99).) Indeed, in allowing the '196 patent claims to issue, the Examiner concluded that the prior art, including Goldenberg '99 and Baselga '96, "fails to teach or fairly suggest the recited minimum dosages and dosage schedules where the subsequent doses are separated from each other by at least 2 weeks." (Ex. 2012 at 145; *see also id.* at 130-31.) 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. (*See* Ex. 1024 at 266-70; *id.* at 227-38.) 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, the claimed dosing intervals of two and three weeks are not disclosed in the prior art, and the prior art does not provide any motivation to pursue the claimed dosing regimens. If it did, skilled clinicians would not have pursued the weekly dosing intervals used in the clinic. The conclusory opinions of Petitioner's experts that the invention involved nothing more than routine calculation and optimization ignore this historical reality and employ hindsight to arrive at the teachings set forth in the '379 patent. Based on these facts, the Examiner previously 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 the Examiner did not raise those same arguments again in the 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. 2001 at 310-11.) 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 311). 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." (*Id.* 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. Unlike conventional drugs for which initial dosing estimates can be inferred from their *in vitro* activity, therapeutic antibodies often mediate their effects through other components of the immune system (e.g., complement activation, ADCC, etc.) and this greatly complicates dose selection.

(Ex. 2004 at 11.)[2] Accordingly, a skilled person would consider many factors, including pharmacokinetics, when designing an alternative dosing regimen for trastuzumab.

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

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* Ex. 2005 at 7-8.) "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, which typically occurs before the next dose is administered.[3] (*See, e.g.*, Ex. 1003, Jusko Decl. ¶ 40 ("When a drug is administered repeatedly, the concentration of a drug rises to a peak after a dose is

[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 18:33-36.)

given, and falls to a trough just before the next dose is given."); Ex. 1001, 18:27-36.) 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. 1022 at 1:67-71.)

With respect to anti-ErbB2 antibodies, the prior art taught that maintaining certain trough serum concentrations was associated with efficacy in treating cancer. For example, the 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 seeking to develop alternative dosing regimens for trastuzumab would thus have understood that maintaining therapeutic trough concentration levels would be important to achieve efficacy. (*See, e.g.*, Ex. 1013 at 13-14; Ex. 1008 at 1.)

2. Trastuzumab was known to have dose-dependent (*i.e.*, non-linear) kinetics.

To determine whether a particular dosing regimen will sustain therapeutic trough concentrations, a pharmacokineticist must understand the kinetics of the drug at issue, including how quickly the drug is eliminated from the body after administration. 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. 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. For example, a skilled person could use the elimination rate to determine that extending a dose interval without increasing the dose amount would likely cause serum trough concentration to drop below the desired level, and thus compromise 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. 2006 at 179, 143; Ex. 1022 at 3:108-09.) 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 will remain constant, regardless of the concentration of drug in the body. (*Id.*) For dose-independent

drugs, the half-life[4] of the drug also remains constant regardless of concentration. (Ex. 2006 at 143.)

In contrast, drugs exhibiting dose-dependent kinetics are eliminated at different rates depending on the concentration of the drug in the body. (Ex. 2008 at 119-20; Ex. 2006 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. 2008 at 120-21; Ex. 2006 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." (*See* Ex. 2008 at 119; Ex. 2006 at 180-82.) 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 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. 2008 at 123-24.)

[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. 2006 at 145-46.) The faster a drug is eliminated from the body, the shorter the half-life. (*See, e.g.*, *id.* at 143-44.)

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. (*Cf.* Ex. 1022 at 3:109.) However, with drugs that exhibit dose-dependent pharmacokinetics, pharmacokinetic parameters change with the size of the dose administered or the dosing interval, when all other factors are held constant. (*Id.* at 3:108.) As a consequence, with "*dose-dependent kinetics*, ***any one or a combination of these parameters appears to change with administration of different doses***." (*Id.* at 3:109 (emphasis added).) As Petitioner's pharmacokinetics expert explained in a recent publication, nonlinear kinetics make direct comparisons of pharmacokinetic parameters of interest—including the "volume of distribution" parameter used in Petitioner's expert's analysis here—"difficult because these values change with dose when calculated by traditional methods." (Ex. 2009 at 1672-73.)

Developing dosing regimens for dose-dependent drugs is therefore more complex than developing dosing regimens for more predictable linear or dose-independent drugs. As Petitioner's pharmacokinetics expert explained in a textbook published in 2001, "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 at 519, 522.) Indeed, Petitioner's pharmacokinetics expert

has urged 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. (Ex. 2007 at 153.)

The prior art upon which Petitioner relies explicitly discloses that trastuzumab is dose-dependent and therefore exhibits non-linear kinetics. 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 (emphasis added); *see also* Goldenberg, Ex. 2001 at 312 ("Short-duration IV infusions of 10 to 500 mg once weekly showed ***dose-response kinetics***.") (emphasis added).) Similarly, 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. 1013 at 9.) This characterization is consistent with the prior art teaching that the half-life of trastuzumab varied with dose amount. For example, the Pharmacokinetics Section of the Label teaches that the half-life of 10 mg of trastuzumab administered weekly was 1.7 days, while the half-life of 500 mg administered weekly was 12 days. (Ex. 1008 at 1.) Given this information, a skilled person would expect trastuzumab to have non-linear kinetics and therefore would anticipate challenges in developing an appropriate dosing regimen.

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 a new, effective regimen for treating cancer with anti-ErbB2 antibodies. The new dosing regimens described in the '379 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; 57:31-46.) Before the invention, the only trastuzumab dosing regimens used to treat patients were weekly. (*See, e.g.*, Ex. 1008 at 1; Ex. 1013 at 9; Ex. 1014 at 8; Ex. 1015 at 5; Ex. 1016 at 32.) 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.)

The specification also provides important information about the drug'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 mean trough serum concentrations over the first eight weeks of treatment with weekly dosing. (Ex. 1001, 39:40-59.) Figure 3 provides additional information with respect to mean trough concentration

[5] Petitioner incorrectly questions the legitimacy of the invention because the patent specification does not contain clinical trial data specific to the claimed regimens. Clinical trial data is clearly not required to provide support for a claimed dosing regimen. *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 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).

over even a 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 Petition challenges claims 1-3, 5, 7, 9-11, 16-28, and 30-40 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 1 at 4.) 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. 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 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 subsequent doses, the time interval between the subsequent 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, 31, and 36 are directed to dosing intervals of at least three weeks. The remaining challenged claims (1-4, 7, 9, 16-28, 30, 32-35, and 37-40) require dosing intervals of at least two weeks.

IV. PETITIONER'S ASSERTED REFERENCES

As noted above, the references upon which Petitioner relies to support its obviousness claim describe only weekly dosing of trastuzumab. None of these references mention convenience or suggest less frequent dosing, even though the authors were aware of the data upon which Petitioner relies. The cited prior art also does not contain sufficient pharmacokinetic data to permit a skilled person to conclude 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—including half-life values—would have discouraged efforts to dose at the claimed two- or three-week intervals.

A. The 1998 Herceptin Label

1. The 1998 Herceptin Label does not suggest or support the claimed regimen.

The Label (Ex. 1008) describes 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; Ex. 2001 at 309–10, 314–15.)

The Label contains limited pharmacokinetic data. For example, the Label states that trastuzumab exhibited dose-dependent kinetics. (Ex. 1008 at 1; Ex. 2001 at 312 (noting trastuzumab exhibited "dose-response kinetics").) The Label

also reports a mean half-life of 5.8 days (range of 1 to 32 days) for regimens using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg. (Ex. 1008 at 1; Ex. 2001 at 309, 312-13.) The Label further indicates that in 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. (Ex. 1008 at 1; Ex. 2001 at 312-13.) No half-life is reported for doses between 10 and 500 mg.

The Label only refers to weekly dosing, and says nothing about the possibility of longer dosing intervals such as the claimed two- or three-week regimens. 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.

2. The information in the 1998 Herceptin Label was considered during prosecution of the '379 patent and its parent.

Petitioner's allegation that the pharmacokinetic information in the Label was not before the Examiner during prosecution (Paper 1 at 12-13, 27-28) is incorrect. All of the pharmacokinetic data in the Label that Petitioner deems "important" (Paper 1 at 12) was in Goldenberg '99, a reference specifically considered by the Examiner during prosecution of the '379 patent's parent, and again considered during prosecution of the '379 patent.

Both Goldenberg '99 and the Label report results of Phase II and Phase III trials where patients were administered trastuzumab at a 4 mg/kg loading dose followed by 2 mg/kg weekly maintenance doses. (Ex. 2001 at 309, 312-315; Ex. 1008 at 1.) Likewise, both references discuss trastuzumab's pharmacokinetics, safety and efficacy, prescribing information, and preclinical studies. (Ex. 2001 at 309, 311-316; Ex. 1008 at 1-2.) A comparison of the relevant pharmacokinetic information in Goldenberg '99 and the Label shows that the pharmacokinetic information Petitioner cites from the Label was before the Examiner in Goldenberg '99:

Goldenberg '99	1998 Herceptin Label
PHARMACOKINETICS The pharmacokinetic properties of trastuzumab have been studied in patients with metastatic breast cancer. Short-duration IV infusions of 10 to ***500 mg once weekly showed dose-response kinetics.*** That is, mean half-life increased and clearance decreased with increasing doses. ***The half-life averaged***	**Pharmacokinetics** The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to ***500 mg once weekly demonstrated dose-dependent pharmacokinetics***. Mean half-life increased and clearance decreased with increasing dose level.

Goldenberg '99	1998 Herceptin Label
1.7 and 12 days at the 10- and 500-mg doses, respectively. The volume of distribution was approximately equal to that of serum volume (44 mL/kg). At the highest weekly dose (500 mg) studied, mean peak serum concentrations were 377 μg/mL. In studies of trastuzumab using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, the ***mean half-life was 5.8 days (range, 1 to 32 days).*** Between weeks 16 and 32, trastuzumab serum concentrations reached steady-state with mean trough and peak concentrations of approximately 79 and 123 μg/mL, respectively.	***The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively.*** Trastuzumab's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377 microgram/mL. In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a ***mean half-life of 5.8 days (range = 1 to 32 days) was observed.*** Between weeks 16 and 32, Trastuzumab serum concentrations reached a steady-state with a mean trough and peak concentrations of approximately 79

Goldenberg '99	1998 Herceptin Label
(Ex. 2001 at 312–13 (emphasis added).)	microgram/mL and 123 microgram/mL, respectively. (Ex. 1008 at 1 (emphasis added).)

During prosecution of the '379 patent's parent, the '196 patent, the Examiner issued an obviousness rejection based, in part, on Goldenberg '99. (Ex. 2012 at 101-02.) The Examiner relied on Goldenberg '99 to teach administration of a weekly 10 to 500 mg dose of trastuzumab, concluding that range corresponded to "about 1.6 mg/kg and 8 mg/kg". (*Id.* at 101.) As set forth below, these rejections

were overcome.[7] (*See infra* pp. 29-33.) The Goldenberg reference was again considered during prosecution of the '379 patent but did not form the basis of a rejection. (Ex. 1024 at 267.)

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

Baselga '96 presents 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. 1013 at 9 (emphasis added).) Patients received a loading dose of 250 mg of trastuzumab followed by weekly doses of 100 mg. (Ex. 1013 at 10.) According to the authors, the weekly regimen was determined to be the "***optimal dose and***

[7] The Petition also refers to the Label's teaching that serum trough concentrations of trastuzumab were higher when the drug was administered with the chemotherapy agent paclitaxel (Petition at 12, 27), but does not explain the relevance of that disclosure to its obviousness position. In any event, Goldenberg discloses the administration of paclitaxel with trastuzumab (Ex. 2001 at 314-15) and Pegram '98, which was considered by the Patent Office, discloses elevated trough serum concentrations of trastuzumab when the drug is administered with the chemotherapy agent cisplatin. (*See* Ex. 1014 at 14, Table 6*; infra* pp. 30-31.)

schedule of rhuMAb HER2 … based on two prior phase I clinical trials…." (Ex. 1013 at 10 (emphasis added).) Baselga '96 notes that trastuzumab has "documented dose dependent pharmacokinetics" (*id.* at 10), and reports, for the weekly regimen tested, a mean serum half-life of 8.3 +/- 5.0 days (*id.* at 11).

Baselga '96 does not reference or suggest administering trastuzumab at any dose 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 (Ex. 1013 at 15), there is no mention or hint as to the desirability of administering trastuzumab on the same schedule as chemotherapy.

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

Pegram '98 (Ex. 1014) describes the results of a Phase II clinical study involving 39 patients with metastatic breast cancer who received trastuzumab in combination with a chemotherapeutic agent known as cisplatin. (Ex. 1014 at 11, Table 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 9-10.) 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.*) Despite involving administration of both trastuzumab and cisplatin, there is no discussion in Pegram '98 of convenience or whether to align the treatments such that both therapies are given on the same day. Notably, while Petitioner's expert Dr. Lipton now proffers the "convenience" theory in this proceeding, there is no mention of convenience at all in Pegram '98, even though Dr. Lipton is a co-author.

Pegram '98, like Baselga '96, provides only limited pharmacokinetic information on trastuzumab. Specifically, Table 6 of Pegram reports that trastuzumab had a mean half-life of 9.2 ± 5.3 days based on results from Baselga '96, and a half-life of 11.0 ± 4.0 days for patients treated with trastuzumab and cisplatin. (*Id.* at 14, Table 6.)

D. Pegram '95 And Vogel '98 Only Describe Weekly Dosing.

Cited in the Petition only as background, Pegram '95 (Ex. 1015) is a meeting abstract reporting early results of the same Phase II study discussed by Pegram '98. The abstract provides no pharmacokinetic information, and makes no mention or suggestion of any dosing regimen besides the initial 250 mg dose followed by a weekly 100 mg maintenance dose for eight weeks (along with cisplatin on days 1, 29, and 57). (Ex. 1015 at 5.)

Also cited in the Petition only as background, Vogel is a meeting abstract describing an ongoing clinical trial in which patients are being treated with a weekly dosing regimen of either (1) a 4 mg/kg loading dose and a weekly 2 mg/kg maintenance dose or (2) an 8 mg/kg loading dose and a weekly 4 mg/kg maintenance dose. (Ex. 1016 at 32.) Vogel provides no pharmacokinetic information or discussion regarding alterations in dosing frequency. (*Id.*)

V. PERSON OF ORDINARY SKILL

For purposes of this proceeding, Patent Owner does not dispute Petitioner's proposed definition of a person of ordinary skill. (Paper 1 at 23-24.)

VI. CLAIM CONSTRUCTION

Patent Owner requests that the Board construe "effective amount" in claims 1-3, 5, 7, 9-11, and 16-28 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 an 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.").[8]

VII. ARGUMENT

A. The Board Should Deny Institution Pursuant To 35 U.S.C. § 325(d).

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

[8] Petitioner's proposed construction for "ErbB2 receptor" incorrectly omits "c-Erb-B2." (*See* Paper 1 at 24 ("[T]he patent specification … states that 'the human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor (p185HER2) ….'" (quoting (Ex. 1001, 1:44-50); *see also* Ex. 1002, Lipton Decl. ¶ 23 (quoting the same).) Should the Board decide to construe "ErbB2 receptor," it should construe it consistent with the specification, which explicitly states that "[t]he terms 'HER2', 'ErbB2' '***c-Erb-B2***' are used interchangeably." (Ex. 1001, 9:52-53 (emphasis added).)

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 that primary reference and how it allegedly 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. 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 rehashes the same arguments already considered and rejected by the Patent Office during prosecution of the'379 patent's parent—the

very same arguments that the Patent Office chose not to raise during prosecution of the '379 patent.[9]

First, the Patent Office already twice-considered the substance of Petitioner's references. Petitioner alleges that pharmacokinetic information contained in the Label is critical to the obviousness analysis and that it was not considered during prosecution. (Paper 1 at 12-13, 27-28.) But as noted above, that is simply not true. The relevant pharmacokinetic information in the Label is ***identical*** to that in Goldenberg '99, a prior art reference that was overcome during prosecution of the '379 patent's parent and again considered during prosecution of the '379 patent. (*See supra* pp. 21-23; Ex. 1024 at 267.) Under such circumstances, the fact that the Label 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

[9] In the pending prosecution of U.S. Patent Application No. 14/073,659, a continuation application in a chain of applications in the '196 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. Genentech is disputing that rejection on substantially the same grounds set forth in this preliminary response.

significant, substantive difference" between the reference considered during prosecution and the reference cited in the petition). In addition, the Patent Office twice-considered both secondary references—Baselga '96 and Pegram '98. (Ex. 2012, '196 Patent Prosecution History Excerpts, at 89, 91; Ex. 1024, '379 Patent Prosecution History, at 266, 268). During prosecution of the '379 patent's parent, the applicants successfully overcame an obviousness rejection based on Baselga '96 (Ex. 2012 at 102-03, 145) and did not receive a rejection based on Pegram '98, though the reference was considered, (*id.* at 91).

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 30, 2003, shortly after the Examiner issued a notice of allowance for the '196 patent. (Ex. 1001; Ex. 2012 at 148-50.) 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. 1024 at 7-67 *and id.* at 72-82 *with* Ex. 2012 at 1-47, 58-64 *and id.* at 86-92, 122.). Having already concluded that claims to two- or three-week dosing intervals were patentable over Baselga '96 and Goldenberg '99, the Examiner allowed the claims that included such limitations. (Ex. 1024 at 419-20.)

Second, Petitioner's arguments merely rehash arguments the Patent Office has already heard. For example, Petitioner makes the same argument the Examiner

considered during prosecution of the '196 patent—that the extended dosing schedule of chemotherapy agents used in combination with trastuzumab would provide a motivation to find a similarly less frequent dosing schedule for trastuzumab. (*Compare* Paper 1 at 26-27 *with* Ex. 2012 at 101-02.) Much as Petitioner argues here, the Examiner reasoned that "[t]he prior art also teaches that docetaxel, a drug that is used together with Herceptin®, is often administered on a 3-weekly schedule . . . thus providing a motivation to find a dosage schedule that was less frequent tha[n] a weekly schedule for Herceptin®." (Ex. 2012 at 101-02.) 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 117-18, 130.) 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 145 (emphasis added).)

The Examiner also considered Petitioner's argument that it would have been obvious to optimize a known dosing regimen through routine experimentation in view of the higher dosage levels and the half-lives taught in the prior art.

(*Compare* Paper 1 at 27-28, *with* Ex. 2012 at 106, 126.) In particular, the Examiner relied on Goldenberg '99 to teach administration of weekly 10 to 500 mg doses of trastuzumab, concluding that the range corresponded to "about 1.6 mg/kg and 8 mg/kg." (Ex. 2012 at 101.) But the applicants overcame this argument as well, with the Examiner concluding that the prior art did not teach or suggest the claimed dosages and dosing schedules. (*Id.* at 145.)

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. There is no reason to revisit these arguments again 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 Would Have Been Obvious Over The 1998 Herceptin Label In View Of Baselga '96 And Pegram '98.

Petitioner's obviousness argument is a textbook case of hindsight-driven analysis. At every turn, Petitioner chooses the path leading to the claimed invention even when the prior art points in a different direction. First, the prior art does not disclose or even suggest dosing intervals of more than one week; indeed, the prior art disclosures with respect to the half-life of trastuzumab would have discouraged a skilled person from pursuing an extended interval regimen. Second, the utter absence of any reference to convenience in the prior art fatally undermines Petitioner's motivation argument and cannot be cured with conclusory

expert testimony. Third, Petitioner's alleged "reasonable expectation of success" cannot be reconciled with the explicit teachings in the prior art that trastuzumab exhibits dose-dependent/non-linear kinetics, a phenomenon that "def[ies] easy quantitative description and prediction." (Ex. 1022 at 3:109.)

The Federal Circuit has consistently rejected this 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 claimed invention. *Id.* at 1311-13; *see also W.L. Gore & Associates, 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 experts have done here. 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 prior art did not disclose or suggest administration of "doses separated in time from each other by at least two weeks" or "at least three weeks."

At the time of the claimed inventions in August 1999, the only approved dosing of trastuzumab was weekly. The prior art consistently taught that weekly dosing was not only "recommended," but "optimal." Each and every one of the references that Petitioner cites discloses nothing longer than a weekly dosing interval with trastuzumab. Nor do any of the prior art references refer in any way to the possibility—let alone the likely success—of the extended intervals in the claims.

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 doses. (*See, e.g.*, Ex. 1022 at 32:22.) ***All*** of the challenged claims require an interval of "at least two weeks;" and claims 5, 10, 11, 25, and 30 specifically require an interval of "at least three weeks." But the asserted obviousness ground in the Petition is based entirely upon references that describe only ***weekly*** dosing. 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); *see also infra* pp. 40. Nor does Petitioner's 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 Petitioner 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. (*See supra* pp. 19-27.) And unlike in *BioMarin*, the prior art at issue here expressly teaches that trastuzumab exhibits dose-dependent kinetics that defy predictability, and that a weekly regimen was the "optimal" regimen. (*See infra* pp. 47-51.)

2. Petitioner's articulated motivation has no basis or support in the prior art.

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

Petitioner's theory that a three-week dose interval would have been obvious in view of the available data not only lacks basis in the prior art; it is directly contradicted by what skilled artisans actually concluded at the time: ***weekly*** dosing was the optimal schedule.

First, the same convenience factors that allegedly would have motivated skilled persons in August 1999 (Ex. 1002, Lipton Decl. ¶¶ 38-45) existed well before the priority date, when the studies reported in Baselga '96, Pegram '98 and the Label were conducted. Trastuzumab was being administered with chemotherapy agents that had three-week dosing regimens, and the same generic patient concerns described in Dr. Lipton's declaration existed. Yet, Petitioner cites no information to indicate that skilled artisans would have viewed convenience differently in August 1999 than at the time the prior art studies were conducted. If anything, the FDA's September 1998 approval of a safe and effective *weekly* dose regimen would point away from the claimed extended dose interval.

Second, the same Phase I dose-rising trials analyzed by Petitioner's expert were already known to the extraordinarily skilled individuals who conducted the

early clinical trials on trastuzumab that are reported in Baselga '96, Pegram '98 and the Label. (Ex. 1013 at 10; Ex. 1008 at 1; Ex. 1003, Jusko Decl. at ¶ 48.) But unlike Petitioner's expert, the authors of Baselga '96 ***did not*** opt for a three-week dose interval. The Baselga '96 authors studied the "optimal dose and schedule" of 250 mg loading dose followed by 100 mg weekly doses. (*See* Ex. 1013 at 10; Ex. 1008 at 1 (describing Phase I studies).) Given the unpredictability associated with dose-dependent kinetics, it is not surprising that Baselga '96—like Pegram '98 and ultimately the Label—moved forward with a weekly regimen.

b. Not a single prior art reference expresses any motivation to develop a dosing regimen based on convenience.

Petitioner asserts that convenience, and a desire to avoid frequent injections and hospital visits, would have led a person of skill in the art "to have tried decreasing the frequency of rhuMAb HER2 injections to every three weeks (tri-weekly) to match the schedule of chemotherapy." (Paper 1 at 26.) But it is only with hindsight that Petitioner can make this argument, as no prior art reference suggests a skilled person would have been motivated to change an approved dosing regimen for cancer therapy based on these "convenience" factors. Say-so is simply not enough to carry the day in an obviousness challenge. *See, e.g.*, *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)).

First, 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 simply presents results from the weekly administration of trastuzumab. And while the Label and Pegram '98 report studies where trastuzumab was administered in conjunction with a multi-week chemotherapy dosing regimen (Ex. 1008 at 1; Ex. 1014 at 8), there is no hint in those references that the therapies should be administered on the same schedule or even on the same day. Indeed, far from suggesting that "convenience" would motivate aligning trastuzumab dosing with a chemotherapy, Pegram '98 suggests the exact opposite as it discloses that trastuzumab was dosed on ***different*** days than when the chemotherapy agent was administered. (*See* Ex. 1014 at 9 (describing administration of cisplatin the day after trastuzumab, even when the two drugs were administered during the same week).) And this is the case even though the factors Petitioner's expert now claims would drive patient convenience and satisfaction would have been well known to the authors of the prior art. (*See, e.g.*, Ex. 1002, Lipton Decl. ¶¶ 38-45). Indeed, the prior art not only fails to express any desire for less frequent dosing, but describes weekly dosing as "optimal." (Ex. 1013 at 10.)

Second, the gaps in the prior art cannot be cured with generalized and conclusory expert opinions 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., Inc. v. Novartis AG*, IPR2016-01461, Paper 9 at 10 (Feb. 13, 2017); *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). In addition, generic assertions of "convenience" cannot substitute for evidence that a skilled artisan would have known the extended dosing regimens to be safe and effective. *Nuvasive*, 842 F.3d 1376 at 1383. 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 his own article, Pegram '98, which teaches administering chemotherapy the day after trastuzumab treatment. (*Compare* Ex. 1002, Lipton Decl. ¶ 63, *with* Ex. 1014 at 10.)

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 *1011. 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 the 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 even though there is no evidence in the prior art that a skilled artisan would risk reducing the efficacy of a life-saving drug for the sake of convenience.

Indicative of the fact that Petitioner has no evidence that convenience would motivate changing an established safe and effective dosing regimen, Petitioner attempts to reach beyond the relevant art to cite to expert testimony of one of the named inventors given in a different proceeding. (Paper 1 at 27-28 (citing Ex. 1017).) This is spurious. That declaration involves a different invention, different prior art, a different therapeutic field, and a different relevant time period and is thus irrelevant to what would have motivated skilled persons with respect to the inventions at issue here.

In sum, Petitioner's alleged motivation, untethered to the asserted prior art, 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); *see also Ortho-McNeil Pharm*, 520 F.3d at 1364 ("it is always inappropriate" to fail to consider the art as a whole when evaluating obviousness).

c. The half-life data reported in the prior art would have discouraged a skilled person from treating breast cancer by dosing at extended intervals.

Petitioner also argues that a skilled artisan would have been motivated to use a three-week dosing regimen in view of trastuzumab's "known pharmacokinetic properties," citing to its expert's declaration. (Paper 1 at 36-37.) However, the declaration does not explain precisely what pharmacokinetic properties of trastuzumab would have motivated a person of skill to try the extended dosing intervals, let alone three-week dosing. (*See* Ex. 1003, Jusko Decl. ¶ 67.)

This is not surprising given that the prior art taught information about half-life that is incompatible with three-week dosing. When evaluating a potential change in dose, skilled artisans often look to the reported half-life of a drug to predict whether extending the dosing regimen would be safe and effective. (*See*

e,g., Ex. 2007 at 149 (explaining that administering a maintenance dose "every half-life … should maintain a desired steady-state commencing with the first dose"); *id*. at 152 ("half-life: dosage interval can generally be extended in relation to half-life").) A skilled artisan would doubt that efficacy would be maintained at intervals substantially greater than the reported half-life. (*See id.*; *cf.* Ex. 2006 at 145 ("Since most drugs require a minimum effective concentration in the plasma, a drug which is eliminated quickly requires more frequent dosing than a drug with a long half-life.").) Here, the prior art did not report a half-life for trastuzumab that would have led a skilled artisan to expect success with a three-week dosing regimen.

The reported half-life for trastuzumab in Petitioner's references ranges from 1.7 days at the lowest (10 mg) dose tested to 12 days at the highest (500 mg) dose. Moreover, the Label reports a mean half-life 5.8 days (range of 1 to 32 days) for regimens using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg. (Ex. 1008 at 1.) Baselga '96 reports a half-life of 8.3 ± 5.0 days. (Ex. 1013 at 11.) Pegram '98 reports a half-life of 9.2 ± 5.3 days in some subsets of patients and 2.9 ± 3.2 days in other subsets of patients. (Ex. 1014 at 14.) None of these reported half-lives come close to supporting a 21-day dose interval with an 8 mg/kg loading dose and 6 mg/kg maintenance dose.

On the contrary, these reported half-lives would have led a skilled artisan to doubt that efficacy could be maintained while extending the dose interval to three weeks.

d. The prior art does not lead to the claimed dosing regimen.

None of the prior art referenced in the asserted grounds 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 engages 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 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 Petitioner appears to 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 and the dose "had been successfully administered to patients" (Paper 1 at 31), Petitioner ignores that the 500 mg half-life was reported based on ***weekly*** dosing, not extended dosing. *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 produce the claimed invention.'" (citing *Ortho-McNeil Pharm.*, 520 F.3d at 1358)).

To overcome the deficiencies in the prior art, Petitioner argues that selecting from a known range is "conventional" activity. (*See, e.g.*, Paper 1 at 25-26, 31-33, 47-48, 49.) But the cases on which Petitioner relies 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.

Here, Petitioner's argument that there was a "range" of overlapping dose regimens in the prior art (*see, e.g.*, Paper 1 at 31-33) ignores the key fact that the only dosing interval disclosed was weekly. Petitioner cannot manufacture a "range" without basis. The range must already exist in the prior art, something that it is indisputably not present here. Again, this type of hindsight analysis is fatal. *See Zoltek Corp.*, 815 F.3d at 1311-13; *see also 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).

Even more fundamentally, designing effective antibody dosing regimens for cancer treatment is ***not*** a predictable art. This was certainly the case with trastuzumab—a first-in-class antibody with documented dose-dependent kinetics. Indeed, at the time of the invention, selecting an antibody dosing regimen for clinical use was described as a "complicated task" and "largely an empiric science." (Ex. 2004 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. (*See supra* pp. 6-7.) As a result, Petitioner's 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].").

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

Based on the incorrect assumption that a skilled person would be motivated to dose trastuzumab every three weeks, Petitioner ignores what was known about the pharmacokinetic properties of trastuzumab to support its claim that developing an extended dosing regimen would be "routine." (Paper 1 at 36-42; Ex. 1003, Jusko Decl. ¶¶ 46-67.) Petitioner's approach rests on the fundamentally flawed assertion, contrary to the prior art, that a skilled person would assume that trastuzumab exhibits linear, dose-independent kinetics. Petitioner's failure to address the complexity of the prior art—including the explicit teaching that trastuzumab exhibits dose-dependent kinetics—is fatal. *See Ortho-McNeil Pharm.,* 520 F.3d at 1364 (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.***" (emphasis added)).

In rendering his opinions, Petitioner's expert erroneously assumed that trastuzumab exhibits linear kinetics, *i.e.*, that the pharmacokinetic properties of trastuzumab remain constant with changes in dose amount or dose interval. (*See, e.g.*, Ex. 1003, Jusko Decl. ¶ 71(assuming kinetics of trastuzumab "remain constant with multiple dosing"); *id.* at ¶ 60 (deriving dose amounts based on "linear" kinetics).) This assertion contradicts the teaching of the prior art and ignores the

true complexity of developing an alternative therapeutic dosing regimen for trastuzumab.

The prior art unequivocally describes trastuzumab as exhibiting dose-dependent kinetics. Baselga '96 explains that trastuzumab displayed "dose-dependent kinetics" in Phase I clinical trials. (Ex. 1013 at 9.) The Label states the same, reporting that:

> Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated ***dose-dependent*** pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life average 1.7 and 12 days at the 10 and 500 mg dose levels, respectively.

(Ex. 1008 at 1 (emphasis added); *see also* Ex. 2001 at 312-13.) The teaching that trastuzumab's clearance and half-life vary as the dose increases directly contradict Petitioner's assumption of linear kinetics. (*See, e.g.*, Ex. 2008 at 123 ("The half-life is a function of plasma concentration for the nonlinear system."); Ex. 2006 at 143 (noting that "half-life is independent of the dose administered" for "first order processes").)

There can be no dispute that a skilled artisan developing a cancer treatment regimen in 1999 would take account of the teaching that a drug was dose-

dependent. Indeed, Petitioner's expert himself has explained that dose-dependent kinetics do not "remain constant with multiple dosing" and that dose-dependent kinetics is a form of non-linear kinetics. (Ex. 2011 at 669-70 (describing dose-dependence as a form of non-linear kinetics); *see also* Ex. 1022 at 3:109 (noting that dose dependent kinetics is a type of non-linearity); Ex. 2006 at 181 ("Nonlinear pharmacokinetics are also called DOSE-DEPENDENT pharmacokinetics.").) The very same prior art textbook on which Petitioner relies confirms that drugs with "dose-dependent … kinetic behavior[] defy easy quantitative description and prediction." (Ex. 1022 at 3:109.) Indeed, Petitioner's expert himself has advised 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. (Ex. 2007 at 153.) An expert opinion that is inconsistent with the teachings of the prior art is insufficient to support an obviousness determination. *See, e.g.*, *Ortho-McNeil Pharm*, 520 F.3d at 1364.

Without the incorrect assumption of linear kinetics, Petitioner's "routine optimization" argument falls apart. The equations upon which Petitioner relies to predict serum trough concentrations with the claimed three-week dosing regimen incorrectly assume linear, dose-***in***dependent kinetics. (*Compare, e.g.*, Ex. 1003, Jusko Decl. at ¶ 46 (equation (1)) *with* Ex. 1022 at 1:34 (describing the same

equation as indicative of why elimination of "most … drugs" is linear) *and id.* at 1:44 ("The possibility for a change with dose exists … and these are dealt with in Chap. 22 under the title of Dose and Time dependencies," but "[t]hroughout the majority of the book … pharmacokinetic parameters are assumed ***not to change with either dose or time***.") (emphasis added); *see also* Ex. 1003, Jusko Decl. ¶ 60 (explicitly assuming linear kinetics).)

Petitioner's assumption of linear kinetics ignores the complexity and uncertainty that existed with respect to trastuzumab at the time of the invention. For example, Petitioner's expert assumes that the observed 12-day half-life from weekly administration of 500 mg trastuzumab reported in the Label will remain constant when the dose interval is tripled from one week to three weeks. But as explained above, with dose-dependent kinetics, the half-life and the rate at which the drug is eliminated from the body changes as the concentration of the drug changes. Thus, after week one, the drug remaining in the body would be eliminated at a different rate. There is thus no basis to assume that the drug's half-life would remain constant over time. (*See supra* pp. 11-14.) Indeed, the disclosure of dose-dependency in the prior art suggests it would not.

Petitioner compounds its flawed assumptions about how 500 mg dosed every three weeks would be eliminated from the body by assuming that a larger dose—*i.e.*, 712 mg—would behave the same way. (Paper 1 at 40-42, 44, 47; Ex.

1003, Jusko Decl. ¶¶ 59-66.) But given the teachings in the prior art that trastuzumab exhibits dose-dependent kinetics, one of ordinary skill in the art would have had no reason to assume that a 712 mg dose will behave the same as a 500 mg dose. As the concentration of a dose-dependent drug changes, so too does its elimination rate and corresponding half-life. (*See supra* pp. 11-14.) And the changes may defy easy quantification and prediction. (Ex. 1022 at 3:109.)

C. Foreign Proceedings Are Not Relevant.

Petitioner's reference to proceedings regarding a European counterpart to the '379 patent is of little relevance in this matter, insofar as that proceeding did not involve the patent at issue in this proceeding and was not decided under U.S. law. *See Smith & Nephew v. ConvaTec Techs. Inc*., IPR2013-00097, Paper 76 at 3 (Feb. 24, 2014) (explaining that a decision from the European Patent Office relating to a foreign counterpart "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").

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, 16-28, and 30-40 of the '379 patent.

Respectfully submitted,

Date: May 4, 2017

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response, contains 11,216 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: May 4, 2017

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CERTIFICATE OF SERVICE

I hereby certify that, on May 4, 2017, I caused a true and correct copy of the following materials:

- Patent Owner's Preliminary Response
- Patent Owner's Exhibit List
- Exhibits 2001-2012

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

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PATENT OWNER'S EXHIBIT LIST
IPR2017-00805

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)
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)

Patent Owner's Exhibit Number	**Exhibit Name**
2012	Excerpt of Certified File History for U.S. Patent No. 6,627,196 (full Certified File History at IPR2017-00804 (Ex. 1024))