2019-1173, -1174

United States Court of Appeals for the Federal Circuit

SAMSUNG BIOEPIS CO., LTD.,

Appellant,

– v. –

GENENTECH, INC.,

Appellee.

On Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2017-00804, IPR2017-00805, IPR2017-01958 and IPR2017-01959

BRIEF FOR APPELLANT

DIMITRIOS T. DRIVAS
STEFAN MENTZER
AMIT THAKORE
SCOTT T. WEINGAERTNER
WHITE & CASE LLP
1221 Avenue of the Americas
New York, New York 10020
(212) 819-8200
ddrivas@whitecase.com
smentzer@whitecase.com
athakore@whitecase.com
sweingaertner@whitecase.com

Counsel for Appellant

MARCH 21, 2019

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, Counsel for Appellant certify the following:

1. The full name of the party represented by me is:

Samsung Bioepis Co., Ltd.

2. The name of the real party in interest represented by me is:

Same as above.

3. All parent corporations and publicly held companies that own 10% or more of the stock in the party represented by me are:

Samsung BioLogics Co., Ltd.

Biogen, Inc.

4. The names of all law firms and the partners or associates that appear for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

Eric M. Majchrzak*, WHITE & CASE LLP.

5. The titles and numbers of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal are:

***Genentech, Inc. v. Samsung Bioepis Co., Ltd.*, No. 1:18-cv-01363 (D. Del. filed Sept. 4, 2018).**

***Genentech, Inc. et al. v. Amgen, Inc.*, No. 1-18-cv-00924 (D. Del. filed June 21, 2018).**

Dated: March 21, 2019

/s/ Stefan Mentzer
Stefan Mentzer
Counsel for Appellant
Samsung Bioepis Co., Ltd.

* Attorney has since left the firm.

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, counsel for Appellant Samsung Bioepis Co., Ltd., certify that, to their knowledge, no appeal from this civil action was previously before this or any other appellate court.

There are two district court cases currently pending that involve U.S. Patent Nos. 7,371,379 and 6,627,196: (1) *Genentech, Inc., et al. v. Samsung Bioepis Co., Ltd.*, No. 1:18-cv-01363 (D. Del. filed Sept. 4, 2018), and (2) *Genentech, Inc. et al. v. Amgen, Inc.*, No. 1-18-cv-00924 (D. Del. filed June 21, 2018).

JURISDICTIONAL STATEMENT

The Patent Trial and Appeal Board (the "Board") asserted jurisdiction under 35 U.S.C. § 6. The Board entered a final written decision in consolidated reviews IPR2017-00804 and IPR2017-01958 regarding U.S. Patent No. 6,627,196 (the "'196 patent") on October 3, 2018. The Board entered a final written decision in consolidated reviews IPR2017-00805 and IPR2017-01959 regarding U.S. Patent No. 7,371,379 (the "'379 patent") on October 3, 2018.

On November 7, 2018, Appellant Samsung Bioepis Co., Ltd. ("Bioepis") timely filed a notice of appeal for both final written decisions. This Court has jurisdiction over this appeal pursuant to 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. § 319.

ISSUES PRESENTED

1. Whether the Board's finding that a person of ordinary skill in the art ("POSA") would have had no reasonable expectation of success in extending the dosing regimen of trastuzumab from weekly to once every two or three weeks is supported by substantial evidence, where (a) the prior art taught that higher doses of trastuzumab (500 mg) were safe and effective and resulted in a longer half-life and decreased clearance of the drug from the body over time, (b) higher doses of therapeutic antibodies and similar target-mediated drugs generally were known to have longer half-lives and decreased clearance from the body over time, and

(c) well-known pharmacokinetic modeling could predict that at three weeks the trough serum concentration level of trastuzumab in the body would be far above the minimum levels reported in the prior art as required for efficacy.

2. Whether the Board's finding that *two*-week administration of trastuzumab was not obvious is supported by substantial evidence, where (a) the Board failed to comply with the Administrative Procedures Act ("APA") by failing to provide an articulated, reasoned explanation for its conclusion that claim 1 and related claims to administration of trastuzumab every two weeks, rather than weekly, are not obvious, and (b) where the prior art taught that a 500 mg dose was safe and effective and that the half-life of trastuzumab at this dose was 12 days.

STATEMENT OF THE CASE

I. Preliminary Statement

The '196 and '379 patents relate to improved dosing regimens for the drug trastuzumab used to treat cancers characterized by the overexpression of the protein ErbB2 (also known as "HER2"). Trastuzumab, also known as rhuMAb HER2, is a recombinant, humanized monoclonal antibody and is sold by the Patent Owner Genentech, Inc. ("Genentech") under the tradename Herceptin®. The FDA approved trastuzumab on September 25, 1998 to treat patients with ErbB2-overexpressing metastatic breast cancer.

By August 27, 1999, the patents' earliest effective filing date, trastuzumab had been sold by Genentech for almost a year. The FDA-approved prior-art dosing regimen at that time was a 4 mg/kg initial "loading dose" administered as a 90-minute intravenous infusion, followed by weekly "maintenance doses" of 2 mg/kg, which could be administered as 30-minute intravenous infusions if the initial loading dose was well-tolerated. The patents' claims are directed to "greater front loading" of the drug and less frequent subsequent dosing, such that the patient receives an initial dose of 5 mg/kg or greater, followed by a plurality of maintenance doses in an equal or lower amount, where the subsequent doses are separated in time from each other by at least two or three weeks.

Bioepis is a biosimilar developer that has recently obtained FDA approval to market its trastuzumab biosimilar product in the United States. Bioepis challenged various claims of the patents in two *inter partes* review proceedings. The Board found that Bioepis had not shown by a preponderance of the evidence that the challenged claims are unpatentable for obviousness. Specifically, the Board found that while skilled artisans would have been motivated to extend the dosing interval to three weeks, they would not have had a reasonable expectation of success in doing so based on the prior art.

The Board's finding is not supported by substantial evidence. The prior art demonstrates that, as a matter of routine optimization, a POSA would have applied

a well-known pharmacokinetic model and textbook equations to Genentech's own disclosure that 500 mg doses were safe and effective and would have predicted that such doses administered at three-week intervals would work. There is no prior art to the contrary. Moreover, the Board failed to separately address the obviousness of claims to two-week administration of trastuzumab, which are also obvious in view of the prior art.

II. Relevant Pharmacokinetic Principles

The patent claims at issue here are straightforward, as are the fundamental pharmacokinetic principles that would have been understood and used by a POSA given the information available on trastuzumab in the prior art.

Pharmacokinetics is the study of how a person's body absorbs, distributes, metabolizes, and excretes a drug over time. Appx00545.[1] Pharmacologists measure drug concentration in blood, tissues, and excreta to obtain serum concentration values, including maximum and minimum levels, for each drug dose. *Id.* This information is used to understand the extent and duration of time the drug remains in the body. Appx00545-00546.

[1] The Board joined IPR2017-01958 with IPR2017-00804 and IPR2017-01959 with IPR2017-00805. The records in the two consolidated reviews are substantially identical. For convenience, all record cites are to the Appendix in IPR2017-00804, except where otherwise noted.

A drug's half-life is a commonly reported pharmacokinetic parameter. Appx00546. A "half-life" is the time required for the serum concentration level of a drug in the blood to reach half of any previously selected concentration, such as the concentration shortly after a dose is delivered. *Id.* A drug's half-life was routinely used to develop an appropriate dosing regimen for the drug (i.e., what dosage amounts and dosing intervals would likely be efficacious) and to model multiple-dose treatment regimens. *Id.*; Appx01075.

The treatment of chronic diseases, such as cancer, usually requires long treatment periods and multiple doses of therapeutic drugs. Appx00546. When a drug is administered repeatedly, its concentration level rises to a "peak" shortly after a dose is given and falls to a "trough" just before the next dose is given. *Id.* The concentration in the body eventually approaches a "steady-state," i.e., a plateau of consistent peak and trough values. Appx00546-00547. For such repeat dosing, a higher initial dose – or "loading dose" – was commonly used to reach steady-state more rapidly. Appx00547. The loading dose would then be followed by "maintenance doses" that are the same as or less than the amount of the loading dose.

Pharmacokinetic models are mathematical equations that can be used to predict the concentration of a drug that remains in the body after a given period of time. Appx00543-00544. Compartmental models are one type of theoretical

pharmacokinetic model. Appx00544. The one-compartment model was commonly used in clinical medicine. *Id.* Both one-compartment and two-compartment models were used in the prior art for therapeutic antibodies. *See, e.g.,* Appx14775. In a one-compartment model, the drug is modelled as distributing throughout the body, i.e., the "compartment," after an intravenous injection. Appx16372. In a "two-compartment model," the drug is modelled as diffusing from a central compartment (i.e., blood) to a peripheral compartment where it is subsequently eliminated from the body. *Id.* The choice of model is determined by the available data. Appx00544. For a one-compartment model, there are basic textbook equations used by pharmacologists to estimate an appropriate loading dose and dosing intervals. Appx00549-00555, Appx00559.

III. The Patents

The '196 and '379 patents share the same specification and claim priority to the same application filed August 27, 1999. Both patents claim methods of treating disorders characterized by the overexpression of HER2, a receptor known to be associated with cancer. The patents differ only in that the claims of the '379 patent all require the extra step of "administering an effective amount of a chemotherapeutic agent."

The purported invention of the '196 and '379 patents was "greater front loading," i.e., providing a higher initial dose of trastuzumab than the prior art

4 mg/kg dose, and longer dosing intervals, i.e., every two or three weeks. Appx00343 (4:21-26; 4:46-49). According to the patent, "[t]he front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment." Appx00344 (5:5-8).

The specifications contain no data for the claimed dosing regimens. Although the claims require administering an initial dose of "at least approximately 5 mg/kg," the patents contain no data or explanation as to whether it resulted in any unexpected benefit over the prior-art dosing regimen. Similarly, although the claims require subsequent doses "separated in time from each other by at least two weeks," the patents contain no data on that dosing regimen or any explanation as to how this length of time was determined. The patents contain no experimental data for *any* dosing regimen in humans other than the prior art "weekly" regimen. *See* Appx00345 (8:33-39), Appx00338 (Fig. 3).

All of the examples for the claimed dosing regimens are prophetic. Example 5 proposes various dosing regimens, including an 8 mg/kg initial dose followed by 6 mg/kg maintenance doses every three weeks, and predicts that the regimen will maintain a desired trough serum concentration. Appx00363-00364 (43:39-45:32). Example 6 similarly describes a proposed clinical trial in which patients would be administered an 8 mg/kg initial dose followed by 6 mg/kg

maintenance doses every three weeks, in combination with paclitaxel every three weeks, Appx00364-00365 (46:9-48:14), and states that "[i]t is *believed* that the above treatment regimen will be effective in treating metastatic breast cancer," Appx00365 (48:1-2) (emphasis added). The patent provides no data to support either of those predictions.

A. The '196 Patent

Claim 1 of the '196 patent covers a loading dose of "at least approximately 5 mg/kg" followed by maintenance doses in the same or lower amounts administered every two weeks:

> 1. 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 at least approximately 5 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 the subsequent doses are separated in time from each other by at least *two weeks*.

Appx00369-00370 (emphasis added).

Claims depending from claim 1 cover different dosage amounts for the initial and subsequent doses, as well as different dosing time intervals. *Id.* For

example, dependent claims 2-4 cover the same two-week dosing interval with different loading and maintenance dosage amounts. *Id.* Of the challenged claims, claims 5, 10, 11, and 30 cover three-week administration of the subsequent doses, and the remaining claims cover two-week dosing intervals. *Id.*

B. The '379 Patent

Claim 1 of the '379 patent is to a loading dose of "at least approximately 5 mg/kg" followed by maintenance doses in the same or lower amounts administered every two weeks, coupled with another chemotherapeutic agent.

> 1. 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 at least approximately 5 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 the subsequent doses are separated in time from each other by at least *two weeks*; and
> >
> > further comprising administering an effective amount of a chemotherapeutic agent to the patient.

Appx18613 (emphasis added). As with the '196 patent, other claims of the '379 patent cover various dosage amounts for the loading and maintenances doses, as well as different dosing intervals. Appx18613-18614. Of the challenged claims,

claims 5, 10, 11, and 36 cover three-week administration of the subsequent doses, and the remaining claims cover two-week dosing intervals. *Id.*

IV. The *Inter Partes* Reviews

A. Procedural Background

On January 30, 2017, Hospira, Inc. ("Hospira") filed two Petitions for *Inter Partes* Review, one challenging claims 1-3, 5, 7, 9-11, and 17-33 of the '196 patent (IPR2017-00804) and the other challenging claims 1-3, 5, 7, 9-11, 16-28, and 30-40 of the '379 patent (IPR2017-00805). Appx14980, Appx22483. On July 27, 2017, the Board instituted reviews in the Hospira proceedings. Appx15390, Appx23047. On August 25, 2017, Bioepis filed two Petitions for *Inter Partes* Review challenging the same claims, IPR2017-01958 and IPR2017-01959, and moved to join the proceedings with IPR2017-00804 and IPR2017-00805, respectively. Appx26147, Appx40946. The Board granted Bioepis's motion for joinder on December 1, 2017. Appx40938, Appx45075. The Board issued its Final Written Decisions on October 3, 2018 in both consolidated reviews. Appx00001, Appx00040. Hospira and Bioepis timely appealed. On December 7, 2018, Hospira withdrew from these appeals. Appeal Dkt. 31.

B. The Petitions

1. The Asserted Prior Art

In support of their petitions for *inter partes* review, Petitioners submitted Baselga '96, Pegram '98, the Herceptin® Label, Pegram '95 and Vogel '98 as prior art to the '196 and '379 patents.

(a) Baselga '96

Baselga '96[2] reported the results of a phase II clinical trial in which 46 patients with ErbB2-overexpressing metastatic breast cancer were treated with trastuzumab. Appx00873. Each patient received a 250 mg loading dose, followed by ten weekly 100 mg doses. *Id.* The objectives of the trial were to determine the antitumor activity of trastuzumab, and to define further its toxicity profile and pharmacokinetics. Appx00874. The clinical trial was successful. "Toxicity was minimal," Appx00873, treatment was "remarkably well tolerated," and no immune response against the antibody was detected, Appx00875.

The pharmacokinetic goal of the trial was to achieve trough serum concentrations greater than 10 μg/mL, the target level reported as the minimum for

[2] José Baselga, et al., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14(3) J. Clin. Onc. 737-44 (Mar. 1996) ("Baselga '96"). Appx00873-00880.

efficacious treatment based on preclinical models. Appx00874. Baselga '96 reports that "[s]erum levels of [trastuzumab] as a function of time were analyzed for each patient using a one-compartment model." *Id*. More than 90% of patients achieved a trough serum concentration greater than the 10 μg/ml target. Appx00875. The mean serum half-life was 8.3 ±5 days. *Id.*

Baselga '96 also reported the effect of shed antigen on serum half-life. Shed antigen, or ECD^{HER2}, is the circulating extracellular domain of the HER2 receptor in the blood plasma. Appx15058. It was known at the time that patients with a high level of shed antigen were more likely to have lower serum trough concentrations. Appx00878. This was confirmed by Baselga '96: five patients (11%) with high shed antigen levels (above 0.5 μg/ml) had a mean serum half-life of 1.8 ±1.0 days, while the remaining patients with low shed antigen (below 0.5 μg/ml) had a mean serum half-life of 9.1 ±4.7 days. Appx00875 (Table 2).

(b) Pegram '98

Pegram '98[3] reported the results of a phase II clinical trial of trastuzumab in combination with cisplatin, a chemotherapy drug, involving 39 patients with

[3] Mark D. Pegram, et al., *Phase II Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185$^{HER2/neu}$ Monoclonal Antibody Plus Cisplatin in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment*, 16(8) J. Clin. Onc. 2659-71 (Aug. 1998) ("Pegram '98"). Appx00888-00900.

HER2/neu overexpressing advanced metastatic breast cancer. Appx00888, Appx00892. Patients received a 250 mg loading dose followed by nine weekly 200 mg doses, plus cisplatin administered every four weeks. *Id.* The study's objectives were to determine trastuzumab's overall response rate and duration, tolerance and toxicity, and pharmacokinetics when combined with cisplatin. Appx00889.

Pegram '98 concluded from earlier phase I trials that "the *pharmacokinetics of [trastuzumab] were predictable* . . . ." *Id.* (emphasis added). Pegram '98 reported using a target trough serum concentration of 10 to 20 µg/mL, "which is associated with antitumor activity in preclinical models." *Id.* The combination was effective, with an overall objective response rate of 24%, compared to 7% for prior studies of cisplatin alone, Appx00893, and trastuzumab did not enhance the toxicity of cisplatin, Appx00897.

Similar to Baselga '96, Pegram '98 found that there was "an inverse relationship" between serum half-life and high shed antigen levels, i.e., ".5 µg/ml or greater," Appx00894, and that 7 patients (18%) had high shed antigen. *Id.* (Table 6). The paper observed, however, that "significant loss of quantitation of trough [trastuzumab] concentration was *not* observed unless that ratio of [trastuzumab] to shed [antigen] was less than 10:1. This occurred in only a *small number* of samples." Appx00898 (emphasis added).

Pegram '98 concluded that "measurable [shed antigen] does not preclude clinical responses" to treatment because eight of the nine responders had measurable shed antigen during the course of this study, including one with a "very high level." *Id.* Significantly, for patients with any detectible shed antigen who responded to treatment, "there was a significant decrease" in shed antigen levels over time. Appx00896 (Fig. 4(B)). As a result, Pegram '98 concluded that shed antigen "may have limited use as a predictive factor for objective clinical response." Appx00898.

(c) The Herceptin Label

The FDA-approved label for Herceptin® (trastuzumab) was published in September 1998 (the "Herceptin Label"), almost one year before the patents' effective filing date. Appx00747. Genentech has not challenged the Herceptin Label as prior art, but did not submit it to the USPTO during prosecution of the '196 and '379 patents. The Herceptin Label discloses two phase III clinical trials of trastuzumab involving 691 patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Appx00746. Patients who received trastuzumab were given a loading dose of 4 mg/kg followed by weekly maintenance doses of 2 mg/kg. *Id.*

The Herceptin Label reported important pharmacokinetic data for trastuzumab. It disclosed that the "[s]hort duration intravenous infusion of 10 to

500 mg once weekly demonstrated *dose-dependent pharmacokinetics*. Mean half-life *increased* and clearance *decreased* with increasing dose level." *Id.* (emphasis added). At the lowest dose, 10 mg per week, serum half-life was 1.7 days, while at the highest dose, 500 mg per week, serum half-life was 12 days. *Id.* The label reported that the volume of distribution for trastuzumab was approximately that of serum volume (44 ml/kg) and that "at the highest weekly dose studied (500 mg) mean peak serum concentrations were 377 microgram/ml." *Id.*

It also revealed that the approved, prior-art weekly dosing regimen – a 4 mg/kg loading dose followed by 2 mg/kg maintenance doses – resulted in mean trough serum concentration levels of approximately 79 μg/mL, almost eight times higher than the minimum target trough concentration level. *Id.* The label reports that with this dosing regimen, the mean half-life was 5.8 days. *Id.*

The Herceptin Label observed that 64% of patients in one study had "*detectable* concentrations" of shed antigen, and that "patients with *higher* baseline shed antigen levels were more likely to have lower serum trough concentrations." *Id.* (emphasis added). The label also observed that "with weekly dosing, most patients with elevated shed antigen levels achieved target serum concentrations of Trastuzumab by week 6." *Id.*

In addition, the Herceptin Label disclosed that when trastuzumab was co-administered with the chemotherapy drug paclitaxel, mean serum concentration

levels "were consistently elevated approximately 1.5-fold" as compared with trastuzumab used in combination with two other chemotherapy drugs. *Id.* The label states that "[i]n primate studies, administration of Trastuzumab with paclitaxel resulted in a reduction in Trastuzumab clearance." *Id.* In other words, trastuzumab has a longer half-life and slower clearance when administered in combination with paclitaxel.

The Herceptin Label further teaches that trastuzumab was FDA-approved for administration in combination with paclitaxel, *id.*, which was administered every three weeks. The label also contemplates administering trastuzumab in combination with other chemotherapeutic drugs such as doxorubicin and epirubicin, which were administered every three weeks, or cisplatin, which was administered every four weeks. *Id.*

(d) Pegram '95 and Vogel '98

Two prior art abstracts disclosed yet more information about trastuzumab. Pegram '95[4] reported the results of a phase II study involving a loading dose of 250 mg followed by eight weekly 100 mg doses, plus the chemotherapeutic drug

[4] Mark D. Pegram, et al., *Phase II Study of Intravenous Recombinant Humanized Anti-p185 HER-2 Monoclonal Antibody (rhuMAb HER-2) Plus Cisplatin in Patients with HER-2/NEU Overexpressing Metastatic Breast Cancer,* 14(Abstract 124) Proc. Of ASCO 106 (Abstract 124) (Mar. 1995) ("Pegram '95"). Appx00906.

cisplatin co-administered with the loading dose and every four weeks thereafter. Appx00906. The abstract reported that earlier phase I studies showed "no substantial toxicity at any dose level" for trastuzumab. It also concluded for the phase II study that co-administration with cisplatin increased response rates of trastuzumab without increasing toxicity. *Id.*

Vogel '98[5] reported on the use of a "higher dose regimen" of trastuzumab in a trial involving 114 women with HER2-positive metastatic breast cancer without prior chemotherapy. Appx00939. Patients were randomized to receive either (a) a loading dose of 4 mg/kg followed by weekly 2 mg/kg doses, or (b) a higher loading dose of 8 mg/kg followed by weekly 4 mg/kg doses. *Id.* The abstract reported that trastuzumab was "generally very well tolerated in both dose groups." *Id.* The results showed "[p]atients in the two dose groups were generally comparable," but the response rate for the higher dose (28%) was higher than for the lower dose (21%). *Id.* Vogel '98 concluded that trastuzumab is "active, well-tolerated, and has a favorable safety profile." *Id.*

[5] Charles L. Vogel, et al., *Efficacy and Safety of Herceptin™ (Trastuzumab, Humanized Anti-HER2 Antibody) as a Single Agent in First-Line Treatment of HER2 Overexpressing Metastatic Breast Cancer (HER2+/MBC)*, 50(Abstract 23) Breast Cancer Research & Treatment 232 (July 1998) ("Vogel '98"). Appx00939.

2. Petitioners' Expert Testimony

Petitioners also submitted the declarations of Dr. Allan Lipton, an expert oncologist, and Dr. William Jusko, an expert pharmacologist.

(a) Dr. Lipton's Testimony

Dr. Lipton testified that a POSA in 1999 would have been motivated to increase the dosage intervals for trastuzumab because fewer administrations result in (a) greater patient convenience with fewer clinic trips, (b) lower hospital and patient costs, (c) better patient compliance, and (d) better patient quality of life. Appx00403-00405. He concluded that a POSA "would have arrived at the claimed dosing schedule by routine optimization of the therapy disclosed by the Herceptin Label." Appx00403. He also testified that a POSA would have been motivated to increase the dosing interval for trastuzumab to three weeks to match the three-week dosing schedule of commonly administered chemotherapeutic drugs such as paclitaxel. Appx00404-405.

Dr. Lipton testified that, based on his knowledge and experience, 55-85 kg is a reasonable range for patient weight, and that 70 kg is a representative example. Appx00401. He testified that the Herceptin Label's disclosure of a 500 mg absolute dose converts to a weight-based dose of 5.88 mg/kg for a patient weighing 85 kg and 9.09 mg/kg for a patient weighing 55 kg. Appx00402. For a patient

weighing 70 kg, a 500 mg absolute dose converts to a weight-based dose of 7.14 mg/kg (500 mg/70 kg = 7.14 mg/kg). Appx00401.

Dr. Lipton analyzed each of the challenged claims separately – including claim 1 of the '196 and '379 patents, which expressly cover a two-week dosing regimen, Appx00399-00405 – and attached a claim chart to his declaration demonstrating that the Herceptin Label in view of Baselga '96, Pegram '98, and the knowledge of skilled artisans renders the challenged claims obvious, Appx00521-00522. Dr. Lipton specifically addressed the two-week dosing regimen of claim 1 for each patent, stating:

> [I]t is my opinion that a POSITA would have been motivated to decrease the frequency of [trastuzumab] injections and would have arrived at the *claimed dosing schedule* by routine optimization of the therapy disclosed by the Herceptin Label.

Appx00403 (emphasis added). Petitioners argued the same in their petitions for *inter partes* review. Appx00301.

(b) Dr. Jusko's Testimony

Dr. Jusko testified that a POSA in 1999 would have used a one-compartment model and textbook equations to determine whether tri-weekly doses of 500 mg would be effective. Appx00544. As Dr. Jusko testified, Baselga '96 used a one-compartment model. *Id.* The Herceptin Label also reported only single half-life values for 10 mg and 500 mg doses, as well as for studies using the

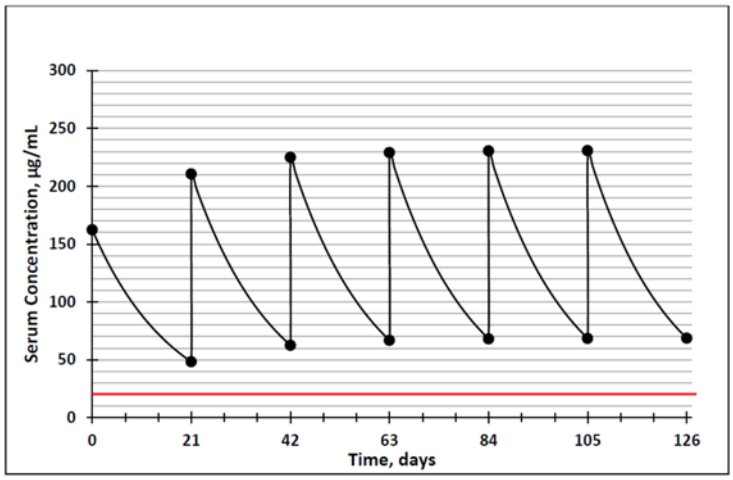
approved dosing regimens, suggesting that Genentech, too, used a one-compartment model to analyze the data for trastuzumab. Appx00544-00545. As Dr. Jusko testified, there is a single half-life in a one-compartment model, two half-lives in a two-compartment model, and so on. Appx00545. Genentech has not denied that it used a one-compartment model, nor has it produced evidence to the contrary. In addition, Genentech does not dispute that, as Dr. Jusko testified, there was no publicly available data in 1999 that would have supported using anything but a one-compartment model for trastuzumab. *Id.*

Dr. Jusko testified that the Herceptin Label reports that trastuzumab "demonstrated dose-dependent pharmacokinetics" and that "[m]ean half-life increased and clearance decreased with increasing dose level." Appx00542. He also testified that the small volume of distribution reported in the Herceptin Label, 44 mL/kg, is not unusual for therapeutic antibodies because they are primarily localized in plasma, rather than interstitial fluids and cell water (i.e., other compartments).[6] *Id.* This fact "supports use of the one-compartment model reported in Baselga '96." *Id.* In addition, it was known that therapeutic antibodies have "very low clearances as the limited tissue distribution and protective

[6] The volume of distribution is the apparent volume that the drug distributes throughout when in the body. Appx00549.

recycling processes prevent their degradation by tissue enzymes called proteases. This also results in their observed relatively long half-life." *Id.*

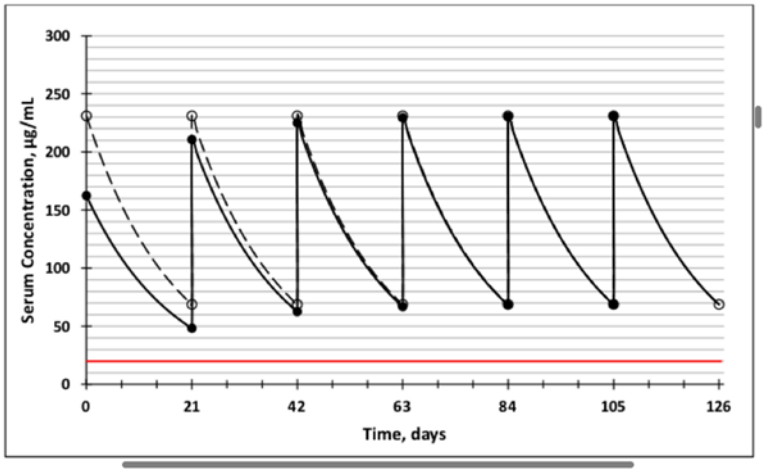
Dr. Jusko testified that because the Herceptin Label reports that a 500 mg dose was safe and effective and had a 12-day half-life, a POSA would have reasonably modeled the 500 mg initial dose followed by tri-weekly 500 mg maintenance doses. Appx00549. Using a one-compartment model and textbook equations, Dr. Jusko calculated that the trough serum concentration for an initial 500 mg dose after three weeks would be 48.3 µg/ml, Appx00550, and that after several 500 mg maintenance doses the trough serum concentration would reach a steady-state level of 68.7 µg/ml, Appx00552, as depicted in the chart below.



Appx00553. The red line depicts the high end of the range for target trough serum concentration (10-20 µg/ml) reported in Pegram '98. Appx00554. This is a conservative estimate: both Baselga '96 and Pegram '98 report that levels as low

as 10 µg/ml would also be efficacious. Appx00874, Appx00889. Dr. Jusko concluded that these calculations would have given a POSA confidence that trastuzumab could be administered safely and effectively in a 500 mg tri-weekly dosing regimen. Appx00553.

Dr. Jusko testified that it is often desirable to reduce the time required to reach steady-state. Appx00554. Accordingly, he used similarly well-known textbook equations to calculate the optimum loading dose and maintenance doses necessary to reach steady-state concentrations after the first dose. Appx00554-00556. He determined that a 712 mg loading dose followed by 500 mg maintenance doses every three weeks would achieve that level, Appx00556, as depicted in the chart below.



Appx00555. The dashed line shows the concentration level of trastuzumab over time during a treatment regimen of a 712 mg loading dose followed by 500 mg maintenance doses every three weeks. *Id.*

Dr. Jusko provided a thorough explanation for the three assumptions made in connection with his analysis. Appx00557-00559. First, he assumed that trastuzumab exhibits mono-exponential kinetics. Appx00557. This was reasonable because the Herceptin Label and Baselga '96 used the one-compartment model in analyzing data from clinical trials on trastuzumab, and there was no publicly available data at the time to support using anything else. *Id.* Second, he assumed that the initial concentration can be estimated by multiplying the dose by the volume of distribution and average mass of a patient. Appx00557-00558. This was reasonable because the initial infusion time, 90 minutes, is very short as compared to the antibody's half-life, 12 days, and because the "upcurve" (increase) in plasma concentration diminishes the influence of the early distribution process of the antibody to other tissues causing a biexponential curve to look more mono-exponential. Appx00558.

Third, he assumed that the kinetics of trastuzumab remain constant with multiple dosing. *Id.* This was reasonable because the metabolism of antibodies is relatively uniform across most antibodies within the class to which trastuzumab belongs. *Id.* That is, "most IgG1 antibodies[7] are metabolized in roughly the same

[7] Trastuzumab is an IgG1 antibody.

way over similar time periods," as reported in King '98.[8] *Id.* "[A]bsent an immune response to the antibody itself – something that Baselga '96 reports did not occur – there is no reason the kinetics would change over subsequent doses." Appx00558-00559. He also explained that this assumption "may somewhat underestimate" serum concentration levels because it was known that the half-life of trastuzumab *increased* with higher doses. Appx00559.

3. The UK Decisions

The Petition also provided evidence of the findings of fact made by courts in the United Kingdom regarding the European counterpart of the challenged patents, European Patent 1 210 115 B1 ("EP '115 patent"). In 2014, the UK High Court of Justice, Patents Court invalidated the EP '115 patent as obvious in view of the same prior art cited here. Appx00706. *Hospira UK Ltd. v. Genentech Inc.*, Case No. HC12C03487, [2014] EWHC (CH) 1094 (Pat) (Apr. 10, 2014). The court found that a POSA would have considered the Herceptin Label, Baselga '96 and Pegram '98, and that it would have been obvious and desirable to extend the dosing schedule of trastuzumab to three weeks, particularly given the three-week dosing schedule for paclitaxel. Appx00701-00706.

[8] David J. King, *Applications and Engineering of Monoclonal Antibodies*, Taylor & Francis Ltd. (1998) ("King '98"). Appx14774-14778.

As the court explained, a POSA would have used a one-compartment model to calculate the trough serum concentration over time for three reasons:

> First it is clear that in general pharmacokinetics experts are quite prepared to use a simple one compartment model to make assessments of this kind. Second the only model which could be used based on the FDA label was a one compartment model. Indeed it is clear from the information in the FDA label that a one compartment model was used. Third Baselga indicates that Genentech had used a one compartment model for trastuzumab. Accordingly a skilled person would have confidence that a one compartment model was sufficient in order to draw conclusions in relation to the pharmacokinetics of trastuzumab.

Appx00704. The court concluded that "[t]here is no doubt about the mathematics. Based on this calculation the trough serum concentration would be 48 μg/ml on day 21." Appx00702. The decision was affirmed on appeal in 2015. *Hospira UK Ltd. v. Genentech, Inc.*, Case No. A3 2014 1800, [2015] WECA (Civ) 57 (Feb. 6, 2015). Appx00745.

C. Patent Owner's Response

In responses to each IPR, Genentech opposed the arguments to all challenged claims and stated that it would refer to claims 11, 18, and 22 of the '196 patent and claims 11, 17, and 21 of the '379 patents as "exemplary." Appx15491, Appx23153. Genentech, however, never expressly referred to any specific claim in its analyses. Instead, Genentech focused on the three-week dosing regimen of claim 11 of each patent, rewriting it in independent form. Appx15492,

Appx23154-23155. Genentech did not separately address claims 18 and 22 of the '196 patent and claims 17 and 21 of the '379 patent, which depend indirectly from claim 1 and are directed to two-week administration.

In support, Genentech submitted the declarations of Dr. Karen Gelmon, an oncologist, and Dr. George Grass, a PhD in pharmaceutics.

1. Dr. Gelmon's Testimony

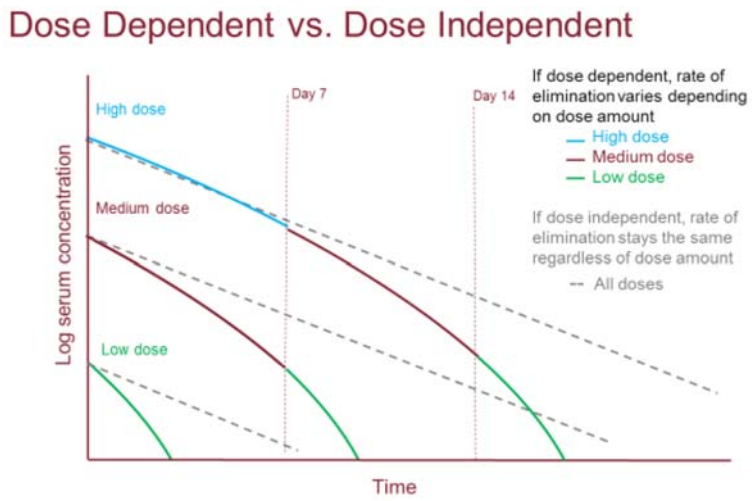
Dr. Gelmon testified that a POSA would not have been motivated to decrease the number of trastuzumab doses because safety and efficacy concerns would have outweighed other considerations such as patient convenience. Appx16391-16392. She also testified that weekly dosing does not reduce a patient's quality of life. Appx16419. She further testified that a POSA would not have been motivated to match the three-week dosing schedule of other commonly administered chemotherapeutic drugs like paclitaxel. Appx16392.

2. Dr. Grass's Testimony

Dr. Grass testified that a POSA would not have used the one-compartment model to predict serum concentration levels for three-week administration of trastuzumab, as Dr. Jusko did, because the drug was known to have dose-dependent, nonlinear kinetics. Appx16349. Dr. Grass testified that for dose-dependent drugs generally, the half-life and elimination rate "*can vary* as drug concentration changes." Appx16354 (emphasis added); *see also* Appx16353

("[F]or dose-dependent drugs, the elimination rate and half-life vary depending upon concentration of drug in plasma.").

To illustrate that point, Dr. Grass presented a chart intending to show "differences in kinetics that *can* exist between dose-independent and dose-dependent drugs." Appx16353 (emphasis added).

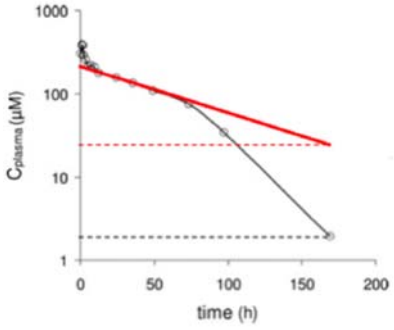


Id. Thus, according to Dr. Grass, "[a]s illustrated in the graph above," applying a constant half-life value over a three-week period, based on one-week data in the prior art, to a dose-dependent drug like trastuzumab "could *overestimate* trough serum concentration levels." Appx16355 (emphasis added).

In his deposition, Dr. Grass admitted that his chart is not based on any actual data or found in any reference. He essentially made it up for these proceedings. Appx17785 (116:16-21). This made-up chart appears to show that all dose-dependent drugs necessarily have shorter half-lives and faster elimination rates

than dose-independent drugs over time. Dr. Grass, however, never acknowledged in his declaration that dose-dependent drugs may "vary" in the *other* direction. That is, they may have *longer* half-lives and *decreased* elimination rates over time with higher doses, as Dr. Jusko testified and the Herceptin Label expressly taught. *See* Appx00542, Appx00746.

As his sole example of a dose-dependent drug with the pharmacokinetics depicted in his chart, Dr. Grass cited to data for indisulam, a small molecule drug (not an antibody), published in 2006, seven years after the critical date. Appx16355. He presented a chart showing a downward-sloping curve for indisulam serum concentration levels, as compared to a linear model (red line):



Appx16356. From this example, he opined that applying a constant value for trastuzumab's half-life over a three-week period would likely overestimate trough serum concentration levels. *Id.*, Appx16362. Dr. Grass continued that "not all drugs with non-linear kinetics will have deviations of this magnitude," suggesting

that all such drugs will have some downward deviation, but perhaps not as severe as indisulam. Appx16356.

At his deposition, Dr. Grass admitted that antibodies and small molecule drugs behave differently in a number of ways, and that he could not identify *any* paper showing that *any* antibody follows the downward-sloping pharmacokinetic profile depicted in his made-up chart. Appx17774-17775 (73:21-75:16), Appx17785-17786 (116:24-119:18). In contrast to Dr. Grass, Dr. Gelmon testified that she "would have had concerns about extrapolating from a small molecule to an antibody." Appx17633 (121:8-18).

Dr. Grass also opined that a POSA would understand the Herceptin Label's express teaching that "[m]ean half-life increased and clearance decreased with increasing dose level" to mean that "as the concentration of trastuzumab in the bloodstream decreased, the half-life decreased." Appx16362. Dr. Grass did not cite any prior art to support this opinion.

He also testified that the actual rates of elimination for trastuzumab would have been unpredictable without collecting sufficient data, such as by conducting a "washout study" where serum concentration is collected over several half-lives following a single administration of the drug. Appx16345. Dr. Grass admitted at his deposition, however, that a washout study is not required to determine whether a three-week dosing regimen for trastuzumab would be safe and effective and,

indeed, the '196 and '379 patents contain no washout study data. Appx17789 (130:15-131:10).

Dr. Grass further opined that a POSA would have been dissuaded from administering trastuzumab every three weeks because of concerns about shed antigen. Appx16376. He stated that "[t]he prior art reported that 64% of patients had shed antigen present and that shed antigen had a direct effect on the half-life of trastuzumab," Appx16346, suggesting incorrectly that 64% of patients would be at some risk from a three-week dosing regimen. Again, Dr. Grass did not cite any prior art to support his opinions on shed antigen, other than the Herceptin Label, Baselga '96 and Pegram '98 which teach the contrary, or explain how the prior art FDA-approved dosing regimen was found safe and effective despite the shed antigen issue.

D. Petitioners' Reply

To rebut Dr. Grass's testimony that the dose-dependent nature of trastuzumab would have dissuaded a POSA from extending the dosing interval, Petitioners submitted prior art scientific publications and a reply declaration of Dr. Jusko evidencing the well-known pharmacokinetics of therapeutic monoclonal antibodies as of the patents' priority date. Namely, it was known at the time that therapeutic antibodies, including trastuzumab, were "dose dependent" and exhibit "non-linear pharmacokinetics," as both Dr. Jusko and Grass testified and the

Herceptin Label disclosed. Contrary to Dr. Grass's opinion, however, the prior art showed that while small molecule drugs might follow the downward-sloping curve in Dr. Grass's made-up chart, "it was known that drugs that exhibit 'receptor-mediated' disposition, such as antibodies, behave in the *opposite* way, i.e., as drug concentrations decrease over time, half-life *increases*, which means that elimination *decreases*." Appx17556 (emphasis in original). This evidence further supported Dr. Jusko's use of the one-compartment model and his conclusions. Appx17560.

Petitioners also introduced three post-filing date references that comment on the teachings of Baselga '96 and Pegram '98. While not prior art, these references further evidenced the knowledge and understanding of a skilled artisan as of the priority date and directly contradicted Dr. Grass's testimony on what the prior art taught.

1. Prior Art Showing that Higher Doses Result in Longer Half-Lives and Decreased Clearance

(a) King '98

King '98 is the only prior art reference generally focused on therapeutic monoclonal antibodies and reviewing their pharmacokinetics. King '98 described the known pharmacokinetics of human IgG antibodies, including trastuzumab, as having longer half-lives in humans. Appx14774-14778. King '98 noted that "[i]n

both human and animal systems, antibody clearance from the blood follows a classical two-compartment kinetic model," an initial short distribution (alpha) phase followed by an elimination or clearance (beta) phase in which the antibody is metabolized and excreted, and that "these two phases are commonly calculated and quoted as half-life values ($t_{½}\alpha$ and $t_{½}\beta$)." Appx14775. King '98 also stated that "[a]lternatively, *a single-compartment kinetic model may be used*, in which case a single half-life [$t_{½}\beta$] can be calculated." *Id.* (emphasis added). King '98 provided a chart showing the half-life values of 13 fully-characterized monoclonal antibodies, including trastuzumab:

Table 2.7 Pharmacokinetics of some chimeric and humanised antibodies in humans

Antibody	Indication	$t_{½}\alpha$	$t_{½}\beta$	Reference
c17-1A (γ1)	Colorectal carcinoma	18 ± 2 hours	101 ± 16 hours	LoBuglio *et al.*, 1989 Meredith *et al.*, 1991
cB72.3 (γ4)	Colorectal carcinoma	18 ± 7 hours	224 ± 66 hours	Khazaeli *et al.*, 1991 Meredith *et al.*, 1992a
c14.18 (γ1)	Melanoma	24 ± 1 hours	181 ± 73 hours	Saleh *et al.*, 1992
cL6 (γ1)*	Carcinoma		54–109 hours	Goodman *et al.*, 1993
C2B8 (γ1)*	B-cell lymphoma		106 (38–252 hours)	Maloney *et al.*, 1994
cAnti-CEA (γ4)*	Colorectal carcinoma	7 (1.4–18 hours)	91 (30–292 hours)	Buchegger *et al.*, 1995
hu2PLAP (γ1)*	Carcinoma		73.1 ± 30.2 hours	Hird *et al.*, 1991
Humanised anti-Tac(γ1)*	Graft v. host disease		88† hours (44–360)	Anasetti *et al.*, 1994
Humanised M195 (γ1)*	Myeloid leukemia	0.3 ± 0.4 hours	38 ± 9 hours	Caron *et al.*, 1994
CDP571 (γ4)	Healthy volunteers	19.6 hours (1–49)	225† hours (87–537)	Stephens *et al.*, 1995
hMN-14 (γ1)*	CEA producing cancer	5.3 ± 6.2 hours	56 ± 32 hours	Sharkey *et al.*, 1995
rhuMAb HER2 (γ1)	Breast cancer		199 ± 120 hours	Baselga *et al.*, 1996
hCTM01 (γ4)*	Ovarian cancer	4.2 ± 6.1 hours	64.7 ± 20.2 hours	van Hof *et al.*, 1996

*In these cases circulating antigen, or large pools of readily accessible antigen, are known to be present which may reduce antibody half-life in some cases.
†Increase in $t_{½}$ with increasing dose.

Appx14777. As Dr. Jusko testified, all eight antibodies with initial distribution phase data ($t_{½}\alpha$) demonstrated a short initial half-life and quick clearance followed by a longer half-life ($t_{½}\beta$) and slower clearance. Appx17552. The chart includes

data from five other antibody studies using the one-compartment model (i.e., studies reporting only $t_{½}\beta$ data), including trastuzumab data from Baselga '96. Appx14775.

King '98 concludes that "[h]uman IgG molecules have a long circulating half-life in humans, with $t_{½}\alpha$ of 18-22 hours and $t_{½}\beta$ of *21-23 days* for human IgG1, 2 or 4." *Id.* (emphasis added). King notes that "the half-life varies with concentration," and that "at very high IgG levels . . . a prolonged half-life is observed." *Id.* He added that "[i]t has been postulated that a receptor-mediated event" is responsible for this prolonged half-life by "preventing degradation and resulting in recirculation to the plasma." *Id.* This hypothesis "has been supported by subsequent experimental investigations." *Id.*

(b) Koizumi '86

The characteristic reported by King '98 – higher antibody doses result in increased half-life and decreased clearance – had been predicted 12 years earlier by Koizumi '86.[9] In that paper, the authors reported on a multi-compartmental analysis of the pharmacokinetic behavior of monoclonal antibodies generally. Appx17375. "When the amount of injected antibody was increased in the model,

[9] Kiyoshi Koizumi, et al., *Multicompartmental Analysis of the Kinetics of Radioiodinated Monoclonal Antibody in Patients with Cancer*, 27 J. Nucl. Med. 1243-54 (Aug. 1986) ("Koizumi '86"). Appx17375-17386.

the simulated blood clearance of [antibody] was decreased. . . . Higher tumor uptake [of the antibody] can be anticipated and has been observed in animal and patient studies when larger amounts of [antibody] are administered." Appx17382.

Koizumi '86 concluded that higher doses of antibodies lead to increased half-life and decreased clearance from the body, as shown in the figure below:

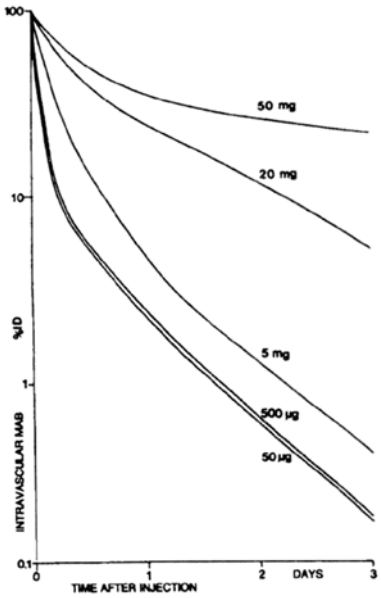


FIGURE 8
Model simulated curves for intravascular MAb reflecting effect of different amount of injected MAb on blood clearance of MAb. Clearance rate of larger injection amount is decreased

Appx17384. It further concluded that this characteristic was related to "a receptor-mediated process apparently existing in the liver." Appx17385.

(c) Levy '94

In 1994, Dr. Gerhard Levy reported on the known pharmacokinetic profile of "receptor-mediated" drugs, i.e., drugs "that are bound with high affinity to pharmacologic target sites such as receptors" like the antibodies discussed in

King '98 and Koizumi '86.[10] Appx17316. Levy concluded that such drugs have the following "[t]ypical concentration-time profile":

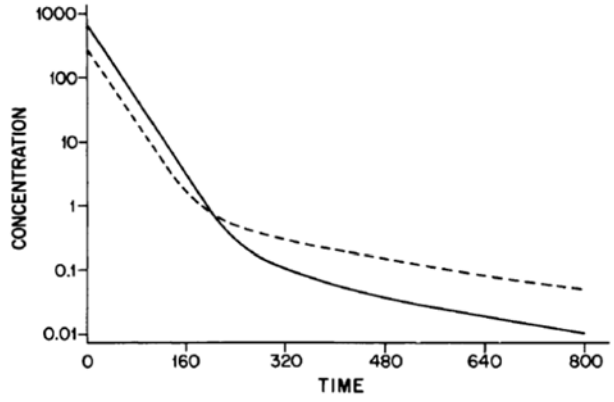


Fig. 1. Typical concentration-time profile in plasma *(continuous line)* and tissues *(broken line)* for a drug that is subject to high-affinity low-capacity binding in tissues. Distribution of drug from plasma to tissues was assumed to be practically instantaneous.

Appx17317. Levy '94 also concluded that "the apparent volume of distribution and total clearance decrease with increasing dose but reach a limiting value," i.e., steady-state. Appx17319.

[10] Gerhard Levy, *Pharmacologic target-mediated drug disposition*, 56(3) Clin. Pharmacology & Therapeutics 248-52 (Sept. 1994) ("Levy '94"). Appx17316-17320.

2. Post-Filing Art Showing How POSAs Understood the Teaching of Baselga '96 and Pegram '98

(a) Leyland-Jones '99

While not prior art, Leyland-Jones '99[11] was provided as evidence of the knowledge and understanding of a skilled artisan as of the priority date. In November 1999, just three months after the Patents' first effective filing date, a published report from a conference on HER2 revealed the work of Dr. Leyland-Jones. App17174. He concluded that the known dose-dependent nature of trastuzumab, as revealed in the prior art references Baselga '96 and Pegram '98, favored a decreased dosage interval.

> Herceptin demonstrates dose-dependent, non-linear pharmacokinetics. This means that higher doses of the drug can be administered *less frequently*.

Id. (emphasis added). The paper further announced that Dr. Leyland-Jones was, at that time, conducting a study involving dosing Herceptin once every three weeks, predicting that the "minimum trough concentration produced by this dose regiment will be in the range of 40-50 μg/ml," *id.*, consistent with Dr. Jusko's analyses.

[11] Brian Leyland-Jones, *Pharmacological insights into the future of Herceptin®*, HER2 State-of-the-Art Conference Report at 16 (Nov. 21-23, 1999) ("Leyland-Jones '99"). Appx17174.

(b) Leyland-Jones 2001(a)

Two years later, Leyland-Jones 2001(a)[12] summarized the data in Baselga '96 and Pegram '98 and stated that the "dose-related, non-linear pharmacokinetic profile [of trastuzumab] is consistent with saturation of a specific receptor-mediated clearance mechanism." Appx17195, Appx17574. This "receptor-mediated clearance mechanism" is the same characteristic described in King '98, Levy '94 and Koizumi '86.

(c) Leyland-Jones 2001(b)

Also in 2001, Leyland-Jones 2001(b)[13] described the prior art phase I and II data as "important because it indicated that it may be possible to administer trastuzumab for longer intervals while maintaining serum concentrations above the minimum required for therapeutic activity." Appx17201. Leyland-Jones 2001(b) thus confirmed that Dr. Grass's opinions do not reflect the understanding of the POSA at the patents' priority date.

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[12] Brian Leyland-Jones, *Dose Scheduling – Herceptin®,* 61(suppl. 2) Oncology 31-36 (2001) ("Leyland-Jones 2001(a)"). Appx17194-17199.

[13] Brian Leyland-Jones, et al., *Pharmacologic insights into the future of trastuzumab*, 12(Suppl. 1) Annals of Oncology S43-Sf47 (2001) ("Leyland-Jones 2001(b)"). Appx17200-17204.

E. The Board's Final Written Decisions

The Board found that no claim terms required construction. Appx00008. The Board next found that it was undisputed that a POSA here would be a team consisting of (1) a breast cancer oncologist with experience in breast cancer research or clinical trials, and (2) a person with a Ph.D. in pharmaceutical sciences with an emphasis in pharmacokinetics and three years of relevant experience in protein-based drug kinetics. Appx00008-00009.

The Board correctly found that a POSA "would have been motivated to extend the dosing interval for the simple (yet compelling) reasons that doing so would have been more cost-effective and less burdensome for the patient undergoing such treatment, which required in-person visits to the clinic for each antibody infusion." Appx00016-00017. The Board cited this Court's *Hoffman-La Roche* decision for the proposition that "[a] relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance." Appx00017 (quoting *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014)). The Board additionally found that "the skilled artisan would have been motivated to match trastuzumab and chemotherapy dosing," i.e., a three-week dosing regimen. Appx00019. The Board found that a POSA would have been motivated to use a 500 mg or 712 mg loading dose, followed by 500 mg maintenance doses, as Dr. Lipton and Dr. Jusko testified. Appx00020-00022.

The Board, however, found that Petitioners had not met their burden of establishing a reasonable expectation of success by a preponderance of the evidence. Appx00022. The Board dismissed Dr. Jusko's analysis as follows:

> While Dr. Jusko's calculations are based on 'textbook' equations that were known in the prior art, the actual pharmacokinetic analysis set forth in his declaration for determining the serum trough concentration associated with a tri-weekly dosing regimen of trastuzumab *was not found in any prior art reference.* Thus, we find Dr. Jusko's analysis to be largely based on *impermissible hindsight*.

Appx00024 (emphasis added). In other words, the Board found that because the claimed treatment method was not *anticipated* by any prior art reference, it could not be *obvious* in light of the prior art, and Dr. Jusko's testimony was merely "impermissible hindsight."

Even though Baselga '96, a Genentech publication, used the one-compartment model with trastuzumab, the Board found that a POSA would not have used a one-compartment model to "reasonably predict the expected serum concentrations for tri-weekly administration using higher doses of the antibody." Appx00025. The Board appears to have credited Dr. Grass's opinion about the need for a "washout study" but made no finding on the issue. Appx00027.

The Board also found that a "skilled artisan would have been concerned that the effect of shed antigens – not taken into account by Dr. Jusko's analysis – could indeed significantly affect serum trough concentrations for tri-weekly

administration of trastuzumab." *Id.* Contrary to the Board's finding, however, Dr. Jusko actually did account for shed antigen in his reply declaration. Appx17572-17573. Moreover, the prior art taught that this concern related only to a small number of patients with high shed antigen, and the regimen for trastuzumab was approved and used despite the shed antigen issue.

The Board credited Dr. Grass's chart, despite there being no data to support it, and cited his example of indisulam, a small molecule rather than an antibody. Appx00027-00028. Of the post-filing 2006 paper reporting on indisulam, the Board found that it "demonstrates at least one example in which assuming linear kinetics could result in an overestimation of trough serum concentration for a dose-dependent drug." Appx00028-00029. The Board then stated: "[W]e find *nothing in the record to suggest that a similar overestimation would not have been a concern* for tri-weekly trastuzumab administration." Appx00029 (emphasis added).

After finding that "nothing in the record" suggested that the one-compartment model would not overestimate trastuzumab serum concentration levels, the Board addressed Petitioners' reply evidence which did just that. The Board dismissed King '98, Levy '94, and Koizumi '86 on various grounds, Appx00029-00033, despite that all three showed that monoclonal antibodies and receptor-mediated drugs, like trastuzumab, have the same pharmacokinetic profile:

they all have dose-dependent, nonlinear pharmacokinetics such that higher doses result in *longer half-lives* and *decreased elimination* over time, and that the one-compartment model had been used to predict their pharmacokinetics.

Finally, the Board addressed Genentech's motion to exclude Petitioners' reply evidence. The Board ruled that Dr. Jusko's reply declaration, King '98, Levy '94 and Koizumi '86 were proper rebuttal evidence, and stated that it did not rely on the three post-priority date Leyland-Jones references. Appx00035-00036. The Board, therefore, denied the motion in part and dismissed the motion in part as moot. Appx00036.

The Board never separately analyzed whether claim 1, or any other claim to a *two*-week dosing regimen, would have been obvious. Specifically, having determined that a POSA would have been motivated to decrease the frequency of dosing for "simple (yet compelling) reasons," Appx00016-00017, the Board failed to articulate any rationale for (apparently) concluding that a POSA would not have had a reasonable expectation of success administering trastuzumab every two weeks, especially in light of the 12-day half-life for the 500 mg dose reported in the Herceptin Label. Nor did the Board address the contrary findings of fact from the UK decisions.

SUMMARY OF ARGUMENT

A. The Board's finding that a POSA, although motivated to extend the dosing interval for trastuzumab from weekly to tri-weekly administration, would not have had a reasonable expectation of success in doing so is not supported by substantial evidence. In making this finding, the Board made three underlying erroneous findings of fact that are also not supported by substantial evidence.

First, the Board incorrectly found that a POSA would not use the well-known, commonly used one-compartment model to predict serum concentration levels for a tri-weekly dosing regimen. There is no prior art to suggest that a POSA would not have done so, and the prior art evidence showed that POSAs, in fact, had used the one-compartment model for trastuzumab. Instead, the Board erroneously relied on a made-up chart and conclusory testimony from Dr. Grass, as well as data from a 2006 post-priority date article discussing a small molecule drug, not a therapeutic monoclonal antibody.

Second, the Board wrongly found that there was "no evidence to suggest" that the one-compartment model would not overestimate serum concentration levels. The only relevant prior art evidence showed that the one-compartment model would actually *under*estimate such levels. The only evidence to the contrary was Dr. Grass's conclusory testimony, his made-up chart, and his testimony about an irrelevant small molecule drug.

Third, the Board wrongly found that a POSA would have been deterred from using a three-week dosing regimen because of the effects of shed antigen. The prior art clearly showed that only *high* shed antigen levels had an effect on serum concentration levels of trastuzumab, and that only a small number of patients had high levels of shed antigen. The shed antigen issue did not, in fact, deter POSAs from conducting clinical trials of trastuzumab, nor did it prevent Genentech from obtaining FDA approval for Herceptin.

B. The Board erred in finding that claims to *two*-week administration of trastuzumab were not obvious and failed to set forth its reasoning for that finding as required by the APA. The Board apparently believed that its finding that three-week administration is nonobvious also applied to two-week administration. But that is not the case. Claims to two-week administration were expressly at issue, and under the APA the Board had a duty to set forth a "statement of findings and conclusions, and the reasons or basis therefor" with respect to these claims. *See* 5 U.S.C. § 557(c)(3)(A). Nevertheless, the record evidence establishes that a POSA would have had a reasonable expectation that a two-week dosing regimen with 500 mg doses would work, given that the reported half-life of this dose was 12 days.

ARGUMENT

I. STANDARDS OF REVIEW

This Court reviews the Board's ultimate determination of obviousness de novo and its underlying factual determinations for substantial evidence. *E.I. du Pont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1005 (Fed. Cir. 2018). "Substantial evidence is more than a scintilla." *In re Gartside*, 203 F.3d 1305, 1312 (Fed. Cir. 2000) (quoting *Consolidated Edison Co. v. NLRB*, 305 U.S. 197, 229-30 (1938)). For factual determinations, the Court "asks whether a reasonable fact finder could have arrived at the agency's decision," which requires examination of the "record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *Id.* The presence or absence of a reasonable expectation of success is a question of fact reviewed for substantial evidence. *Alza Corp. v. Mylan Labs*., Inc., 464 F.3d 1286, 1289 (Fed. Cir. 2006).

This case also involves the question of whether the Board complied with the APA, which requires the Board to "include a statement of findings and conclusions, and the reasons or basis therefor, on all the material issues of fact, law, or discretion presented on the record." 5 U.S.C. § 557(c)(3)(A); *see also Power Integrations, Inc. v. Lee*, 797 F.3d 1318, 1323 (Fed. Cir. 2015).

II. THE BOARD'S FINDING THAT A POSA WOULD NOT HAVE HAD A REASONABLE EXPECTATION OF SUCCESS IN THREE-WEEK DOSING OF TRASTUZUMAB IS NOT SUPPORTED BY SUBSTANTIAL EVIDENCE

A patent claim is invalid as obvious if the differences between the patented subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). To prove obviousness, the challenger must show that a POSA would have been motivated to combine the teachings of the prior art and would have had a reasonable expectation of success in doing so. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting *In re Aller,* 220 F.2d 454, 456 (C.C.P.A. 1955)). "It is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree, or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kin[d] [*sic*] may produce better results than prior inventions." *In re*

Williams, 36 F.2d 436, 438 (C.C.P.A. 1929). Thus, "[n]ormally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification." *In re Aller,* 220 F.2d at 456.

"Obviousness does not require absolute predictability of success." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); *see also Pfizer*, 480 F.3d at 1364 ("[T]he expectation of success need only be reasonable, not absolute."). In the pharmaceutical context, "[c]onclusive proof of efficacy is not necessary to show obviousness." *Hoffman La Roche, Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014). Moreover, the "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364.

Here, the Board erroneously made three critical underlying factual findings to support its determination that a POSA would not have had a reasonable expectation that three-week dosing of trastuzumab would have achieved serum concentration levels above the target minimum: (1) that a POSA would not have used a one-compartment model to predict serum concentration levels for trastuzumab, (2) that "nothing in the prior art" showed that the one-compartment model would not have overestimated trough serum concentration levels, and (3) that shed antigen would have deterred a POSA from moving to three-week administration. None are supported by substantial evidence.

A. The Board's Finding that a POSA Would Not Use a One-Compartment Model is Not Supported by Substantial Evidence

It is undisputed that, at the relevant time, the one-compartment model was well known and commonly used to model the pharmacokinetic properties of drugs, including therapeutic antibodies, and to determine appropriate dosing regimens. There is also no dispute about Dr. Jusko's math: using the one-compartment model, he correctly applied textbook mathematical equations to the prior art data to calculate that trough serum concentration levels of trastuzumab three weeks after the first dose would be 48.3 μg/ml – almost five times higher than the minimum target level reported by Baselga '96 and Pegram '98 – and would reach a steady-state of 68.7 μg/ml. It is also undisputed that there was insufficient publicly available data for trastuzumab at the relevant time to apply the two-compartment model.

The Board incorrectly found that a POSA would not have used a one-compartment model because trastuzumab demonstrates dose-dependent, nonlinear pharmacokinetics. The evidence is to the contrary. Not only *would* a POSA have used the one-compartment model, POSAs *did* use it. The Board incorrectly relied on the conclusory testimony of Dr. Grass that a POSA would have believed that the dose-dependent nature of trastuzumab would result in an overestimation of trough serum concentration levels over time. Dr. Grass cited no relevant prior art

to support that assertion, and the prior art of record shows he was wrong. Instead, he relied on a made-up chart and data about a small molecule drug from 2006, seven years after the priority date, with a different mechanism of action. That is not substantial evidence.

1. POSAs Used the One-Compartment Model for Trastuzumab and Other Monoclonal Antibodies

The prior art shows that POSAs used the one-compartment model to determine half-lives and predict serum concentration levels over time for trastuzumab and similar drugs. Baselga '96 expressly stated that "[s]erum levels of [trastuzumab] as a function of time were analyzed for each patient using a one-compartment model." Appx00874. The Herceptin Label also suggests that Genentech used a one-compartment model to analyze serum levels, Appx00544-00545, a fact that Genentech did not deny or present evidence to contradict. Moreover, the UK court found that a POSA would have used the one-compartment model and that Genentech did, in fact, use it for Herceptin at that time, findings affirmed on appeal. Appx00704, Appx00745. Furthermore, the King '98 textbook stated that "a single-compartment kinetic model may be used," as an alternative to the two-compartment model, and described five fully-characterized therapeutic antibodies, including trastuzumab, whose half-lives were determined using the one-compartment model. Appx14775.

Further supporting the use of a one-compartment model, "the pharmacokinetics of [trastuzumab] were *predictable*," as Pegram '98 concluded based on earlier phase I trials. Appx00889 (emphasis added). Indeed, by 1998 much was known about the pharmacokinetics of trastuzumab. There had been numerous clinical studies of trastuzumab, and Baselga '96, Pegram'98 and the Herceptin Label alone report that over 500 women had received the drug in clinical trials.

Dr. Grass baldly asserted that a POSA would read this statement from Pegram '98 to mean that "administration of the same dose with the same dosing schedule would likely yield the same serum concentrations if given to a similar patient population." Appx16369. But that conclusory opinion is belied by the plain meaning of the phrase "the pharmacokinetics . . . were predictable," by Pegram '98 itself which reported on the extensive prior art research involving trastuzumab, and by the prior art as a whole.

The very same predictability described by Pegram '98 was evident to Dr. Leyland-Jones, who stated that the known dose-dependent, non-linear pharmacokinetics of trastuzumab demonstrated by prior art preclinical studies *actually means* that the drug could be delivered *less frequently*.

> Herceptin demonstrates dose-dependent, non-linear pharmacokinetics. This means that higher doses of the drug can be administered *less frequently*.

App17174 (emphasis added). While it is not prior art because it was published three months after the priority date, Leyland-Jones '99 sheds light on how POSAs understood the dose-dependent nature of trastuzumab reported in the prior art as of August 1999.

The Board also erred in concluding that Dr. Jusko's analysis was "impermissible hindsight." Appx00024. Dr. Jusko simply used well-known principles of pharmacokinetics, commonly used at the relevant time, and applied them to the known trastuzumab data to calculate serum concentration levels for three-week administration. He concluded that a POSA – motivated to decrease the frequency of doses to improve patient compliance and quality of life and to reduce hospital and patient costs – would have done the same calculations in 1999 and would have known that the trough serum level after the first dose would be far above the target minimum level reported as effective in Baselga '96 and Pegram '98.

That is the opposite of hindsight. It is an analysis guided every step of the way by what was known – indeed, *widely* known – in the art at the time of the supposed invention. *See Genzyme Therapeutic Prods. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1372 n.5 (Fed. Cir. 2016) ("That is not hindsight; it is simply the use of one's current knowledge to determine, as well as possible, what the state of the art was at some point in the past."). Indeed, if Dr. Jusko's analysis

can be so casually dismissed as hindsight, then any expert analysis could be, too. Expert testimony on obviousness issues, by necessity, is an analysis of what a POSA would have done in the past. But unlike Dr. Grass, Dr. Jusko's analysis is firmly rooted in the teachings of the prior art.

The Board also confused anticipation with obviousness, faulting Dr. Jusko's analysis because his precise calculations for three-week administration of trastuzumab "was not found in any prior art reference." Appx00024. The issue is what would have been obvious to a POSA at the time of the purported invention in light of the prior art as a whole, not whether all limitations of the claimed invention (i.e., administering higher doses of trastuzumab every three weeks) were disclosed in a single prior art reference.

While the Board took note of the "relative novelty of using antibodies for the treatment of cancer as of the August 27, 1999 priority date," Appx00023, therapeutic antibodies and their pharmacokinetic properties were well known at the time. *See, e.g.,* King '98 (Appx14774-14778). Regardless, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364.

Although the Board did not find that a POSA would have needed to do a "washout study" before moving to tri-weekly dosing, it did note Dr. Grass's testimony on the subject. In this regard, it is significant that Dr. Grass admitted at

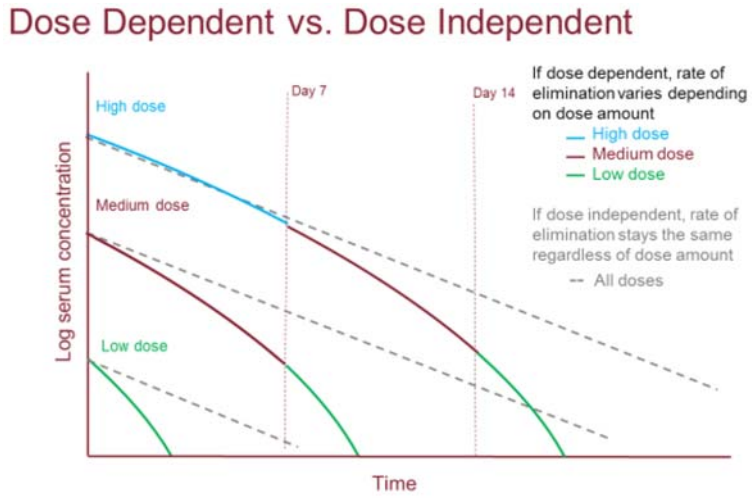
his deposition that such a study was not necessary to predict serum concentration of trastuzumab at three weeks, and that the concentration can be estimated from weekly data. Appx17789 (130:15-132:10).

The Board cited no evidence *in the prior art* that a POSA would not, or could not, use a one-compartment model to reasonably predict serum concentration levels for three-week administration of trastuzumab. The only evidence the Board relied on was Dr. Grass's conclusory opinions, his made-up chart and data from a wholly irrelevant small molecule. As discussed below, that falls far short of *substantial* evidence.

2. The Board Erred in Crediting Dr. Grass's Made-Up Chart and Testimony about Indisulam

"In the determination of obviousness, there must be factual support for an expert's conclusory opinion." *Upjohn Co. v. Mova Pharm. Corp.*, 225 F.3d 1306, 1311 (Fed. Cir. 2000); *see Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1338 (Fed. Cir. 2013) (expert's "*ipse dixit* statements that co-administration would be 'difficult' and 'complicated,'" was not enough to prove lack of enablement); *see also .Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations . . . may render the testimony of little probative value in a validity determination.").

Here, Dr. Grass's testified that for dose-dependent drugs *generally*, the half-life and elimination rate "*can vary* as drug concentration changes." Appx16354 (emphasis added). He then offered his made-up chart showing the variation going in only one direction, downward, and purporting to show "differences in kinetics that *can* exist between dose-independent and dose dependent drugs." Appx16353 (emphasis added).



Id. That chart, however, is not based on pharmacokinetic data for trastuzumab or even monoclonal antibodies generally. It is not based on any data at all. Dr. Grass created it for these proceedings. Appx17785 (116:16-21).

Dr. Grass never acknowledged in his declaration that dose-dependent drugs "can vary" in the *other direction*. That is, they may have *longer* half-lives and *decreased* elimination rates over time with higher doses, as Dr. Jusko testified and the Herceptin Label expressly taught. *See* Appx00542, Appx00746. He simply

applied this sweeping and conclusory statement to trastuzumab: "As illustrated in the graph above, applying a constant value for half-life over a three-week period, based on one-week data reported in the prior art, to a dose-dependent drug like trastuzumab could *overestimate* trough serum concentration levels." Appx16355 (emphasis added).

Dr. Grass offered no prior art data to support his opinion that trastuzumab's kinetics would be anything like the downward-sloping curve in his made-up chart. Instead, he reached for data from a 2006 publication regarding a small molecule drug, indisulam, which apparently displays similar non-linear kinetics, as an "example" in which assuming linear kinetics could result in an overestimation of trough serum concentration. Appx16355. The indisulam data, however, is not prior art and is, in any event, irrelevant. It sheds no light on what a skilled artisan would have understood about trastuzumab or monoclonal antibody behavior at the time of the invention.

Even though Dr. Grass chose indisulam to illustrate his point, he did not explain why a POSA would have looked to data regarding *any* small-molecule drug, rather than available data for trastuzumab or monoclonal antibodies generally. Dr. Grass conceded that it was known that monoclonal antibodies and small molecule drugs behave differently, and that he could not identify *any* paper showing that *any* antibody follows the downward-sloping pharmacokinetic profile

depicted in his made-up chart. Appx17774-17775 (73:21-75:16), Appx17785-17786 (116:24-119:18).

For these reasons, there simply is no evidentiary support for the Board's conclusion that a skilled artisan would have rejected a one-compartment model on grounds that it "could overestimate" trough serum levels. Appx16355. Dr. Grass's generalized opinions about dose-dependent drugs and his fictional chart are conclusory, and the indisulam example is precisely the "scintilla of evidence" that fails to qualify as substantial evidence required to support the Board's finding. *See In re Gartside*, 203 F.3d at 1312.

B. The Board's Finding that "Nothing in the Record" Suggested that a One-Compartment Model Would Not Overestimate Serum Levels is Not Supported by Substantial Evidence

The Board compounded its error by finding that there was "*nothing in the record* to suggest that a similar overestimation [shown in Dr. Grass's made-up chart and indisulam example] would not have been a concern for tri-weekly trastuzumab administration." Appx00029 (emphasis added). The record evidence was otherwise. The Board incorrectly rejected Petitioners' evidence that the one-compartment model would have actually *under*estimated serum concentration levels of trastuzumab precisely because of its dose-dependent nature.

Unlike Dr. Grass's chart and post-priority date small-molecule example, Dr. Jusko offered several *prior art* references showing that monoclonal antibodies and

receptor-mediated drugs like trastuzumab have longer half-lives and decreased clearance over time. Thus, the linear model would have actually *under*estimated the actual serum concentration levels of trastuzumab in a three-week dosing regimen. This is the exact opposite of Dr. Grass's speculative downward-sloping serum concentration curve. At his deposition, Dr. Grass admitted that a POSA would have considered the known properties of antibodies and other receptor-mediated drugs. Appx17770 (57:2-12), Appx17772 (64:21-65:8), Appx17773 (68:7-69:12).

The Board's reasons for rejecting this prior art evidence are entirely unfounded. The Board dismissed King '98 because it reported only $t_{½}\beta$ (and not $t_{½}\alpha$) data for trastuzumab, Appx00029, ignoring that a one-compartment model results in only one half-life value and that this same model was used for *five* therapeutic antibodies in King '98. The Board also ignored the fundamental conclusion from the data for all 13 therapeutic antibodies: all of them, including trastuzumab, exhibit the same pharmacokinetic profile, i.e., "long circulating half-life in humans" and "at very high IgG levels . . . a prolonged half-life is observed." Appx14775. The Board noted that King '98 concluded that for antibodies generally "the half-life varies with concentration," Appx00029, but ignored that the half-life uniformly varies in the *same direction*.

The Board found that Levy '94 was not relevant because it analyzes small molecules such as ACE inhibitors, not antibodies, and "does not make any definitive conclusions as to their pharmacokinetic behaviors." Appx00029-00031. Not so. Levy '94 expressly concluded that receptor-mediated drugs – and the prior art showed that trastuzumab acts as a receptor-mediated drug, *see, e.g.,* Appx14775 – "can persist much longer than indicated by its *apparent* plasma [half-life]," Appx17319 (emphasis in original), as depicted in its chart showing "[t]ypical concentration-time profile" for receptor-mediated drugs. Appx17317.

The Board also criticized Dr. Jusko's allegedly "inconsistent opinion" in relying on Levy '94 which concerns small molecule drugs, while faulting Dr. Grass for relying on the small molecule drug indisulam. Appx00030-00031. But this ignores Levy '94's teaching that receptor-mediated drugs – like trastuzumab and monoclonal antibodies generally, and *unlike* indisulam – exhibit the same pharmacokinetic profile, i.e., with the increase in dose, there is an increased half-life and decreased elimination over time. Appx17317.

Similarly, the Board's dismissal of Koizumi '86 is erroneous. Appx00031-00033. Koizumi '86 concluded that higher doses of antibodies lead to increased half-life and decreased clearance from the body. Appx17384. The Board did not reject this conclusion, but focused on the extremely low dose and short time interval depicted in its representative chart, stating that the linear model "could

overestimate actual serum concentrations for certain doses (e.g., 20 mg) or at certain times after injection (e.g., less than 2 days)." Appx00032. The Board again ignored the reference's fundamental teaching: *higher* doses of monoclonal antibodies doses lead to *longer* half-lives and *decreased* elimination over time.

The Board also focused on Koizumi '86's use of a multi-compartmental model and the statement that a one-compartment model was "vulnerable to error in a system such as [a monoclonal antibody], wherein many processes remain to be clarified." Appx00033. But Koizumi '86 was published *13 years* before the patents' priority date. By 1999, many of those processes *were* clarified. *See, e.g.,* King '98. The reference, therefore, says nothing about how a POSA in 1999 would have understood the one-compartment model as applied to a monoclonal antibody.

C. The Board's Finding that Shed Antigen Would Have Deterred a POSA from Tri-Weekly Administration is Not Supported by Substantial Evidence

The Board wrongly found that a skilled artisan would have been concerned that shed antigens could "significantly affect" serum trough concentrations for tri-weekly administration of trastuzumab. Appx00027. In reaching this finding, the Board muddled the teachings of the prior art:

> [T]his prior art data appears to show that patients with *any* detectable shed antigen levels (i.e., 64% of patients as set forth

> in the Herceptin label) had a mean antibody trough level that was close to the 10-20 μg/mL threshold for efficacy.

Id. (emphasis in original). The prior art says nothing of the kind.

The Board cited the Herceptin Label's observation that 64% of patients had "*detectible*" shed antigen and then tied this statement to Pegram '98's observation that "patients with *any measurable* shed [antigen] serum level . . . had lower mean trough [trastuzumab] concentrations . . . across all time points . . . ." Appx00026 (emphasis added). The Board, however, ignored the actual teaching of Pegram '98: (a) there was "an inverse relationship" between serum half-life and patients with *high* shed antigen, i.e., ".5 μg/ml or greater," Appx00894, (b) only 18% of patients had high shed antigen, *id.*, and (c) overall there was *no* "significant loss of quantitation" of trough trastuzumab concentration unless the ratio of trastuzumab to shed antigen was less than 10:1, which occurred in a "*small number* of samples," Appx00898 (emphasis added). Notably, in Baselga '96 and Pegram '98, patients received much lower dosages of trastuzumab – a loading dose of 250 mg and weekly doses of 100 mg – than the 500 mg or 712 mg loading dose and tri-weekly doses of 500 mg in Dr. Jusko's analyses.

The Board also entirely missed Pegram '98's ultimate conclusions from this data: (a) "measurable [shed antigen] *does not preclude clinical response*" to treatment because "eight of the nine responders had measurable shed [antigen]

during the course of this study," including one with a "very high level," and (b) shed antigen "may have limited use as a predictive factor for objective clinical response," Appx00898 (emphasis added). Relying on the actual teachings of the prior art, Dr. Jusko testified that for the vast majority of patients, shed antigen had no significant impact on serum trough levels or efficacy, even when detectable. Appx17572.

The Board also ignored that the approved dose of the Herceptin Label – a 4 mg/kg loading dose followed by weekly doses of 2 mg/kg – resulted in serum trough levels lower than those predicted by Dr. Jusko for 500 mg tri-weekly doses. Yet these dosage levels were sufficient to obtain approval despite the known shed antigen concern. There simply is no evidence in the prior art to support the finding that shed antigen would have deterred a POSA from tri-weekly administration of trastuzumab.

As Dr. Jusko testified, even if a tri-weekly dosing regimen might not work for *all* patients, that does not suggest that the dosing regimen would not be considered successful. "The relevant question is only whether three-weekly dosing would be considered feasible as an option, not whether it should replace weekly dosing for all patients." Appx17573. A reasonable expectation that tri-weekly dosing would work for the vast majority of patients is more than enough to

establish a reasonable expectation of success. *See Hoffman La Roche*, 748 F.3d at 1331; *Pfizer*, 480 F.3d at 1364.

III. THE BOARD'S FINDING THAT TWO-WEEK ADMINISTRATION IS NOT OBVIOUS IS NOT SUPPORTED BY SUBSTANTIAL EVIDENCE

The Board determined that there was no reasonable expectation of success for three-week administration of trastuzumab and found, as a result, two-week administration is also not obvious. That does not follow. While a determination that three-week dosing was obvious would have rendered, *ipso facto*, two-week dosing obvious, the converse is not true. The Board never specifically addressed the claims to two-week administration, but a POSA would, without doubt, have understood that there was a reasonable expectation of success for 14-day administration where the reported half-life of trastuzumab at 500 mg was 12 days.

A. The Board Failed to Address Claims to Two-Week Administration

In order to "allow effective judicial review, . . . the agency is obligated to 'provide an administrative record showing the evidence on which the findings are based, accompanied by the agency's reasoning in reaching its conclusions.'" *Synopsys, Inc. v. Mentor Graphics Corp.*, 814 F.3d 1309, 1322 (Fed. Cir. 2016) (quoting *In re Lee*, 277 F.3d 1338, 1342 (Fed. Cir. 2002). The Board, as an administrative agency, "must articulate 'logical and rational' reasons for [its]

decision[]." *Synopsys*, 814 F.3d at 1322 (quoting *Allentown Mack Sales & Serv., Inc. v. NLRB*, 522 U.S. 359, 374 (1998)); *see also Power Integrations, Inc. v. Lee*, 797 F.3d 1318, 1326 (Fed. Cir. 2015) ("Under the APA, the board is obligated not only to come to a sound decision, but to fully and particularly set out the bases upon which it reached that decision.").

In their petitions, Petitioners expressly identified the two-week dosing interval of claim 1 as an independent basis for their petitions and specifically argued that this regimen is obvious in light of the prior art. Appx00301. Similarly, in his claim-by-claim analysis, Petitioners' expert Dr. Lipton separately analyzed the two-week dosing interval and included it as a separate limitation in his claim chart. Appx00399-00405, Appx00521-00522. Specifically addressing two-week dosing, Dr. Lipton concluded that a POSA "would have been motivated to decrease the frequency of [trastuzumab] injections and would have arrived at the *claimed dosing schedule* by routine optimization of the therapy disclosed by the Herceptin label." Appx00403 (emphasis added). That Genentech chose to focus its arguments on the three-week administration of claim 11 does not diminish that two-week administration was properly raised, argued, and at issue. The Board had a duty to address it.

Initially, the Board recognized that "[i]n general terms, the challenged claims are directed to a dosing regimen for the treatment of cancer in which

trastuzumab is administered at an initial dose, followed by administration of the antibody at subsequent doses that are the same or less than the initial dose and separated in time by *at least two weeks.*" Appx00011-00012 (emphasis added). The Board even acknowledged Dr. Lipton's claim chart. Appx00011 ("Petitioners have provided a claim-by-claim explanation for the basis of their contention that claims 1-3, 5, 7, 9-11, and 17-33 are obvious . . . ."). Nevertheless, the Board focused *only* on three-week administration, stating: "[o]ur obviousness analysis *assumes* a treatment method in which trastuzumab is administered *once every three weeks*, as that dosing interval is encompassed by all the challenged claims and is the focus of the parties' arguments and evidence in this proceeding." Appx00012 (emphasis added). Without ever addressing claim 1 of either patent, the Board concluded that "Petitioners have not established the reasonable expectation of success required for obviousness" for *all* claims. Appx00033.

B. The Board's Finding that Claims to Two-Week Administration are Unobvious is Erroneous

While such a failure might require remand in some circumstances, there is no need here. The undisputed evidence clearly establishes that a POSA would have had the same motivation to decrease dosing frequency by moving from a weekly to a bi-weekly dosing regimen: (a) greater patient convenience with fewer clinic trips, (b) lower hospital and patient costs, (c) better patient compliance, and

(d) better patient quality of life. Appx00403-00405. Moreover, the record shows that the chemotherapy drug cisplatin was co-administered with trastuzumab every four weeks. Appx00888, Appx00906. Thus, similar to the three-week dosing regimen of trastuzumab plus paclitaxel, a two-week dosing regimen of trastuzumab plus cisplatin would have enabled an oncologist to match the trastuzumab doses with cisplatin's four-week dosing regimen, and such co-administration would lead to the same patient and hospital benefits.

The record demonstrates that a POSA would have had a reasonable expectation that dosing trastuzumab every 14 days, rather than weekly, would be effective. The Herceptin Label revealed that a 500 mg dose has a *half*-life of 12 days and resulted in a trough serum level greatly exceeding that required for efficacy. The prior art disclosed that high doses resulted in increased half-lives and decreased elimination from the body. Appx00746. A POSA – indeed, a lay person – reasonably would have expected trastuzumab to easily exceed the target trough serum concentration level of 10-20 μg/ml at day 14.

Thus, claims 1-3, 7, 9, 17-29, and 31-33 of the '196 patent and claims 1-3, 7, 9, 16-28, 30-35 and 37-40 of the '379 patent, all of which are directed to two-week dosing regimens, are obvious.

CONCLUSION

For the foregoing reasons, the Court should reverse the Board's IPR decisions and find that all claims of the '196 and '379 patents are invalid as obvious.

Dated: March 21, 2019

Respectfully submitted,

/s/ Stefan Mentzer

Stefan Mentzer
WHITE & CASE LLP
1221 Avenue of the Americas
New York, New York 10020
smentzer@whitecase.com

Counsel for Appellant
Samsung Bioepis Co., Ltd.

ADDENDUM

Trials@uspto.gov
571-272-7822

Paper No. 83
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00804[1]
Patent 6,627,196 B1

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

PAULRAJ, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

[1] Case IPR2017-01958 has been joined with IPR2017-00804

I. INTRODUCTION

Hospira, Inc. ("Hospira") filed a Petition (Paper 1, "Pet."), requesting institution of an *inter partes* review of claims 1–3, 5, 7, 9–11, and 17–33 of U.S. Patent No. 6,627,196 B1 (Ex. 1001, "the '196 patent"). Genentech, Inc. timely filed a Patent Owner Preliminary Response (Paper 6, "Prelim. Resp."). We determined, based on the information presented in the Petition and Preliminary Response, that there was a reasonable likelihood that Hospira would prevail in challenging claims 1–3, 5, 7, 9–11, and 17–33 as unpatentable under 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, the Board instituted trial on July 27, 2017, as to those claims of the '196 patent. Paper 13 ("Institution Decision" or "Inst. Dec."). Following our institution based on Hospira's Petition, Samsung Bioepis Co., Ltd. ("Samsung") filed a substantially identical Petition challenging the same claims of the '196 patent and requested joinder in this proceeding, which we granted. Paper 40. Thus, Hospira and Samsung together are the "Petitioners" in this proceeding.

Patent Owner filed its Response to the Petition (Paper 41, "PO Resp.") and Petitioners filed a Reply to Patent Owner's Response (Paper 55, "Reply"). Patent Owner filed a Motion to Exclude certain evidence (Paper 68), to which Petitioners filed an Opposition (Paper 69) and Patent Owner filed a Reply in support thereof (Paper 73). Patent Owner also filed a Motion for Observations on Cross-Examination of Petitioners' Reply Declarants (Drs. Allan Lipton and William Jusko) (Paper 64) to which Petitioners filed a Response (Paper 70). Additionally, pursuant to our authorization, Patent Owner filed an Identification of Improper New Reply Materials (Paper 67), to which Petitioners filed a Response (Paper 72) and Patent Owner filed a Reply (Paper 74). An oral hearing was held on May 8,

2018. The transcript of the hearing has been entered into the record. Paper 80 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Based on the record before us, we conclude that Petitioners have *not* demonstrated by a preponderance of the evidence that claims 1–3, 5, 7, 9–11, and 17–33 of the '196 patent are unpatentable.

A. Related Proceedings

As a related matter, Petitioners and Patent Owner identify a concurrently-filed petition for *inter partes* review (IPR2017-00805) for a related patent, U.S. Patent 7,371,379 ("the '379 patent"). *See* Pet. 2. We issue our Final Written Decision in IPR2017-00805 concurrently with this decision. Additionally, also concurrently with this Decision, we issue Final Written Decisions in two other *inter partes* review proceedings concerning the '196 and '379 patents brought by another petitioner. IPR2017-01139; IPR2017-001140.

The parties also identify litigation matters pending in the U.S. District Courts for the Northern District of California and the District of Delaware and on appeal before the Federal Circuit Court of Appeals concerning the '379 and '196 patents, as well as foreign proceedings concerning counterparts to these patents, as related matters. Paper 81; Paper 82.

B. The '196 Patent (Ex. 1001)

The '196 patent issued on September 30, 2003, with Sharon A. Baughman and Steven Shak as the listed co-inventors. Ex. 1001, (45), (75). The '196 patent issued from an application filed August 25, 2000, and claims priority to provisional applications filed June 23, 2000, and August

27, 1999. *Id.* at (22), (60). The parties have not disputed the claimed priority date for the '196 patent.

The '196 patent relates generally to dosages for the treatment of disorders characterized by the overexpression of ErbB2 (also known as HER2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR). *Id.* at 1:13–25, 42–48. The overexpression of ErbB2 has been associated with breast cancer. *Id.* As noted in the '196 patent, a recombinant humanized anti-ErbB2 monoclonal antibody (alternatively referred to as "rhuMab HER2," "trastuzumab," or by its tradename "Herceptin")[2] had been clinically tested and approved for patients with ErbB2-overexpressing metastatic breast cancers who received prior anti-cancer therapy. *Id.* at 3:54–60. The recommended initial "loading dose" for trastuzumab was 4 mg/kg administered as a 90-minute infusion, and the recommended weekly "maintenance dose" was 2 mg/kg, which could be administered as a 30-minute infusion if the initial loading dose was well-tolerated. *Id.* at 3:61–65.

The invention described in the '196 patent "concerns the discovery that an early attainment of an efficacious target trough serum concentration by providing an initial dose or doses of anti-ErbB2 antibodies, followed by subsequent doses of equal or smaller amounts of antibody (greater front loading) is more efficacious than conventional treatments." *Id.* at 4:21–27. The method of treatment, according to the invention described in the patent, "involves administration of an initial dose of anti-ErbB2 antibody of more

[2] For consistency's sake, we will refer to the antibody at issue in this proceeding as trastuzumab unless we are directly quoting one of its alternative names from another document.

than approximately 4 mg/kg, preferably more than approximately 5 mg/kg," with the maximum dose not to exceed 50 mg/kg. *Id.* at 4:47–51. "[T]he initial dose or doses is/are followed by subsequent doses of equal or smaller amounts of antibody at intervals sufficiently close to maintain the trough serum concentration of antibody at or above an efficacious target level." *Id.* at 4:61–65. Preferably, "the amount of drug administered is sufficient to maintain the target trough serum concentration such that the interval between administration cycles is at least one week," and "the trough serum concentration does not exceed 2500 µg/ml and does not fall below 0.01 µg/ml during treatment." *Id.* at 4:67–5:5. The patent explains that "[t]he front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment." *Id.* at 5:5–8. As a result, "[t]he efficacious target trough serum concentration is reached in 4 weeks or less . . . and most preferably 1 week or less, including 1 day or less." *Id.* at 4:26–29. Additionally, the patent states that the method of therapy may involve "infrequent dosing" of the anti-ErbB2 antibody, wherein the first and second dose are separated by at least two weeks, and optionally at least about three weeks. *Id.* at 6:20–31.

The '196 patent describes embodiments in which the initial dose of trastuzumab is 6 mg/kg, 8 mg/kg, or 12 mg/kg, followed by subsequent maintenance doses of 6 mg/kg or 8 mg/kg administered once every 2 or 3 weeks, in a manner such that the trough serum concentration is maintained at approximately 10–20 µg/ml during the treatment period. *Id.* at 5:16–55, 45:23–28. The treatment regimen according to the invention may further comprise administration of chemotherapy along with trastuzumab. *Id.* at 6:4–8, 7:22–25, 45:64–65. Of particular relevance, the '196 patent includes

a prophetic example describing the administration of trastuzumab intravenously every three weeks in combination with the chemotherapeutic agent paclitaxel. *Id.* at 46:5–48:4. According to this example, "[s]imulation of the proposed treatment regimen suggests that the trough serum concentrations will be 17 [µ]g/ml, in the range (10–20 [µ]g/ml) of the targeted trough serum concentrations from previous HERCEPTIN® IV clinical trials." *Id.* at 46:12–16. The example sets forth inclusion criteria for a study in which patients will be administered trastuzumab every three weeks. *Id.* at 47:9–48:12. The '196 patent concludes that "[i]t is believed that the above treatment regimen will be effective in treating metastatic breast cancer, despite the infrequency with which HERCEPTIN® is administered to the patient." *Id.* at 48:1–4.

C. Illustrative Claim

Petitioners challenge claims 1–3, 5, 7, 9–11, and 17–33 of the '196 Patent. Independent claim 1 is illustrative, and is reproduced below:

> 1. 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 at least approximately 5 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 the subsequent doses are separated in time from each other by at least two weeks.

Ex. 1001, 55:63–57:2.

D. The Asserted Ground of Unpatentability

Petitioners challenge the patentability of the claims of the '196 Patent based on the following ground:

References	Basis	Claims challenged
Herceptin label,[3] Baselga '96,[4] Pegram '98,[5] and the knowledge of a person of ordinary skill in the art	§ 103(a)	1–3, 5, 7, 9–11, and 17–33

Petitioners further rely upon the declarations of Allan Lipton, M.D. (Ex. 1002; Ex. 1056) and William Jusko, Ph.D. (Ex. 1003; Ex. 1057). Patent Owner relies upon the declarations of George Grass, Ph.D. (Ex. 2039) and Karen Gelmon, M.D. (Ex. 2040).

II. ANALYSIS

A. Claim Construction

We interpret claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable construction standard, claim

[3] Genentech, Inc, Herceptin® Trastuzumab, Sept. 1998 (hereinafter "Herceptin Label" (Ex. 1008).
[4] Jose Baselga, *Phase ll Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients With HER2/neu-Overexpressing Metastatic Breast Cancer*, 14 JOURNAL OF CLINICAL ONCOLOGY 737–744 (1996) (hereinafter "Baselga '96") (Ex. 1013).
[5] Mark D. Pegram, *Phase ll Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185^{HER21neu} Monoclonal Antibody Plus Cisplatin in Patients With HER2/neu-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment*, 16 JOURNAL OF CLINICAL ONCOLOGY 2659–71 (1998) (hereinafter "Pegram '98") (Ex. 1014).

terms are generally given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). "Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). "Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioners propose a construction for "ErbB2 receptor." *See* Pet. 24. Patent Owner does not propose any terms to be construed in its post-institution Response. We find that no explicit construction of any claim term is necessary to decide the issues presented in this case. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999))).

B. Level of Skill in the Art

Petitioners contend that a person of ordinary skill in the art for the '196 patent would be a "team" that includes both (1) a clinical or medical oncologist specializing in breast cancer with several years of experience in breast cancer research or clinical trials, and (2) a person with a Ph.D. in pharmaceutical sciences or a closely related field with an emphasis in pharmacokinetics with three years of relevant experience in protein based

drug kinetics. Pet. 23–24 (citing Exs. 1002 ¶ 14; 1003 ¶ 15; 1006 ¶ 32). Patent Owner does not address the requisite level of skill in its Response.

Because it is otherwise undisputed and consistent with the evidence of record, we adopt Petitioners' proposed definition of a person of ordinary skill in the art ("POSITA" or "skilled artisan") for purposes of our analysis. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Patentability Analysis

1. Content of the Prior Art

Petitioners rely upon, *inter alia*, the following prior art teachings to support their challenge.

a. Herceptin Label (Ex. 1008)

As recognized in the '196 patent, trastuzumab was already FDA-approved and commercially sold in the U.S. by 1998 under the tradename Herceptin. Ex. 1001, 3:54–60. The Herceptin label teaches:

> 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. 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.

Ex. 1008, 1.

The Herceptin label also teaches that "[i]n 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 . . . was observed," and "[b]etween week 16 and 32, Trastuzumab serum concentration reached a steady state with a mean trough and peak concentrations of approximately 79 [mg]/mL and 123 [mg]/mL, respectively. *Id.* The label further describes clinical studies in which metastatic breast cancer patients with certain levels of HER2 overexpression were administered chemotherapy either alone or in combination with trastuzumab given intravenously as a 4 mg/kg loading dose followed by weekly doses at 2 mg/kg. *Id.* The chemotherapy in these clinical studies (e.g., paclitaxel) was administered every 3 weeks (21 days). *Id.*

b. Baselga '96 (Ex. 1013)

Baselga '96 reports the results of a phase II clinical trial in which patients with ErbB2-overexpressing metastatic breast cancer were treated with trastuzumab. Ex. 1013, 737. The pharmacokinetic goal of the trial "was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell grown in the preclinical model." *Id.* at 738. Further, the "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." *Id.*

According to the results reported in Baselga '96, "[m]ore than 90% of the examined population (41 patients) had rhuMAb HER2 trough levels above the targeted 10 μg/mL level. *Id.* at 739. Moreover, the treatment "was remarkably well tolerated." *Id.* "Toxicity [from rhuMAb HER2] was

minimal," and no immune response against the antibody was detected. *Id.* at 737. Out of the 768 times trastuzumab was administered, "only 11 events occurred that were considered to be related to the use of the antibody." *Id.* at 739. Baselga '96 also teaches that in preclinical studies (both *in vitro* and in xenografts), trastuzumab "markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." *Id.* at 743.

c. Pegram '98 (Ex. 1014)

Pegram '98 reports the results of a phase II clinical trial using a combination of trastuzumab plus cisplatin. Ex. 1014, 2659. Pegram '98 states that "[t]hese studies showed that the pharmacokinetics of rhuMAb HER2 were predictable, and that the doses delivered achieved a target trough serum concentration of 10 to 20 μg/mL, which is associated with antitumor activity in preclinical models." *Id.* at 2660. Pegram '98 also reports a toxicity profile of the combination that paralleled the toxicity of cisplatin alone, thereby leading to the conclusion that trastuzumab did not increase toxicity. *Id.* at 2668.

2. Obviousness Based on the Herceptin Label, Baselga '96, Pegram '98, and the Knowledge of a Person of Ordinary Skill in the Art of the Prior Art

Petitioners have provided a claim-by-claim explanation for the basis of their contention that claims 1–3, 5, 7, 9–11, and 17–33 are obvious over the Herceptin label in view of Baselga '96, Pegram '98, and the Knowledge of a Person of Ordinary Skill in the Art. Pet. 29–54.

In general terms, the challenged claims are directed to a dosing regimen for the treatment of cancer in which trastuzumab is administered at an initial dose, followed by administration of the antibody at subsequent

doses that are the same or less than the initial dose and separated in time by at least about two weeks. Independent claim 1 specifies an initial dose of approximately 5 mg/kg, while certain dependent claims specify higher initial doses of 6 mg/kg, 8 mg/kg, or 12 mg/kg (e.g., cls. 2, 3, 9), whereas other dependent claims specify that the subsequent doses are separated in time by at least three weeks (e.g., cls. 5, 10). Our obviousness analysis assumes a treatment method in which trastuzumab is administered once every three weeks, as that dosing interval is encompassed by all the challenged claims and is the focus of the parties' arguments and evidence in this proceeding.

Petitioners rely upon the teaching in the Herceptin label that trastuzumab doses of up to 500 mg had been successfully administered to patients. Pet. 31 (citing Ex. 1008, 1). Based on a patient weight range of 55–85 kg, Petitioners calculate that the weight-based dose for the 500 mg absolute dose taught by the Herceptin label ranges from 5.88–9.09 mg/kg. *Id.* at 31–32 (citing Ex. 1002 ¶¶ 55–57; Ex. 1003 ¶ 45; Ex. 1026, 3; Ex. 1027, 334 (Table 7-2)). Petitioners further rely upon the Herceptin label's teaching that trastuzumab doses should be "front-loaded" with a higher initial dose of 4 mg/kg followed by a lower weekly maintenance dose of 2 mg/kg. *Id.* at 33. Additionally, Petitioners rely upon the teaching in the Herceptin label describing the administration of trastuzumab in combination with chemotherapeutic agents, and that these chemotherapeutic agents are administered once every three weeks to patients. *Id.* at 35–36, 43–44. Petitioners further rely upon Baselga '96 and Pegram '98 insofar as they confirm that the weekly dosing regimen encompassed by the Herceptin label was successfully administered to patients in phase II clinical trials, and that

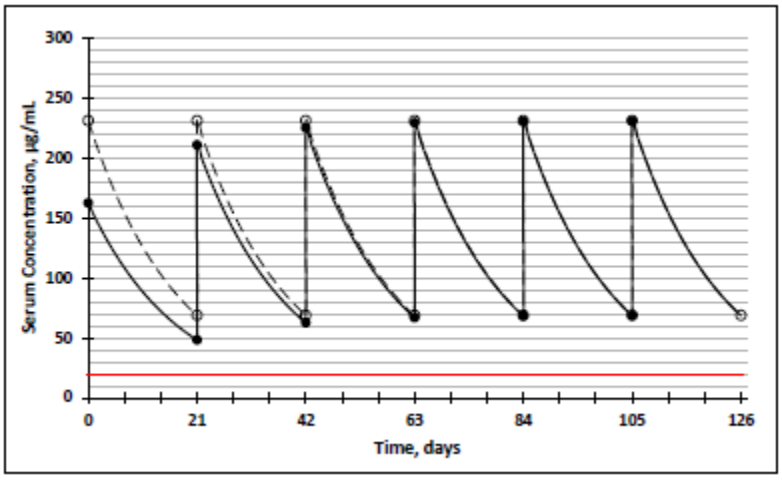
the skilled artisan would have been aware of a target trough serum concentration of 10–20 μg/mL for trastuzumab. Pet. 33, 37.

Petitioners acknowledge that the Herceptin label, along with Baselga '96 and Pegram '98, teach only a *weekly* dosing regimen, but assert that the skilled artisan would nonetheless have been motivated to decrease the frequency of trastuzumab administration to once every three weeks for several reasons. *Id.* at 34–42. First, Petitioners contend that "a skilled artisan would decrease the frequency of injections to improve efficiency, to provide a more convenient dosing regimen—particularly for terminally ill patients—, and to improve patient compliance and quality of life." *Id.* at 34. Second, Petitioners contend that the skilled artisan would have been motivated to apply a tri-weekly (i.e., once every three weeks) regimen for the antibody in order to align with the dosing schedules of the chemotherapy so that a patient would only have to make one trip to the clinic to receive both doses. *Id.* at 36. In support, Petitioners rely upon their oncology expert, Dr. Lipton, who attests that each trip to the clinic to receive even a single infusion of antibody treatment often takes between a half and a full day, which can result in additional time and costs for the patient. Ex. 1002 ¶¶ 42–43.

Petitioners further contend that the skilled artisan would confidently decrease the frequency of injections and use a tri-weekly dosing regimen in view of trastuzumab's known pharmacokinetic properties. *Id.* at 36. Petitioners contend that arriving at the tri-weekly dosing schedule was merely a matter of "routine calculation and optimization" of the therapy outlined in the Herceptin label. *Id.* at 37. In this regard, Petitioners rely upon data from the Herceptin label and Dr. Jusko's opinions to assert that it

would have been a matter of routine calculation for a skilled artisan to determine that a tri-weekly 500 mg trastuzumab dosing regimen would have resulted in a serum concentration well above the target minimum trough concentration of 10–20 µg/mL reported in the prior art. *Id.* at 37–39 (citing Ex. 1003 ¶¶ 46–47, 49–51, 56–58, 62).

Specifically, Dr. Jusko, assuming a "one-compartment" model to approximate drug concentration over time, calculated the initial minimum drug concentration three weeks after first administering a 500 mg antibody dose to a 70 kg patient to be 48.3 µg/mL and the steady-state trough concentration after multiple doses to be 68.7 µg/mL. Ex. 1003 ¶¶ 46–58. Additionally, assuming linear (first-order) kinetics, Dr. Jusko calculated that a 712 mg loading dose followed by 500 mg tri-weekly maintenance doses could be administered to patients while keeping serum drug concentrations within acceptable levels. *Id.* ¶¶ 59–66. Dr. Jusko provides the following graph depicting expected trastuzumab concentrations over time for a 70 kg patient administered 500 mg of trastuzumab every three weeks, with or without an initial 712 mg loading dose (broken and solid lines, respectively):



Ex. 1003 ¶ 62 (Fig. 2). As shown in the figure above, when administering either calculated dosing regimen, Dr. Jusko concludes that the trastuzumab serum concentration would have been expected to stay well above the target minimum trough concentration of 10–20 μg/ml (with 20 μg/ml shown in red). *Id.* ¶ 63.

As noted by Petitioners, Dr. Jusko made three assumptions in performing his calculations: (1) that trastuzumab exhibits non-exponential kinetics; (2) that the initial concentration (C_0) can be estimated by multiplying the dose by the volume of distribution and average mass of a patient; and (3) that the kinetics of trastuzumab remain constant with multiple-dosing. Pet. 42 (citing Ex. 1003 ¶¶ 69–71; Ex. 1028, 91; Ex. 1029, 77).

The two main issues argued in this proceeding are: (a) whether there would have been a motivation to extend the weekly dosing interval taught in the prior art to a tri-weekly dosing interval based on concerns about patient convenience and quality of life, and (b) whether there would have been a reasonable expectation of success in implementing such a dosing regimen based on Dr. Jusko's pharmacokinetic analysis. It is Petitioners' burden to demonstrate both "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (internal citations omitted). As they are distinct legal requirements for obviousness, we address motivation and reasonable expectation of success separately in our analysis. For the reasons explained below, while skilled artisans may have

been motivated to extend the dosing interval, we find that they would not have had a reasonable expectation of success in doing so based on the prior art. Thus, we determine that Petitioners have not shown that the challenged claims are unpatentable for obviousness.

a. Motivation

As discussed above, Petitioners' primary arguments on motivation for extending the dosing interval of trastuzumab from the weekly administration taught in the prior art to tri-weekly is based on a desire to improve patient "convenience," "compliance," "efficiency," and "quality of life." Pet. 34. In its Response, Patent Owner contends these "patient-related" factors would not have served as a reason to extend the dosing interval because the primary focus for skilled artisans in developing a treatment regimen for HER2-positive breast cancer would have been on efficacy. PO Resp. 28–36. Moreover, instead of extending trastuzumab's dosing interval to a tri-weekly schedule, Patent Owner asserts that skilled artisans were actually increasing the frequency of the chemotherapy (paclitaxel) administration in numerous clinical trials so that both drugs could be administered on a weekly schedule. *Id.* at 31–32. Patent Owner also argues that this is not simply a case of selecting an optimal doses from known range of doses in the prior art since the only dosing interval disclosed was weekly. *Id.* at 26. Patent Owner notes that "at the time of the invention, developing an antibody dosing regimen for clinical use was described as a "complicated task" and such drugs "defy easy quantitative description and prediction." *Id.* at 26 (citing Ex. 2004, 11; Ex. 1022, 3:109).

We find that the skilled artisan would have been motivated to extend the dosing interval for the simple (yet compelling) reasons that doing so

would have been more cost-effective and less burdensome for the patient undergoing such treatment, which required in-person visits to the clinic for each antibody infusion. As previously recognized by the Federal Circuit, "[a] relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance." *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014). Patent Owner seeks to limit this statement in *Hoffman-La Roche* to the specific issue addressed in that case, which was whether once-monthly administration of bisphosphonate ibandronate to treat osteoporosis would have been obvious. PO Resp. 38–39. Patent Owner contends that, unlike the facts of *Hoffman-La Roche*, the claimed treatment regimen at issue in this proceeding involves a "first-in-class" therapeutic (i.e., trastuzumab was the only antibody approved at the time for the treatment of "solid" tumors), a fatal disease condition (breast cancer), and a completely different set of prior art. *Id.* at 39. Patent Owner argues that "[c]onvenience considerations that may be applicable in the context of treatments to prevent osteoporosis have little relevance in the context of treating HER2-positive breast cancer." *Id.* at 39. We do not read *Hoffman-La Roche* to stand for a *per se* rule that it would always have been obvious to extend the dosing interval in order to address patient compliance concerns regardless of the particular medical condition or drug at issue. Nonetheless, based on the specific facts of this case, we find that skilled artisans would have been similarly motivated to administer trastuzumab less frequently to treat breast cancer patients.

In support of this finding, we take into account the real-world experiences of the parties' oncology experts, Dr. Lipton (Petitioner's expert) and Dr. Gelmon (Patent Owner's expert), who are both physicians with

extensive experience treating breast cancer patients in clinical settings. Ex. 1002 ¶¶ 4–10; Ex. 2040 ¶¶ 2–5. Dr. Lipton attests that each trip to his clinic to receive even a relatively short infusion of antibody treatment often takes between a half and a full day, which can result in additional time and costs for the patient. Ex. 1002 ¶¶ 42–43. Indeed, some of his patients have had to travel up to one hundred miles each direction to receive treatment at the clinic. *Id.* ¶ 39. As such, we are not persuaded by Dr. Gelmon's contention that efficacy would have taken precedence over convenience as the focus of cancer treatment in the 1990s. Ex. 2040 ¶¶ 30–34. Of course, maintaining efficacy and safety would have been a paramount concern for the skilled artisan seeking to improve upon the weekly dosing regimen that was previously FDA-approved, but that does not mean improving convenience and quality of life for the patient would not have also been motivating concerns. By 1999, efficacy and safety had already been demonstrated for weekly trastuzumab administration as set forth in the Herceptin label. Ex. 1008. Notably, Dr. Gelmon admitted during her deposition that "before 1999 it was known that providing a drug less frequently might provide benefits to certain patients in terms of convenience, cost and quality of life as long as efficacy and safety were shown." Ex. 1058, 328:24-329:7. Indeed, these same concerns factored into Dr. Gelmon's own clinical study involving tri-weekly trastuzumab administration, which took place within months of the '196 patent priority date. *Id.* at 73:19–75:16.[6]

[6] While the publication of Dr. Gelmon's tri-weekly study does not qualify as prior art, we find the fact that she initiated the study so close to the priority date undermines the credibility of her testimony that skilled artisans

Contrary to Patent Owner's arguments, the prior art need not have expressly articulated or suggested patient convenience or quality of life concerns as the motivation to extend the dosing interval. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[T]he [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ."). Nonetheless, the motivation set forth by Dr. Lipton is supported by his citation to prior art articles indicating that quality of life issues for cancer patients have long been a concern to physicians. Ex. 1002 ¶ 44 (citing Coates, et al., *Quality of Life in Oncology Practice: Prognostic Value of EORTC QLQ-C30 Scores in Patients with Advanced Malignanc*y, 33(7) EUROPEAN JOURNAL OF CANCER 1025–30 (1997) (Ex. 1019); Aaronson, et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology*, 85(5) J. NAT'L CANCER INSTITUTE 365–76 (1993) (Ex. 1020); Ferrell, *Quality of Life in Breast Cancer*, 4(6) CANCER PRACTICE 331–40 (1996) (Ex. 1021)).

Additionally, we find that the skilled artisan would have been motivated to match trastuzumab and chemotherapy dosing. As indicated in

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would not have considered extending the dosing interval at the time. In their Reply, however, Petitioners identify additional post-filing evidence supporting their contention that skilled artisans were motivated by "patient-related factors" to investigate tri-weekly dosing of trastuzumab. Reply 14–15. Insofar as these additional references do not qualify as prior art themselves, nor do they purport to recount what was publicly known in the prior art, we decline to give them any weight in our analysis.

the Herceptin label, patients were often prescribed chemotherapy, such as paclitaxel or anthracycline, in combination with trastuzumab. Ex. 1008, 1. The Herceptin label indicates that both paclitaxel and anthracycline were administered once every three weeks (21 days). *Id.* In addition to convenience for the patient, Dr. Lipton notes that "it is also beneficial for the clinic to administer the combined therapies on the same schedule because they only have to prep the patient once." Ex. 1002 ¶ 66. Patent Owner acknowledges that researchers at the time had explored the possibility of administering paclitaxel to match weekly trastuzumab administration. PO Resp. 9; Ex. 2040 ¶¶ 38, 57; *see, e.g.*, M Fornier, *Weekly (W) Herceptin (H) + 1 Hour Taxol (T): Phase II Study in HER2 Overexpressing (H2+) and Non-Overexpressing (H2-) Metastatic Breast Cancer (MBC)*, 18 PROC. AM. SOC'Y CLINICAL ONCOLOGY 126a (Abstract 482) (1999) (Ex. 2029). But, at the time, paclitaxel was FDA-approved for only tri-weekly treatment. Ex. 1058, 180:22–181:1. Regardless, the fact that skilled artisans were considering matching the antibody and chemotherapy treatments on a weekly basis does not mean that they would also not have considered matching the treatments on a tri-weekly basis. Obviousness does not require the claimed regimen to be the only or best choice, nor may a patentee defeat obviousness simply by identifying another alternative. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention.").

Patent Owner also contends that skilled artisans would not have had a reason to select a 500 mg maintenance dose or 712 mg loading dose, as

calculated by Dr. Jusko. PO Resp. 24–27. We are unpersuaded by these arguments because the Herceptin label expressly teaches that a 500 mg dose was considered safe and tolerable, at least when administered on a weekly basis. Dr. Jusko explained that the 500 mg dose level, and associated 12-day half-life, would have been the obvious starting point "because that was the highest reported tolerable weekly dose level with the longest half-life that would give the POSITA the best chance of achieving the minimum serum trough concentrations to establish efficacy at three weeks." Ex. 1057 ¶ 34. Dr. Jusko further notes that "[i]t would have made no sense to choose a lower dose level, as the result of any such simulation would not have been indicative of the feasibility of three-week dosing—a negative result would merely necessitate simulating at the higher dose level, i.e., 500 mg." *Id.* Furthermore, while the 712 mg loading dose is not expressly disclosed in the prior art (Ex. 1003 ¶¶ 59–63), Patent Owner's experts Dr. Grass and Dr. Gelmon do not dispute Dr. Jusko's calculation of this amount, which is based on equations set forth in a basic pharmacokinetics textbook. Ex. 1002 ¶ 72; *see* Rowland, *et al.*, CLINICAL PHARMACOKINETICS: CONCEPTS AND APPLICATIONS (3rd ed. 1995) (vol. 1), at 88 (Ex. 1022) ("Rowland").[7]

[7] Patent Owner also argues that the pharmacokinetic data in the prior art would not have motivated a skilled artisan to extend the dosing interval of trastuzumab. PO Resp. 40–43. We find that the skilled artisan would have been motivated to extend the dosing interval regardless of the pharmacokinetic data set forth in the prior art. But, as discussed below, we find that trastuzumab's non-linear kinetics would not have provided the skilled artisan with a reasonable expectation of success with such an extended dosing interval.

Accordingly, we find that skilled artisans would have been motivated to extend the dosing interval of trastuzumab to once every three weeks, with a 712 mg loading dose followed by 500 mg maintenance doses.

b. Reasonable Expectation of Success

Having found the requisite motivation to arrive at the claimed dosing regimen, we next turn to whether there would have had a reasonable expectation of success with such a treatment regimen. Based on our consideration of the record evidence, we find that Petitioners have not met their burden of establishing a reasonable expectation of success.

In evaluating reasonable expectation of success, we must "consider the appropriate scope of the patent's claimed invention." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965–66 (Fed. Cir. 2014). Here, the claims of the '196 patent are directed to 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." Ex. 1001, 55:63–66 (emphasis added). Petitioners and Patent Owner both focus their arguments and evidence on whether the skilled artisan would have reasonably expected that trastuzumab plasma concentrations would be maintained above 10–20 μg/mL, which the prior art identifies as the minimum serum trough concentration required for efficacy. In view of the claim scope, we agree that this is an appropriate definition of "success" for purposes of our analysis.

Petitioners contend that the skilled artisan would have extended the dosing interval based on Dr. Jusko's pharmacokinetic analysis as set forth above. Patent Owner disagrees that this type of mathematical analysis would have provided the requisite reasonable expectation of success for the

claimed dosing regimen. In particular, Patent Owner criticizes Dr. Jusko's application of linear pharmacokinetics to predict serum trough concentration insofar as the prior art taught that trastuzumab had demonstrated non-linear (dose-dependent) kinetics. PO Resp. 45–48. As noted by Patent Owner, "[f]or drugs with non-linear kinetics, pharmacokinetic parameters such as half-life do not remain constant but change as a function of the concentration of the drug in the plasma." *Id.* at 46 (citing Ex. 1022, 3:109; Ex. 2008, 123; Ex. 2038 ¶¶ 22–25, 27, 34–36). According to Patent Owner, there is insufficient data in the prior art to accurately predict whether a three-week dosing regimen would be clinically effective, and thus a clinical oncologist would not have confidently used three-week dosing based on Dr. Jusko's pharmacokinetic analysis. *Id.* at 55–57.

As part of our evaluation, we take into account the relative novelty of using antibodies for the treatment of cancer as of the August 27, 1999 priority date. Herceptin had been approved by the FDA for weekly administration in September 1998, less than a year before, was the first antibody approved to target "solid tumors," and the first approved to treat any form of breast cancer. Ex. 1008; Ex. 2003, 388; Ex. 2038, 33:8–17; Ex. 2040 ¶ 23.[8] Petitioners have not pointed to any prior art reference discussing the feasibility or viability of a tri-weekly antibody dosing regimen.

[8] Prior to August 1999, the FDA had approved only one other antibody for treating cancer—Patent Owner's rituximab product, which was approved for non-Hodgkin's lymphoma treatment in 1997. Ex. 2003, 388. We find no evidence of record indicating that rituximab had been approved or successfully tested for anything longer than weekly dosing.

While Dr. Jusko's calculations are based on "textbook" equations that were known in the prior art, the actual pharmacokinetic analysis set forth in his declaration for determining the serum trough concentration associated with a tri-weekly dosing regimen of trastuzumab was not found in any prior art reference. Thus, we find Dr. Jusko's analysis to be largely based on impermissible hindsight. *KSR*, 550 U.S. at 421 ("A factfinder should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.").

Petitioners contend that Dr. Jusko applied the same model that Patent Owner and its collaborators did in the prior art. Reply 17. In particular, Petitioners rely upon Baselga '96's statement that "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." Ex. 1013, 738. However, Baselga '96 did not mention a tri-weekly schedule, and instead determined that a regimen in which patients received an initial dose of 250 mg trastuzumab followed by 100 mg weekly doses was the "optimal dose and schedule." *Id.* Petitioners also speculate that the Herceptin label's reporting of only a single half-life for each dosage level "suggest[s] use of a one-compartment model." Reply 17; Ex. 1003 ¶ 34. But the Herceptin label does not explicitly indicate that a one-compartment model was used to model the weekly dosing regimen discussed therein. In any event, the pharmacokinetics discussed in the Herceptin label were based on actual clinical trials rather than just mathematical predictions. Ex. 1008, 1 ("The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease."). Baselga '96 and the Herceptin label both specifically recognize that trastuzumab has "dose dependent pharmacokinetics." Ex. 1008, 1;

Ex. 1013, 738. The very pharmacokinetics textbook relied upon by Dr. Jusko notes that "dose-dependent and time-dependent kinetic behaviors defy easy quantitative description and prediction." Ex. 1022, vol. 3, 395.

We recognize that Pegram'98 states that Phase I clinical "studies showed that the pharmacokinetics of rhuMAb HER2 were predictable." Ex. 1014, 2660. But as explained by Patent Owner's pharmacokinetic expert Dr. Grass, "[a] skilled artisan would understand 'predictable' in this context to mean that administration of the same dose with the same dosing schedule would likely yield the same serum concentrations if given to a similar patient population." Ex. 2039 ¶ 54. It does not suggest predictability across different dosing intervals. Insofar as the pharmacokinetics discussed in the prior art were only based on studies of weekly administration of lower trastuzumab doses, we do not find that the references support Petitioners' conclusion that the same "one-compartment" model could also be used to reasonably predict the expected serum concentrations for tri-weekly administration using higher doses of the antibody.

The evidence shows that the prior art did not contain sufficient data from which the skilled artisan could reliably predict the plasma concentration for trastuzumab over a three-week dosing interval using a one-compartment model. In this regard, we credit the testimony of Dr. Grass. Dr. Grass explains that one potential source of non-linear kinetics for trastuzumab was the presence of "shed antigens" in the patient's serum, which are extra-cellular domain HER2 receptors (ECD^{HER2}) "shed" from the tumor source that circulate in the patient's blood stream. Ex. 2039 ¶¶ 56, 71, 72. We are unpersuaded by Dr. Jusko's opinion that the effect of shed antigens on half-life and serum trough levels would not have been of

concern to the skilled artisan because it was "only shown to be significant in the small percentage of patients for which shed antigen reached 'high levels,' *i.e.*, greater than about 0.5 μg/mL." Ex. 1057 ¶ 46 (citing Ex. 1013 and Ex. 1014).

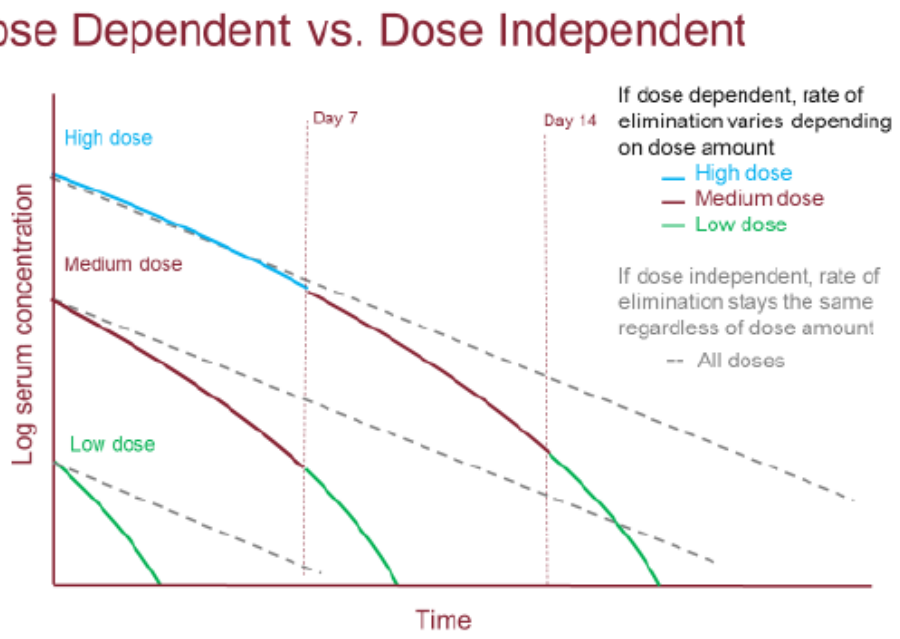
Petitioners' own prior art references highlight the uncertainty caused by the presence of shed antigens on the pharmacokinetics of trastuzumab. For instance, the Herceptin label notes that "64% of patients (287/447) had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL)," and that "[p]atients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations." Ex. 1008, 1. Baselga '96 likewise teaches that "[t]he rhuMAb HER2 serum $t_{1/2}$ was found to be dependent on the presence of circulating ECD^{HER2} released from the tumor into the serum." Ex. 1013, 739. In fact, for those patients with high levels of shed antigen, Baselga '96 teaches that serum levels of the antibody were "suboptimal," and that "the trough levels of rhuMAb HER2 were consistently below detectable levels throughout the treatment course and until disease progression." *Id.* at 739–740 (Fig. 1B). Pegram '98 notes "there was an inverse relationship between rhuMAb HER2 serum half-life and serum shed HER2 ECD of 0.5 μg/mL or greater." Ex. 1014, 2665. Pegram '98 further indicates that "patients with any measurable shed [antigen] serum level, compared with patients without measurable circulating ECD, had lower mean trough rhuMAb HER2 concentrations (18.7 v. 43.6 μg/mL; $P = .0001$) across all time points (n = 443 observations; Fig. 1)." Notably, this prior art data appears to show that patients with *any* detectable shed antigen levels (i.e., 64% of patients as set forth in the Herceptin label) had a mean antibody trough level that was close to the 10–

20 μg/mL threshold for efficacy.[9] As such, we find that skilled artisan would have been concerned that the effect of shed antigens— not taken into account by Dr. Jusko's analysis—could indeed significantly affect serum trough concentrations for tri-weekly administration of trastuzumab.

Contrary to Dr. Jusko's assumptions, Dr. Grass attests that "applying a constant value for half-life over a three-week period, based on the one-week data reported in the prior art, to a dose-dependent drug like trastuzumab could overestimate trough serum concentration levels" because it "fail[s] to account for the nonlinear increase in elimination and corresponding decrease in the half-life that would be expected to occur as serum concentration declines." Ex. 2039 ¶ 25. Dr. Grass also contends that the actual rates of elimination for such a drug would be unpredictable without collecting sufficient data, such as by conducting a "washout study" where serum concentration is collected over several half-lives following a single administration of the drug, but notes that there is no prior art reference for trastuzumab that describes such data. *Id.* ¶ 24.

To illustrate this point, Dr. Grass provides the following graph showing differences that can potentially exist between dose-independent drugs (which exhibit linear kinetics) and dose-dependent drugs (which exhibit non-linear kinetics):

[9] Although Dr. Gelmon testified that later (post-filing) studies showed that shed antigens were not in fact a concern for efficacy of Herceptin, and that dosage is not adjusted based on shed antigen levels today, our analysis is based on what was known in the prior art. Ex. 1058, 62:20–65:6.



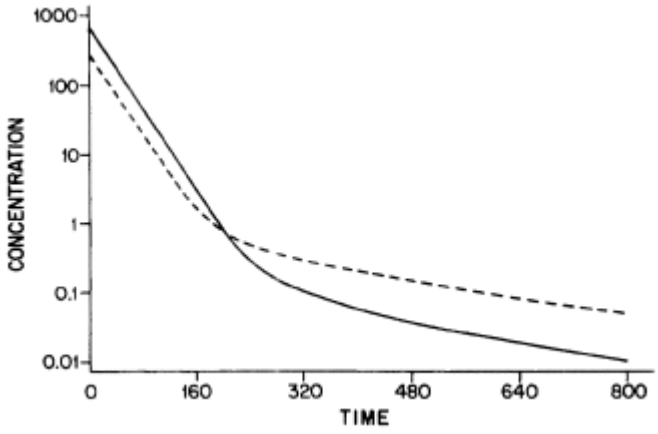
Id. ¶ 23. As shown by the solid lines in the graph above, which correspond to different dosage amounts of a dose-dependent drug, elimination increases (i.e., half-life decreases) as the drug concentration changes over time. Petitioners criticize this graph as being "made up" by Dr. Grass, as it was not derived from any particular data set forth in the prior art. Reply 20 (citing Ex. 1059, 116:16–21). Patent Owner, however, points to post-filing data concerning the anti-cancer agent indisulam as a "real-world example" of a dose-dependent drug that can behave this way, showing how assuming a constant half-life could greatly overestimate the predicted serum concentration over a longer interval. PO Resp. 49–50; Ex. 2039 ¶ 26; Anthe S. Zandvliet et al., *Saturable Binding of Indisulam to Plasma Proteins and Distribution to Human Erythrocytes*, 34 DRUG METABOLISM & DISPOSITION 1041 (2006) (Ex. 2052) ("Zandvliet"). While we recognize that Zandvliet does not qualify as prior art, and concerns a "small molecule" rather than an antibody, we find that it demonstrates at least one example in which assuming linear kinetics could result in an overestimation of trough serum

concentrations for a dose-dependent drug. From the perspective of a skilled artisan as of the August 27, 1999 priority date, we find nothing in the record to suggest that a similar overestimation would not have been a concern for tri-weekly trastuzumab administration.

With its Reply, Petitioners present additional evidence and arguments as to why Dr. Jusko's initial assumptions and analysis were reasonable. In particular, Petitioners contend that Dr. Jusko's analysis would, at worst, have underestimated, not overestimated, serum trough concentrations. Reply 18–23. In support of this contention, Petitioners cite King, APPLICATIONS AND ENGINEERING OF MONOCLONAL ANTIBODIES (1998) (Ex. 1029) ("King '98") as teaching that antibodies follow a common profile associated with "receptor-mediated" (or "target-mediated") drug disposition, with a quick initial clearance and short half-life ($t_{1/2}\alpha$), followed by slower clearance and a longer half-life ($t_{1/2}\beta$). While King '98 includes a table that identifies several antibodies known at the time to have a shorter $t_{1/2}\alpha$ followed by a longer $t_{1/2}\beta$, it *only* reports a $t_{1/2}\beta$ of 199 ± 120 hours for trastuzumab (citing Baselga '96), and Petitioners do not point to any other evidence suggesting a $t_{1/2}\alpha$ for trastuzumab. *See* Ex. 1029, 70 (Table 2.7). Furthermore, King '98 recognizes that the presence of circulating shed antigens could reduce antibody half-life in some cases, and that "[t]he pharmacokinetics of human IgG are unusual in that the half-life varies with concentration." *Id.* at 68, 70. As such, we find that King '98 does not show that Dr. Jusko's linear assumptions would have underestimated serum trough concentrations for trastuzumab.

In further support, Petitioners point to the following graph from Levy, *Pharmacologic target-mediated drug disposition*, 56(3) Clinical

Pharmacology & Therapeutics 248–52 (1994) ("Levy") as demonstrating this type of profile:

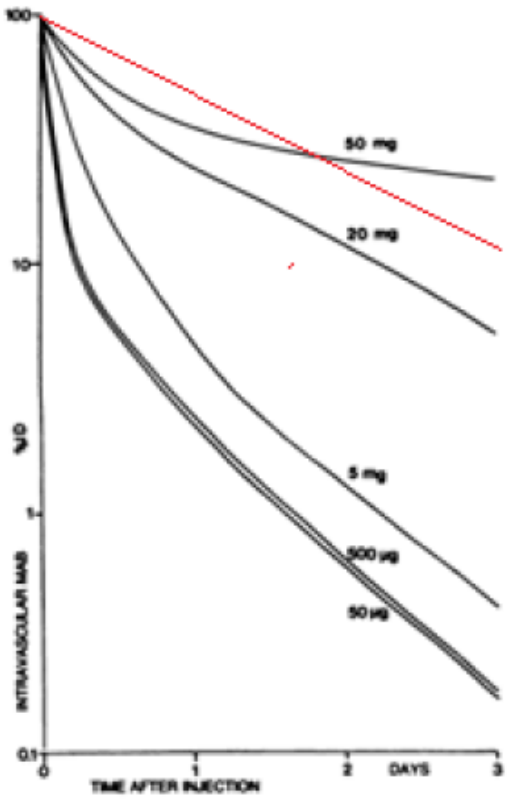


Ex. 1052, 249 (Fig. 1). The figure above shows "[t]ypical concentration-time profile in plasma *(continuous line)* and tissues *(broken line)* for a drug that is subject to high-affinity low-capacity binding in tissues." *Id.*

We do not find that the expected profile for receptor-mediated drug disposition, as shown in Levy, supports the reasonableness of Dr. Jusko's pharmacokinetic analysis for trastuzumab. Levy does not describe the kinetics of antibodies at all, but instead only identifies certain small molecules that might exhibit this "hypothetical behavior." Ex. 2084, 22:10–16, 59:8–16. Specifically, with reference to Figure 1 shown above, Levy notes that "the effect on pharmacokinetics can be quite striking in that the plasma concentration profile exhibits a terminal decay phase with a very long half-life ($t_{1/2}$), as is the case for certain angiotensin-converting enzyme (ACE) and aldose reductase inhibitors." Ex. 1052, 248. In criticizing Dr. Grass's reliance on the indisulam data discussed above, Dr. Jusko notes that skilled artisans would not "rely[] on pharmacokinetic behavior of ***small molecules***, which was known to be fundamentally different to that of antibodies." Ex. 1057 ¶ 5; *see also id.* ¶ 20 n.1 (noting "in addition to the

[differences in] molecular weight, the different mechanisms of disposition of small molecules and antibodies impacts their pharmacokinetic profiles"). Accordingly, we are not persuaded by Dr. Jusko's inconsistent opinion relying upon Levy's teachings with respect to target-mediated disposition of small molecules. Ex. 1057 ¶ 15. Moreover, even with respect to the ACE inhibitors discussed therein, Levy does not make any definitive conclusions as to their pharmacokinetic behavior, noting instead that "[m]ore definitive information can be obtained only in animal studies that permit opening of the 'black box' to explore what goes on in individual tissues." Ex. 1052, 248–49.

Petitioners also point to the following graph from Koizumi, *et al.*, *Multicompartmental Analysis of the Kinetics of Radioiodinated Monoclonal Antibody in Patients with Cancer*, 27(8) J. NUCLEAR MED. 1243–54 (1986) (Ex. 1054) ("Koizumi"):



Reply, 22; Ex. 1054, 1252 (Fig. 8) (annotation in red added by Petitioners). The annotated figure above shows "[m]odel simulated curves" for intravascular monoclonal antibodies (MAb) reflecting the "effect of different amount of injected MAb on blood clearance." *Id.* According to Petitioners, "for a given antibody dose (here 50mg), a linear model (shown in red) would underestimate the actual serum concentration (shown in black) soon after dosing." Reply 21.

We do not find that Koizumi supports the reasonableness of Dr. Jusko's application of a linear model. Indeed, Petitioners' own annotation in the figure above shows that a linear model could overestimate actual serum concentrations for certain doses (e.g., 20 mg) or at certain times after injection (e.g., less than 2 days). For tri-weekly trastuzumab administration, it was unknown whether the actual serum concentration would fall above or

below the linearity assumed in Dr. Jusko's model. Moreover, unlike Dr. Jusko's "one-compartment" analysis in this proceeding, Koizumi specifically describes a "multicompartmental" analysis conducted using a computer simulation. Ex. 1054, 1247. In this regard, Koizumi notes that "[i]nitial model solutions assumed that the model was linear," but "[u]sing this information it was not possible to fit the data observed for the patients with the model simulations." *Id.* at 1245–46. Furthermore, according to Koizumi:

> [C]ompartmental analysis also raises several problems. If the compartmental model is based upon unlikely assumptions, or inadequately validated, then misleading information follows. While this is self-evident, the complexity of a model addressing the pharmacokinetics of a MAb requires simplifications based upon assumptions in order to permit realistic mathematical handling. These simplifications and assumptions are particularly vulnerable to error in a system such as MAb, wherein many processes remain to be clarified.

Id. at 1252. As such, Koizumi underscores the inherent uncertainty associated with using mathematical models to predict the pharmacokinetic behavior of antibodies.

In sum, for the foregoing reasons, we determine Petitioners have not established the reasonable expectation of success required for obviousness. In reaching this conclusion, we are cognizant that "[c]onclusive proof of efficacy is not required to show obviousness." *Hoffman-La Roche*, 748 F.3d at 1331. Nonetheless, the Federal Circuit has also indicated that reasonable expectation cannot come from a mere "hypothesis" that might form the basis for further testing. *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 647–49 (Fed. Cir. 2017) (finding prior art reference that stated the "expected" benefit of a

clinical trial did not establish a reasonable expectation of success); *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

III. ALLEGED IMPROPER REPLY MATERIALS/PATENT OWNER'S MOTION TO EXCLUDE

Pursuant to our authorization, Patent Owner filed a paper identifying allegedly improper arguments and evidence included with Petitioners' Reply. Paper 67. Specifically, Patent Owner identifies the following materials as improper: Exhibits 1043–1048, 1050, 1052, 1054, and 1055, and portions of Dr. Lipton's reply declaration (Ex. 1056) and Dr. Jusko's reply declaration (Ex. 1057) referencing those exhibits. *Id.* Patent Owner also separately filed a motion to exclude the same evidence it identifies as improper reply materials. Paper 68.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[10] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization

[10] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

to file a motion to strike." *Id.* at 17. "In most cases, the Board is capable of identifying new issues or belatedly presented evidence when weighing the evidence at the close of trial, and disregarding any new issues or belatedly presented evidence that exceeds the proper scope of reply or sur-reply." *Id.*

Nevertheless, to the extent necessary, we treat Patent Owner's Motion to Exclude and Identification of Improper New Reply Materials as a motion to strike. We have not relied upon Exhibits 1043–1048, 1050, and 1055 in rendering this decision. We have not given any weight to this evidence to support Petitioners' obviousness arguments because they have publication dates after August 27, 1999, and thus do not qualify as prior art to the '196 patent. *See* Paper 68, 7–10 (explaining why post-priority date references relied upon by Petitioners are irrelevant to obviousness determination in this proceeding). Furthermore, Exhibit 1055 has not been cited or relied upon by Petitioners in their Reply, and we decline to incorporate by reference the opinion in Dr. Jusko's reply declaration concerning that exhibit. *See* 37 C.F.R. § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document."). Accordingly, we dismiss as moot Patent Owner's motion to strike this evidence.

We have taken into consideration Exhibits 1052 and 1054 in our analysis, as discussed above. We determine that these exhibits and Petitioners' arguments in relation to these exhibits are proper reply evidence as they seek to respond to Patent Owner's arguments concerning the reasonableness of Dr. Jusko's pharmacokinetic analysis. Specifically, in relying upon Exhibits 1052 and 1054, and the portions of Dr. Jusko's reply declaration citing those exhibits, Petitioners seek to respond to Patent Owner's criticism that Dr. Jusko's assumptions would have overestimated

serum concentration for dose-dependent drugs such as trastuzumab. With such evidence, Petitioners seek to further support, not modify, their basis for reasonable expectation of success set forth in the Petition. We do not find that Petitioners have presented an "entirely new rationale" worthy of being excluded in their Reply. *Ericsson Inc. v. Intellectual Ventures I LLC*, No. 2017-1521, 2018 WL 4055815, *6 (Fed. Cir. Aug. 27, 2018). Although we find the new exhibits unpersuasive, that does not render them improper reply evidence. We, therefore, deny Patent Owner's motion to strike this evidence.

IV. CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that although Petitioners have shown that a skilled artisan would have been motivated to extend the dosing frequency of trastuzumab from weekly to tri-weekly, Petitioners have not met their burden to show a reasonable expectation of success with respect to such a dosing regimen. As a result, Petitioners have not shown, by a preponderance of the evidence, that claims 1–3, 5, 7, 9–11, and 17–33 of the '196 patent would have been obvious over the combination of the Herceptin Label, Baselga '96, Pegram '98, and the knowledge of the skilled artisan.

V. ORDER

Accordingly, it is:

ORDERED that claims 1–3, 5, 7, 9–11, and 17–33 of the '196 patent have not been shown to be unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2017-00804
Patent 6,627,196 B1

PETITIONERS:

For Hospira, Inc.:

Amanda Hollis
Stefan M. Miller
Benjamin A. Lasky
Sarah K. Tsou
Mark C. McLennan
Christopher J. Citro
Micah Rappazzo
KIRKLAND & ELLIS LLP
amanda.hollis@kirkland.com
stefan.miller@kirkland.com
benjamin.lasky@kirkland.com
sarah.tsou@kirkland.com
mark.mclennan@kirkland.com
christopher.citro@kirkland.com
mich.rappazzo@kirkland.com

For Samsung Bioepis Co., Ltd.:

Dimitrios T. Drivas
Scott T. Weingaertner
Amit H. Thakore
Eric Majchrzak
WHITE & CASE LLP
ddrivas@whitecase.com
scott.weingaertner@whitecase.com
athakore@whitecase.com
eric.majchrzak@whitecase.com

PATENT OWNER:

David L. Cavanaugh
Lauren V. Blakely

Robert J. Gunther, Jr.
Lisa J. Pirozzolo
Kevin S. Prussia
Andrew J. Danford
Robert Galvin
WILMER CUTLER PICKERING HALE AND DORR LLP
david.cavanaugh@wilmerhale.com
lauren.blakely@wilmerhale.com
lisa.pirozzolo@wilmerhale.com
kevin.prussia@wilmerhale.com
andrew.danford@wilmerhale.com
robert.galvin@wilmerhale.com

Adam R. Brausa
Daralyn J. Durie
DURIE TANGRI LLP
abrausa@durietangri.com
ddurie@durietangri.com

Trials@uspto.gov
571-272-7822

Paper No. 83
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00805[1]
Patent 7,371,379 B2

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

PAULRAJ, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

[1] Case IPR2017-01959 has been joined with IPR2017-00805.

I. INTRODUCTION

Hospira, Inc. ("Hospira") filed a Petition (Paper 1, "Pet."), requesting institution of an *inter partes* review of claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of U.S. Patent No. 7,371,379 B2 (Ex. 1001, "the '379 patent"). Genentech, Inc. timely filed a Patent Owner Preliminary Response (Paper 6, "Prelim. Resp."). We determined, based on the information presented in the Petition and Preliminary Response, that there was a reasonable likelihood that Hospira would prevail in challenging claims 1–3, 5, 7, 9–11, 16–28, and 30–40 as unpatentable under 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, the Board instituted trial on July 27, 2017, as to those claims of the '379 patent. Paper 13 ("Institution Decision" or "Inst. Dec."). Following our institution based on Hospira's Petition, Samsung Bioepis Co., Ltd. ("Samsung") filed a substantially identical Petition challenging the same claims of the '379 patent and requested joinder in this proceeding, which we granted. Paper 40. Thus, Hospira and Samsung together are the "Petitioners" in this proceeding.

Patent Owner filed its Response to the Petition (Paper 42, "PO Resp.") and Petitioners filed a Reply to Patent Owner's Response (Paper 56, "Reply"). Patent Owner filed a Motion to Exclude certain evidence (Paper 64), to which Petitioners filed an Opposition (Paper 69) and Patent Owner filed a Reply in support thereof (Paper 73). Patent Owner also filed a Motion for Observations on Cross-Examination of Petitioners' Reply Declarants (Drs. Allan Lipton and William Jusko) (Paper 65) to which Petitioners filed a Response (Paper 70). Additionally, pursuant to our authorization, Patent Owner filed an Identification of Improper New Reply Materials (Paper 68), to which Petitioners filed a Response (Paper 72) and

Patent Owner filed a Reply (Paper 74). An oral hearing was held on May 8, 2018. The transcript of the hearing has been entered into the record. Paper 80 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Based on the record before us, we conclude that Petitioners have *not* demonstrated by a preponderance of the evidence that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 patent are unpatentable.

A. Related Proceedings

As a related matter, Petitioners and Patent Owner identify a concurrently-filed petition for *inter partes* review (IPR2017-00804) for a related patent, U.S. Patent 6,627,196 ("the '196 patent"). *See* Pet. 2. We issue our Final Written Decision in IPR2017-00804 concurrently with this decision. Additionally, also concurrently with this Decision, we issue Final Written Decisions in two other *inter partes* review proceedings concerning the '196 and '379 patents brought by another petitioner. IPR2017-01139; IPR2017-001140.

The parties also identify litigation matters pending in the U.S. District Courts for the Northern District of California and the District of Delaware and on appeal before the Federal Circuit Court of Appeals concerning the '379 and '196 patents, as well as foreign proceedings concerning counterparts to these patents, as related matters. Paper 81; Paper 82.

B. The '379 Patent (Ex. 1001)

The '379 patent issued on May 13, 2008, with Sharon A. Baughman and Steven Shak as the listed co-inventors. Ex. 1001, (45), (75). The '379 patent claims priority as the divisional of an application filed August 25,

2000, as well as to provisional applications filed June 23, 2000, and August 27, 1999. *Id.* at (22), (60). The parties have not disputed the claimed priority date for the '379 patent.

The '379 patent relates generally to dosages for the treatment of disorders characterized by the overexpression of ErbB2 (also known as HER2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR). *Id.* at 1:15–25, 44–50. The overexpression of ErbB2 has been associated with breast cancer. *Id.* As noted in the '379 patent, a recombinant humanized anti-ErbB2 monoclonal antibody (alternatively referred to as "rhuMab HER2," "trastuzumab," or by its tradename "Herceptin")[2] had been clinically tested and approved for patients with ErbB2-overexpressing metastatic breast cancers who received prior anti-cancer therapy. *Id.* at 3:59–65. The recommended initial "loading dose" for trastuzumab was 4 mg/kg administered as a 90-minute infusion, and the recommended weekly "maintenance dose" was 2 mg/kg, which could be administered as a 30-minute infusion if the initial loading dose was well-tolerated. *Id.* at 3:66–4:3.

The invention described in the '379 patent "concerns the discovery that an early attainment of an efficacious target trough serum concentration by providing an initial dose or doses of anti-ErbB2 antibodies, followed by subsequent doses of equal or smaller amounts of antibody (greater front loading) is more efficacious than conventional treatments." *Id.* at 4:26–31.

[2] For consistency's sake, we will refer to the antibody at issue in this proceeding as trastuzumab unless we are directly quoting one of its alternative names from another document.

The method of treatment, according to the invention described in the patent, "involves administration of an initial dose of anti-ErbB2 antibody of more than approximately 4 mg/kg, preferably more than approximately 5 mg/kg," with the maximum dose not to exceed 50 mg/kg. *Id.* at 4:51–55. "[T]he initial dose or doses is/are followed by subsequent doses of equal or smaller amounts of antibody at intervals sufficiently close to maintain the trough serum concentration of antibody at or above an efficacious target level." *Id.* at 4:65–5:2. Preferably, "the amount of drug administered is sufficient to maintain the target trough serum concentration such that the interval between administration cycles is at least one week," and "the trough serum concentration does not exceed 2500 μg/ml and does not fall below 0.01 μg/ml during treatment." *Id.* at 5:4–9. The patent explains that "[t]he front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment." *Id.* at 5:9–12. As a result, "[t]he efficacious target trough serum concentration is reached in 4 weeks or less . . . and most preferably 1 week or less, including 1 day or less." *Id.* at 4:31–34. Additionally, the patent states that the method of therapy may involve "infrequent dosing" of the anti-ErbB2 antibody, wherein the first and second dose are separated by at least two weeks, and optionally at least about three weeks. *Id.* at 6:23–36.

The '379 patent describes embodiments in which the initial dose of trastuzumab is 6 mg/kg, 8 mg/kg, or 12 mg/kg, followed by subsequent maintenance doses of 6 mg/kg or 8 mg/kg administered once every 2 or 3 weeks, in a manner such that the trough serum concentration is maintained at approximately 10–20 μg/ml during the treatment period. *Id.* at 5:19–43, 45:19–45. The treatment regimen according to the invention may further

comprise administration of chemotherapy along with trastuzumab. *Id.* at 6:6–10, 7:26–32, 46:28–58. Of particular relevance, the '379 patent includes a prophetic example describing the administration of trastuzumab intravenously every three weeks in combination with the chemotherapeutic agent paclitaxel. *Id.* at 46:60–48:32. According to this example, "[s]imulation of the proposed treatment regimen suggests that the trough serum concentrations will be 17 [μ]g/ml, in the range (10–20 [μ]g/ml) of the targeted trough serum concentrations from previous HERCEPTIN® IV clinical trials." *Id.* at 47:1–5. The example sets forth inclusion criteria for a study in which patients will be administered trastuzumab every three weeks. *Id.* at 47:9–48:12. The '379 patent concludes that "[i]t is believed that the above treatment regimen will be effective in treating metastatic breast cancer, despite the infrequency with which HERCEPTIN® is administered to the patient." *Id.* at 48:28–31.

C. Illustrative Claim

Petitioners challenge claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 Patent. Independent claim 1 is illustrative, and is reproduced below:

> 1. 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 at least approximately 5 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 the subsequent doses are separated in time from each other by at least two weeks; and
> further comprising administering an effective amount of a chemotherapeutic agent to the patient.

Ex. 1001, 57:33–46.

D. The Asserted Ground of Unpatentability

Petitioners challenge the patentability of the claims of the '379 Patent based on the following ground:

References	**Basis**	**Claims challenged**
Herceptin label,[3] Baselga '96,[4] Pegram '98,[5] and the knowledge of a person of ordinary skill in the art	§ 103(a)	1–3, 5, 7, 9–11, 16–28, and 30–40

Petitioners further rely upon the declarations of Allan Lipton, M.D. (Ex. 1002; Ex. 1056) and William Jusko, Ph.D. (Ex. 1003; Ex. 1057). Patent Owner relies upon the declarations of George Grass, Ph.D. (Ex. 2039) and Karen Gelmon, M.D. (Ex. 2040).

II. ANALYSIS

A. Claim Construction

We interpret claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under the broadest reasonable construction standard, claim

[3] Genentech, Inc, Herceptin® Trastuzumab, Sept. 1998 (hereinafter "Herceptin Label" (Ex. 1008).
[4] Jose Baselga, *Phase ll Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients With HER2/neu-Overexpressing Metastatic Breast Cancer*, 14 JOURNAL OF CLINICAL ONCOLOGY 737–744 (1996) (hereinafter "Baselga '96") (Ex. 1013).
[5] Mark D. Pegram, *Phase ll Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185^{HER21neu} Monoclonal Antibody Plus Cisplatin in Patients With HER2/neu-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment*, 16 JOURNAL OF CLINICAL ONCOLOGY 2659–71 (1998) (hereinafter "Pegram '98") (Ex. 1014).

terms are generally given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). "Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). "Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioners propose a construction for "ErbB2 receptor." *See* Pet. 24. Patent Owner does not propose any terms to be construed in its post-institution Response. We find that no explicit construction of any claim term is necessary to decide the issues presented in this case. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999))).

B. Level of Skill in the Art

Petitioners contend that a person of ordinary skill in the art for the '379 patent would be a "team" that includes both (1) a clinical or medical oncologist specializing in breast cancer with several years of experience in breast cancer research or clinical trials, and (2) a person with a Ph.D. in pharmaceutical sciences or a closely related field with an emphasis in pharmacokinetics with three years of relevant experience in protein based

drug kinetics. Pet. 23–24 (citing Exs. 1002 ¶ 14; 1003 ¶ 15; 1006 ¶ 32). Patent Owner does not address the requisite level of skill in its Response.

Because it is otherwise undisputed and consistent with the evidence of record, we adopt Petitioners' proposed definition of a person of ordinary skill in the art ("POSITA" or "skilled artisan") for purposes of our analysis. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Patentability Analysis

1. Content of the Prior Art

Petitioners rely upon, *inter alia*, the following prior art teachings to support their challenge.

a. Herceptin Label (Ex. 1008)

As recognized in the '379 patent, trastuzumab was already FDA-approved and commercially sold in the U.S. by 1998 under the tradename Herceptin. Ex. 1001, 3:59–4:3. The Herceptin label teaches:

> 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. 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.

Ex. 1008, 1.

The Herceptin label also teaches that "[i]n 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 . . . was observed," and "[b]etween week 16 and 32, Trastuzumab serum concentration reached a steady state with a mean trough and peak concentrations of approximately 79 [mg]/mL and 123 [mg]/mL, respectively. *Id.* The label further describes clinical studies in which metastatic breast cancer patients with certain levels of HER2 overexpression were administered chemotherapy either alone or in combination with trastuzumab given intravenously as a 4 mg/kg loading dose followed by weekly doses at 2 mg/kg. *Id.* The chemotherapy in these clinical studies (e.g., paclitaxel) was administered every 3 weeks (21 days). *Id.*

b. Baselga '96 (Ex. 1013)

Baselga '96 reports the results of a phase II clinical trial in which patients with ErbB2-overexpressing metastatic breast cancer were treated with trastuzumab. Ex. 1013, 737. The pharmacokinetic goal of the trial "was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell grown in the preclinical model." *Id.* at 738. Further, the "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." *Id.*

According to the results reported in Baselga '96, "[m]ore than 90% of the examined population (41 patients) had rhuMAb HER2 trough levels above the targeted 10 μg/mL level. *Id.* at 739. Moreover, the treatment "was remarkably well tolerated." *Id.* "Toxicity [from rhuMAb HER2] was

minimal," and no immune response against the antibody was detected. *Id.* at 737. Out of the 768 times trastuzumab was administered, "only 11 events occurred that were considered to be related to the use of the antibody." *Id.* at 739. Baselga '96 also teaches that in preclinical studies (both *in vitro* and in xenografts), trastuzumab "markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." *Id.* at 743.

c. Pegram '98 (Ex. 1014)

Pegram '98 reports the results of a phase II clinical trial using a combination of trastuzumab plus cisplatin. Ex. 1014, 2659. Pegram '98 states that "[t]hese studies showed that the pharmacokinetics of rhuMAb HER2 were predictable, and that the doses delivered achieved a target trough serum concentration of 10 to 20 μg/mL, which is associated with antitumor activity in preclinical models." *Id.* at 2660. Pegram '98 also reports a toxicity profile of the combination that paralleled the toxicity of cisplatin alone, thereby leading to the conclusion that trastuzumab did not increase toxicity. *Id.* at 2668.

2. Obviousness Based on the Herceptin Label, Baselga '96, Pegram '98, and the Knowledge of a Person of Ordinary Skill in the Art of the Prior Art

Petitioners have provided a claim-by-claim explanation for the basis of their contention that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 are obvious over the Herceptin label in view of Baselga '96, Pegram '98, and the Knowledge of a Person of Ordinary Skill in the Art. Pet. 29–54.

In general terms, the challenged claims are directed to a dosing regimen for the treatment of cancer in which trastuzumab is administered at an initial dose, followed by administration of the antibody at subsequent

doses that are the same or less than the initial dose and separated in time by at least about two weeks. Independent claim 1 specifies an initial dose of approximately 5 mg/kg, while certain dependent claims specify higher initial doses of 6 mg/kg, 8 mg/kg, or 12 mg/kg (e.g., cls. 2, 3, 9), whereas other dependent claims specify that the subsequent doses are separated in time by at least three weeks (e.g., cls. 5, 10). Our obviousness analysis assumes a treatment method in which trastuzumab is administered once every three weeks, as that dosing interval is encompassed by all the challenged claims and is the focus of the parties' arguments and evidence in this proceeding.

Petitioners rely upon the teaching in the Herceptin label that trastuzumab doses of up to 500 mg had been successfully administered to patients. Pet. 31 (citing Ex. 1008, 1). Based on a patient weight range of 55–85 kg, Petitioners calculate that the weight-based dose for the 500 mg absolute dose taught by the Herceptin label ranges from 5.88–9.09 mg/kg. *Id.* at 31–32 (citing Ex. 1002 ¶¶ 55–57; Ex. 1003 ¶ 45; Ex. 1026, 3; Ex. 1027, 334 (Table 7-2)). Petitioners further rely upon the Herceptin label's teaching that trastuzumab doses should be "front-loaded" with a higher initial dose of 4 mg/kg followed by a lower weekly maintenance dose of 2 mg/kg. *Id.* at 33. Additionally, Petitioners rely upon the teaching in the Herceptin label describing the administration of trastuzumab in combination with chemotherapeutic agents, and that these chemotherapeutic agents are administered once every three weeks to patients. *Id.* at 35–36, 43–44. Petitioners further rely upon Baselga '96 and Pegram '98 insofar as they confirm that the weekly dosing regimen encompassed by the Herceptin label was successfully administered to patients in phase II clinical trials, and that

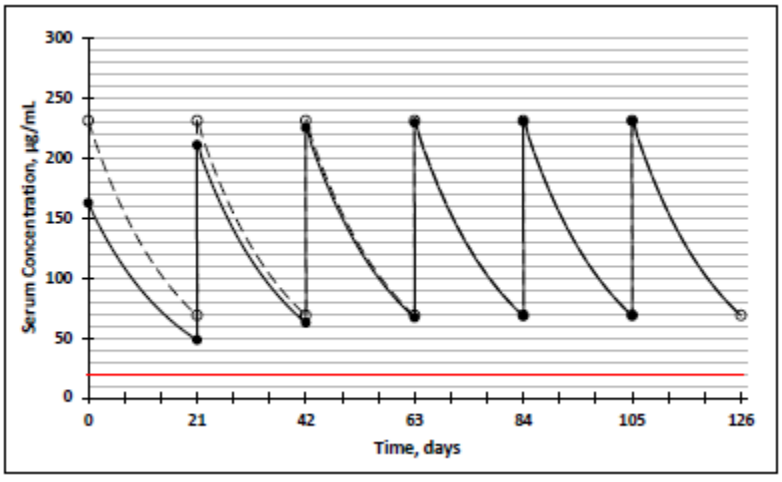
the skilled artisan would have been aware of a target trough serum concentration of 10–20 μg/mL for trastuzumab. Pet. 33, 37.

Petitioners acknowledge that the Herceptin label, along with Baselga '96 and Pegram '98, teach only a *weekly* dosing regimen, but assert that the skilled artisan would nonetheless have been motivated to decrease the frequency of trastuzumab administration to once every three weeks for several reasons. *Id.* at 34–42. First, Petitioners contend that "a skilled artisan would decrease the frequency of injections to improve efficiency, to provide a more convenient dosing regimen—particularly for terminally ill patients—, and to improve patient compliance and quality of life." *Id.* at 34. Second, Petitioners contend that the skilled artisan would have been motivated to apply a tri-weekly (i.e., once every three weeks) regimen for the antibody in order to align with the dosing schedules of the chemotherapy so that a patient would only have to make one trip to the clinic to receive both doses. *Id.* at 36. In support, Petitioners rely upon their oncology expert, Dr. Lipton, who attests that each trip to the clinic to receive even a single infusion of antibody treatment often takes between a half and a full day, which can result in additional time and costs for the patient. Ex. 1002 ¶¶ 42–43.

Petitioners further contend that the skilled artisan would confidently decrease the frequency of injections and use a tri-weekly dosing regimen in view of trastuzumab's known pharmacokinetic properties. *Id.* at 36. Petitioners contend that arriving at the tri-weekly dosing schedule was merely a matter of "routine calculation and optimization" of the therapy outlined in the Herceptin label. *Id.* at 37. In this regard, Petitioners rely upon data from the Herceptin label and Dr. Jusko's opinions to assert that it

would have been a matter of routine calculation for a skilled artisan to determine that a tri-weekly 500 mg trastuzumab dosing regimen would have resulted in a serum concentration well above the target minimum trough concentration of 10–20 µg/mL reported in the prior art. *Id.* at 37–39 (citing Ex. 1003 ¶¶ 46–47, 49–51, 56–58, 62).

Specifically, Dr. Jusko, assuming a "one-compartment" model to approximate drug concentration over time, calculated the initial minimum drug concentration three weeks after first administering a 500 mg antibody dose to a 70 kg patient to be 48.3 µg/mL and the steady-state trough concentration after multiple doses to be 68.7 µg/mL. Ex. 1003 ¶¶ 46–58. Additionally, assuming linear (first-order) kinetics, Dr. Jusko calculated that a 712 mg loading dose followed by 500 mg tri-weekly maintenance doses could be administered to patients while keeping serum drug concentrations within acceptable levels. *Id.* ¶¶ 59–66. Dr. Jusko provides the following graph depicting expected trastuzumab concentrations over time for a 70 kg patient administered 500 mg of trastuzumab every three weeks, with or without an initial 712 mg loading dose (broken and solid lines, respectively):



Ex. 1003 ¶ 62 (Fig. 2). As shown in the figure above, when administering either calculated dosing regimen, Dr. Jusko concludes that the trastuzumab serum concentration would have been expected to stay well above the target minimum trough concentration of 10–20 μg/ml (with 20 μg/ml shown in red). *Id.* ¶ 63.

As noted by Petitioners, Dr. Jusko made three assumptions in performing his calculations: (1) that trastuzumab exhibits non-exponential kinetics; (2) that the initial concentration (C_0) can be estimated by multiplying the dose by the volume of distribution and average mass of a patient; and (3) that the kinetics of trastuzumab remain constant with multiple-dosing. Pet. 42 (citing Ex. 1003 ¶¶ 69–71; Ex. 1028, 91; Ex. 1029, 77).

The two main issues argued in this proceeding are: (a) whether there would have been a motivation to extend the weekly dosing interval taught in the prior art to a tri-weekly dosing interval based on concerns about patient convenience and quality of life, and (b) whether there would have been a reasonable expectation of success in implementing such a dosing regimen based on Dr. Jusko's pharmacokinetic analysis. It is Petitioners' burden to demonstrate both "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (internal citations omitted). As they are distinct legal requirements for obviousness, we address motivation and reasonable expectation of success separately in our analysis. For the reasons explained below, while skilled artisans may have

been motivated to extend the dosing interval, we find that they would not have had a reasonable expectation of success in doing so based on the prior art. Thus, we determine that Petitioners have not shown that the challenged claims are unpatentable for obviousness.

a. Motivation

As discussed above, Petitioners' primary arguments on motivation for extending the dosing interval of trastuzumab from the weekly administration taught in the prior art to tri-weekly is based on a desire to improve patient "convenience," "compliance," "efficiency," and "quality of life." Pet. 34. In its Response, Patent Owner contends these "patient-related" factors would not have served as a reason to extend the dosing interval because the primary focus for skilled artisans in developing a treatment regimen for HER2-positive breast cancer would have been on efficacy. PO Resp. 28–36. Moreover, instead of extending trastuzumab's dosing interval to a tri-weekly schedule, Patent Owner asserts that skilled artisans were actually increasing the frequency of the chemotherapy (paclitaxel) administration in numerous clinical trials so that both drugs could be administered on a weekly schedule. *Id.* at 31–32. Patent Owner also argues that this is not simply a case of selecting an optimal doses from known range of doses in the prior art since the only dosing interval disclosed was weekly. *Id.* at 26. Patent Owner notes that "at the time of the invention, developing an antibody dosing regimen for clinical use was described as a "complicated task" and such drugs "defy easy quantitative description and prediction." *Id.* at 26 (citing Ex. 2004, 11; Ex. 1022, 3:109).

We find that the skilled artisan would have been motivated to extend the dosing interval for the simple (yet compelling) reasons that doing so

would have been more cost-effective and less burdensome for the patient undergoing such treatment, which required in-person visits to the clinic for each antibody infusion. As previously recognized by the Federal Circuit, "[a] relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance." *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014). Patent Owner seeks to limit this statement in *Hoffman-La Roche* to the specific issue addressed in that case, which was whether once-monthly administration of bisphosphonate ibandronate to treat osteoporosis would have been obvious. PO Resp. 38–39. Patent Owner contends that, unlike the facts of *Hoffman-La Roche*, the claimed treatment regimen at issue in this proceeding involves a "first-in-class" therapeutic (i.e., trastuzumab was the only antibody approved at the time for the treatment of "solid" tumors), a fatal disease condition (breast cancer), and a completely different set of prior art. *Id.* at 39. Patent Owner argues that "[c]onvenience considerations that may be applicable in the context of treatments to prevent osteoporosis have little relevance in the context of treating HER2-positive breast cancer." *Id.* at 39. We do not read *Hoffman-La Roche* to stand for a *per se* rule that it would always have been obvious to extend the dosing interval in order to address patient compliance concerns regardless of the particular medical condition or drug at issue. Nonetheless, based on the specific facts of this case, we find that skilled artisans would have been similarly motivated to administer trastuzumab less frequently to treat breast cancer patients.

In support of this finding, we take into account the real-world experiences of the parties' oncology experts, Dr. Lipton (Petitioner's expert) and Dr. Gelmon (Patent Owner's expert), who are both physicians with

extensive experience treating breast cancer patients in clinical settings. Ex. 1002 ¶¶ 4–10; Ex. 2040 ¶¶ 2–5. Dr. Lipton attests that each trip to his clinic to receive even a relatively short infusion of antibody treatment often takes between a half and a full day, which can result in additional time and costs for the patient. Ex. 1002 ¶¶ 42–43. Indeed, some of his patients have had to travel up to one hundred miles each direction to receive treatment at the clinic. *Id.* ¶ 39. As such, we are not persuaded by Dr. Gelmon's contention that efficacy would have taken precedence over convenience as the focus of cancer treatment in the 1990s. Ex. 2040 ¶¶ 30–34. Of course, maintaining efficacy and safety would have been a paramount concern for the skilled artisan seeking to improve upon the weekly dosing regimen that was previously FDA-approved, but that does not mean improving convenience and quality of life for the patient would not have also been motivating concerns. By 1999, efficacy and safety had already been demonstrated for weekly trastuzumab administration as set forth in the Herceptin label. Ex. 1008. Notably, Dr. Gelmon admitted during her deposition that "before 1999 it was known that providing a drug less frequently might provide benefits to certain patients in terms of convenience, cost and quality of life as long as efficacy and safety were shown." Ex. 1058, 328:24-329:7. Indeed, these same concerns factored into Dr. Gelmon's own clinical study involving tri-weekly trastuzumab administration, which took place within months of the '379 patent priority date. *Id.* at 73:19–75:16.[6]

[6] While the publication of Dr. Gelmon's tri-weekly study does not qualify as prior art, we find the fact that she initiated the study so close to the priority date undermines the credibility of her testimony that skilled artisans

Contrary to Patent Owner's arguments, the prior art need not have expressly articulated or suggested patient convenience or quality of life concerns as the motivation to extend the dosing interval. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[T]he [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ."). Nonetheless, the motivation set forth by Dr. Lipton is supported by his citation to prior art articles indicating that quality of life issues for cancer patients have long been a concern to physicians. Ex. 1002 ¶ 44 (citing Coates, et al., *Quality of Life in Oncology Practice: Prognostic Value of EORTC QLQ-C30 Scores in Patients with Advanced Malignanc*y, 33(7) EUROPEAN JOURNAL OF CANCER 1025–30 (1997) (Ex. 1019); Aaronson, et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology*, 85(5) J. NAT'L CANCER INSTITUTE 365–76 (1993) (Ex. 1020); Ferrell, *Quality of Life in Breast Cancer*, 4(6) CANCER PRACTICE 331–40 (1996) (Ex. 1021)).

Additionally, we find that the skilled artisan would have been motivated to match trastuzumab and chemotherapy dosing. As indicated in

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would not have considered extending the dosing interval at the time. In their Reply, however, Petitioners identify additional post-filing evidence supporting their contention that skilled artisans were motivated by "patient-related factors" to investigate tri-weekly dosing of trastuzumab. Reply 14–15. Insofar as these additional references do not qualify as prior art themselves, nor do they purport to recount what was publicly known in the prior art, we decline to give them any weight in our analysis.

the Herceptin label, patients were often prescribed chemotherapy, such as paclitaxel or anthracycline, in combination with trastuzumab. Ex. 1008, 1. The Herceptin label indicates that both paclitaxel and anthracycline were administered once every three weeks (21 days). *Id.* In addition to convenience for the patient, Dr. Lipton notes that "it is also beneficial for the clinic to administer the combined therapies on the same schedule because they only have to prep the patient once." Ex. 1002 ¶ 66. Patent Owner acknowledges that researchers at the time had explored the possibility of administering paclitaxel to match weekly trastuzumab administration. PO Resp. 9; Ex. 2040 ¶¶ 38, 57; *see, e.g.*, M Fornier, *Weekly (W) Herceptin (H) + 1 Hour Taxol (T): Phase II Study in HER2 Overexpressing (H2+) and Non-Overexpressing (H2-) Metastatic Breast Cancer (MBC)*, 18 PROC. AM. SOC'Y CLINICAL ONCOLOGY 126a (Abstract 482) (1999) (Ex. 2029). But, at the time, paclitaxel was FDA-approved for only tri-weekly treatment. Ex. 1058, 180:22–181:1. Regardless, the fact that skilled artisans were considering matching the antibody and chemotherapy treatments on a weekly basis does not mean that they would also not have considered matching the treatments on a tri-weekly basis. Obviousness does not require the claimed regimen to be the only or best choice, nor may a patentee defeat obviousness simply by identifying another alternative. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention.").

Patent Owner also contends that skilled artisans would not have had a reason to select a 500 mg maintenance dose or 712 mg loading dose, as

calculated by Dr. Jusko. PO Resp. 24–27. We are unpersuaded by these arguments because the Herceptin label expressly teaches that a 500 mg dose was considered safe and tolerable, at least when administered on a weekly basis. Dr. Jusko explained that the 500 mg dose level, and associated 12-day half-life, would have been the obvious starting point "because that was the highest reported tolerable weekly dose level with the longest half-life that would give the POSITA the best chance of achieving the minimum serum trough concentrations to establish efficacy at three weeks." Ex. 1057 ¶ 34. Dr. Jusko further notes that "[i]t would have made no sense to choose a lower dose level, as the result of any such simulation would not have been indicative of the feasibility of three-week dosing—a negative result would merely necessitate simulating at the higher dose level, i.e., 500 mg." *Id.* Furthermore, while the 712 mg loading dose is not expressly disclosed in the prior art (Ex. 1003 ¶¶ 59–63), Patent Owner's experts Dr. Grass and Dr. Gelmon do not dispute Dr. Jusko's calculation of this amount, which is based on equations set forth in a basic pharmacokinetics textbook. Ex. 1002 ¶ 72; *see* Rowland, *et al.*, CLINICAL PHARMACOKINETICS: CONCEPTS AND APPLICATIONS (3rd ed. 1995) (vol. 1), at 88 (Ex. 1022) ("Rowland").[7]

[7] Patent Owner also argues that the pharmacokinetic data in the prior art would not have motivated a skilled artisan to extend the dosing interval of trastuzumab. PO Resp. 40–43. We find that the skilled artisan would have been motivated to extend the dosing interval regardless of the pharmacokinetic data set forth in the prior art. But, as discussed below, we find that trastuzumab's non-linear kinetics would not have provided the skilled artisan with a reasonable expectation of success with such an extended dosing interval.

Accordingly, we find that skilled artisans would have been motivated to extend the dosing interval of trastuzumab to once every three weeks, with a 712 mg loading dose followed by 500 mg maintenance doses.

b. Reasonable Expectation of Success

Having found the requisite motivation to arrive at the claimed dosing regimen, we next turn to whether there would have had a reasonable expectation of success with such a treatment regimen. Based on our consideration of the record evidence, we find that Petitioners have not met their burden of establishing a reasonable expectation of success.

In evaluating reasonable expectation of success, we must "consider the appropriate scope of the patent's claimed invention." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965–66 (Fed. Cir. 2014). Here, the claims of the '379 patent are directed to 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." Ex. 1001, 57:33–36 (emphasis added). Petitioners and Patent Owner both focus their arguments and evidence on whether the skilled artisan would have reasonably expected that trastuzumab plasma concentrations would be maintained above 10–20 μg/mL, which the prior art identifies as the minimum serum trough concentration required for efficacy. In view of the claim scope, we agree that this is an appropriate definition of "success" for purposes of our analysis.

Petitioners contend that the skilled artisan would have extended the dosing interval based on Dr. Jusko's pharmacokinetic analysis as set forth above. Patent Owner disagrees that this type of mathematical analysis would have provided the requisite reasonable expectation of success for the

claimed dosing regimen. In particular, Patent Owner criticizes Dr. Jusko's application of linear pharmacokinetics to predict serum trough concentration insofar as the prior art taught that trastuzumab had demonstrated non-linear (dose-dependent) kinetics. PO Resp. 45–48. As noted by Patent Owner, "[f]or drugs with non-linear kinetics, pharmacokinetic parameters such as half-life do not remain constant but change as a function of the concentration of the drug in the plasma." *Id.* at 46 (citing Ex. 1022, 3:109; Ex. 2008, 123; Ex. 2038 ¶¶ 22–25, 27, 34–36). According to Patent Owner, there is insufficient data in the prior art to accurately predict whether a three-week dosing regimen would be clinically effective, and thus a clinical oncologist would not have confidently used three-week dosing based on Dr. Jusko's pharmacokinetic analysis. *Id.* at 55–57.

As part of our evaluation, we take into account the relative novelty of using antibodies for the treatment of cancer as of the August 27, 1999 priority date. Herceptin had been approved by the FDA for weekly administration in September 1998, less than a year before, was the first antibody approved to target "solid tumors," and the first approved to treat any form of breast cancer. Ex. 1008; Ex. 2003, 388; Ex. 2038, 33:8–17; Ex. 2040 ¶ 23.[8] Petitioners have not pointed to any prior art reference discussing the feasibility or viability of a tri-weekly antibody dosing regimen.

[8] Prior to August 1999, the FDA had approved only one other antibody for treating cancer—Patent Owner's rituximab product, which was approved for non-Hodgkin's lymphoma treatment in 1997. Ex. 2003, 388. We find no evidence of record indicating that rituximab had been approved or successfully tested for anything longer than weekly dosing.

While Dr. Jusko's calculations are based on "textbook" equations that were known in the prior art, the actual pharmacokinetic analysis set forth in his declaration for determining the serum trough concentration associated with a tri-weekly dosing regimen of trastuzumab was not found in any prior art reference. Thus, we find Dr. Jusko's analysis to be largely based on impermissible hindsight. *KSR*, 550 U.S. at 421 ("A factfinder should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.").

Petitioners contend that Dr. Jusko applied the same model that Patent Owner and its collaborators did in the prior art. Reply 17. In particular, Petitioners rely upon Baselga '96's statement that "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." Ex. 1013, 738. However, Baselga '96 did not mention a tri-weekly schedule, and instead determined that a regimen in which patients received an initial dose of 250 mg trastuzumab followed by 100 mg weekly doses was the "optimal dose and schedule." *Id.* Petitioners also speculate that the Herceptin label's reporting of only a single half-life for each dosage level "suggest[s] use of a one-compartment model." Reply 17; Ex. 1003 ¶ 34. But the Herceptin label does not explicitly indicate that a one-compartment model was used to model the weekly dosing regimen discussed therein. In any event, the pharmacokinetics discussed in the Herceptin label were based on actual clinical trials rather than just mathematical predictions. Ex. 1008, 1 ("The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease."). Baselga '96 and the Herceptin label both specifically recognize that trastuzumab has "dose dependent pharmacokinetics." Ex. 1008, 1;

Ex. 1013, 738. The very pharmacokinetics textbook relied upon by Dr. Jusko notes that "dose-dependent and time-dependent kinetic behaviors defy easy quantitative description and prediction." Ex. 1022, vol. 3, 395.

We recognize that Pegram'98 states that Phase I clinical "studies showed that the pharmacokinetics of rhuMAb HER2 were predictable." Ex. 1014, 2660. But as explained by Patent Owner's pharmacokinetic expert Dr. Grass, "[a] skilled artisan would understand 'predictable' in this context to mean that administration of the same dose with the same dosing schedule would likely yield the same serum concentrations if given to a similar patient population." Ex. 2039 ¶ 54. It does not suggest predictability across different dosing intervals. Insofar as the pharmacokinetics discussed in the prior art were only based on studies of weekly administration of lower trastuzumab doses, we do not find that the references support Petitioners' conclusion that the same "one-compartment" model could also be used to reasonably predict the expected serum concentrations for tri-weekly administration using higher doses of the antibody.

The evidence shows that the prior art did not contain sufficient data from which the skilled artisan could reliably predict the plasma concentration for trastuzumab over a three-week dosing interval using a one-compartment model. In this regard, we credit the testimony of Dr. Grass. Dr. Grass explains that one potential source of non-linear kinetics for trastuzumab was the presence of "shed antigens" in the patient's serum, which are extra-cellular domain HER2 receptors (ECD^{HER2}) "shed" from the tumor source that circulate in the patient's blood stream. Ex. 2039 ¶¶ 56, 71, 72. We are unpersuaded by Dr. Jusko's opinion that the effect of shed antigens on half-life and serum trough levels would not have been of

concern to the skilled artisan because it was "only shown to be significant in the small percentage of patients for which shed antigen reached 'high levels,' *i.e.*, greater than about 0.5 μg/mL." Ex. 1057 ¶ 46 (citing Ex. 1013 and Ex. 1014).

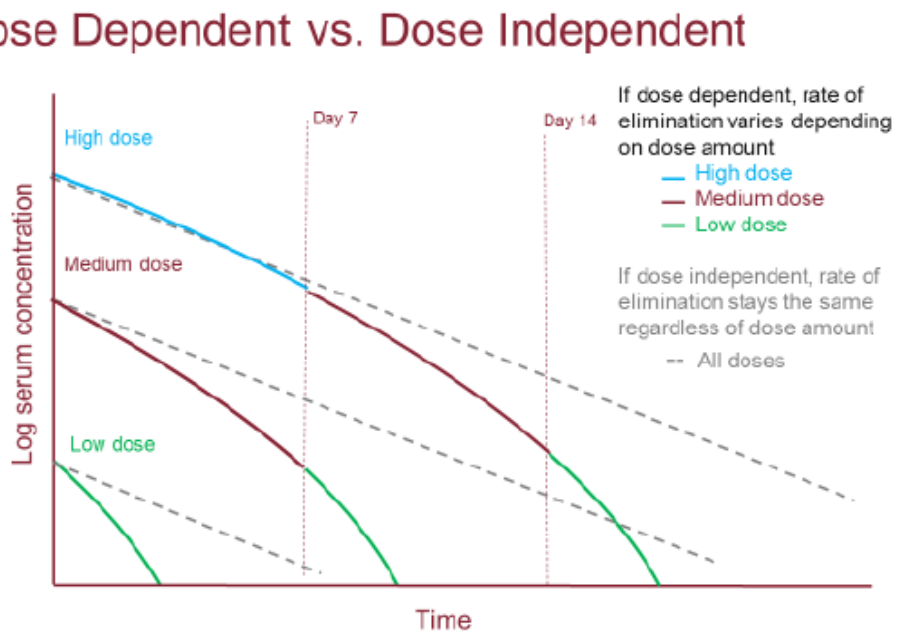
Petitioners' own prior art references highlight the uncertainty caused by the presence of shed antigens on the pharmacokinetics of trastuzumab. For instance, the Herceptin label notes that "64% of patients (287/447) had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL)," and that "[p]atients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations." Ex. 1008, 1. Baselga '96 likewise teaches that "[t]he rhuMAb HER2 serum $t_{1/2}$ was found to be dependent on the presence of circulating ECD^{HER2} released from the tumor into the serum." Ex. 1013, 739. In fact, for those patients with high levels of shed antigen, Baselga '96 teaches that serum levels of the antibody were "suboptimal," and that "the trough levels of rhuMAb HER2 were consistently below detectable levels throughout the treatment course and until disease progression." *Id.* at 739–740 (Fig. 1B). Pegram '98 notes "there was an inverse relationship between rhuMAb HER2 serum half-life and serum shed HER2 ECD of 0.5 μg/mL or greater." Ex. 1014, 2665. Pegram '98 further indicates that "patients with any measurable shed [antigen] serum level, compared with patients without measurable circulating ECD, had lower mean trough rhuMAb HER2 concentrations (18.7 v. 43.6 μg/mL; $P = .0001$) across all time points (n = 443 observations; Fig. 1)." Notably, this prior art data appears to show that patients with *any* detectable shed antigen levels (i.e., 64% of patients as set forth in the Herceptin label) had a mean antibody trough level that was close to the 10–

20 μg/mL threshold for efficacy.[9] As such, we find that skilled artisan would have been concerned that the effect of shed antigens— not taken into account by Dr. Jusko's analysis—could indeed significantly affect serum trough concentrations for tri-weekly administration of trastuzumab.

Contrary to Dr. Jusko's assumptions, Dr. Grass attests that "applying a constant value for half-life over a three-week period, based on the one-week data reported in the prior art, to a dose-dependent drug like trastuzumab could overestimate trough serum concentration levels" because it "fail[s] to account for the nonlinear increase in elimination and corresponding decrease in the half-life that would be expected to occur as serum concentration declines." Ex. 2039 ¶ 25. Dr. Grass also contends that the actual rates of elimination for such a drug would be unpredictable without collecting sufficient data, such as by conducting a "washout study" where serum concentration is collected over several half-lives following a single administration of the drug, but notes that there is no prior art reference for trastuzumab that describes such data. *Id.* ¶ 24.

To illustrate this point, Dr. Grass provides the following graph showing differences that can potentially exist between dose-independent drugs (which exhibit linear kinetics) and dose-dependent drugs (which exhibit non-linear kinetics):

[9] Although Dr. Gelmon testified that later (post-filing) studies showed that shed antigens were not in fact a concern for efficacy of Herceptin, and that dosage is not adjusted based on shed antigen levels today, our analysis is based on what was known in the prior art. Ex. 1058, 62:20–65:6.



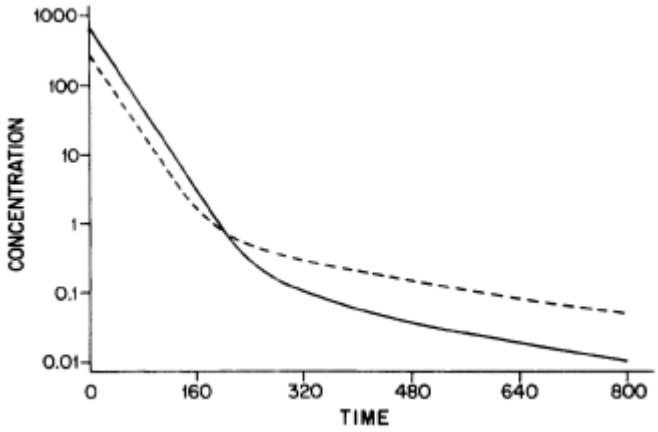
Id. ¶ 23. As shown by the solid lines in the graph above, which correspond to different dosage amounts of a dose-dependent drug, elimination increases (i.e., half-life decreases) as the drug concentration changes over time. Petitioners criticize this graph as being "made up" by Dr. Grass, as it was not derived from any particular data set forth in the prior art. Reply 20 (citing Ex. 1059, 116:16–21). Patent Owner, however, points to post-filing data concerning the anti-cancer agent indisulam as a "real-world example" of a dose-dependent drug that can behave this way, showing how assuming a constant half-life could greatly overestimate the predicted serum concentration over a longer interval. PO Resp. 49–50; Ex. 2039 ¶ 26; Anthe S. Zandvliet et al., *Saturable Binding of Indisulam to Plasma Proteins and Distribution to Human Erythrocytes*, 34 DRUG METABOLISM & DISPOSITION 1041 (2006) (Ex. 2052) ("Zandvliet"). While we recognize that Zandvliet does not qualify as prior art, and concerns a "small molecule" rather than an antibody, we find that it demonstrates at least one example in which assuming linear kinetics could result in an overestimation of trough serum

concentrations for a dose-dependent drug. From the perspective of a skilled artisan as of the August 27, 1999 priority date, we find nothing in the record to suggest that a similar overestimation would not have been a concern for tri-weekly trastuzumab administration.

With its Reply, Petitioners present additional evidence and arguments as to why Dr. Jusko's initial assumptions and analysis were reasonable. In particular, Petitioners contend that Dr. Jusko's analysis would, at worst, have underestimated, not overestimated, serum trough concentrations. Reply 18–23. In support of this contention, Petitioners cite King, APPLICATIONS AND ENGINEERING OF MONOCLONAL ANTIBODIES (1998) (Ex. 1029) ("King '98") as teaching that antibodies follow a common profile associated with "receptor-mediated" (or "target-mediated") drug disposition, with a quick initial clearance and short half-life ($t_{1/2}\alpha$), followed by slower clearance and a longer half-life ($t_{1/2}\beta$). While King '98 includes a table that identifies several antibodies known at the time to have a shorter $t_{1/2}\alpha$ followed by a longer $t_{1/2}\beta$, it *only* reports a $t_{1/2}\beta$ of 199 ± 120 hours for trastuzumab (citing Baselga '96), and Petitioners do not point to any other evidence suggesting a $t_{1/2}\alpha$ for trastuzumab. *See* Ex. 1029, 70 (Table 2.7). Furthermore, King '98 recognizes that the presence of circulating shed antigens could reduce antibody half-life in some cases, and that "[t]he pharmacokinetics of human IgG are unusual in that the half-life varies with concentration." *Id.* at 68, 70. As such, we find that King '98 does not show that Dr. Jusko's linear assumptions would have underestimated serum trough concentrations for trastuzumab.

In further support, Petitioners point to the following graph from Levy, *Pharmacologic target-mediated drug disposition*, 56(3) Clinical

Pharmacology & Therapeutics 248–52 (1994) ("Levy") as demonstrating this type of profile:

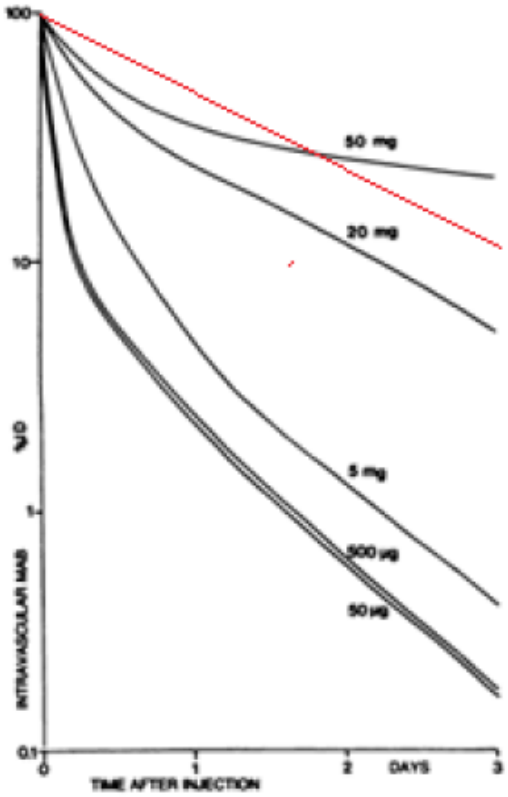


Ex. 1052, 249 (Fig. 1). The figure above shows "[t]ypical concentration-time profile in plasma *(continuous line)* and tissues *(broken line)* for a drug that is subject to high-affinity low-capacity binding in tissues." *Id.*

We do not find that the expected profile for receptor-mediated drug disposition, as shown in Levy, supports the reasonableness of Dr. Jusko's pharmacokinetic analysis for trastuzumab. Levy does not describe the kinetics of antibodies at all, but instead only identifies certain small molecules that might exhibit this "hypothetical behavior." Ex. 2084, 22:10–16, 59:8–16. Specifically, with reference to Figure 1 shown above, Levy notes that "the effect on pharmacokinetics can be quite striking in that the plasma concentration profile exhibits a terminal decay phase with a very long half-life ($t_{1/2}$), as is the case for certain angiotensin-converting enzyme (ACE) and aldose reductase inhibitors." Ex. 1052, 248. In criticizing Dr. Grass's reliance on the indisulam data discussed above, Dr. Jusko notes that skilled artisans would not "rely[] on pharmacokinetic behavior of ***small molecules***, which was known to be fundamentally different to that of antibodies." Ex. 1057 ¶ 5; *see also id.* ¶ 20 n.1 (noting "in addition to the

[differences in] molecular weight, the different mechanisms of disposition of small molecules and antibodies impacts their pharmacokinetic profiles"). Accordingly, we are not persuaded by Dr. Jusko's inconsistent opinion relying upon Levy's teachings with respect to target-mediated disposition of small molecules. Ex. 1057 ¶ 15. Moreover, even with respect to the ACE inhibitors discussed therein, Levy does not make any definitive conclusions as to their pharmacokinetic behavior, noting instead that "[m]ore definitive information can be obtained only in animal studies that permit opening of the 'black box' to explore what goes on in individual tissues." Ex. 1052, 248–49.

Petitioners also point to the following graph from Koizumi, *et al.*, *Multicompartmental Analysis of the Kinetics of Radioiodinated Monoclonal Antibody in Patients with Cancer*, 27(8) J. NUCLEAR MED. 1243–54 (1986) (Ex. 1054) ("Koizumi"):



Reply, 22; Ex. 1054, 1252 (Fig. 8) (annotation in red added by Petitioners). The annotated figure above shows "[m]odel simulated curves" for intravascular monoclonal antibodies (MAb) reflecting the "effect of different amount of injected MAb on blood clearance." *Id.* According to Petitioners, "for a given antibody dose (here 50mg), a linear model (shown in red) would underestimate the actual serum concentration (shown in black) soon after dosing." Reply 21.

We do not find that Koizumi supports the reasonableness of Dr. Jusko's application of a linear model. Indeed, Petitioners' own annotation in the figure above shows that a linear model could overestimate actual serum concentrations for certain doses (e.g., 20 mg) or at certain times after injection (e.g., less than 2 days). For tri-weekly trastuzumab administration, it was unknown whether the actual serum concentration would fall above or

below the linearity assumed in Dr. Jusko's model. Moreover, unlike Dr. Jusko's "one-compartment" analysis in this proceeding, Koizumi specifically describes a "multicompartmental" analysis conducted using a computer simulation. Ex. 1054, 1247. In this regard, Koizumi notes that "[i]nitial model solutions assumed that the model was linear," but "[u]sing this information it was not possible to fit the data observed for the patients with the model simulations." *Id.* at 1245–46. Furthermore, according to Koizumi:

> [C]ompartmental analysis also raises several problems. If the compartmental model is based upon unlikely assumptions, or inadequately validated, then misleading information follows. While this is self-evident, the complexity of a model addressing the pharmacokinetics of a MAb requires simplifications based upon assumptions in order to permit realistic mathematical handling. These simplifications and assumptions are particularly vulnerable to error in a system such as MAb, wherein many processes remain to be clarified.

Id. at 1252. As such, Koizumi underscores the inherent uncertainty associated with using mathematical models to predict the pharmacokinetic behavior of antibodies.

In sum, for the foregoing reasons, we determine Petitioners have not established the reasonable expectation of success required for obviousness. In reaching this conclusion, we are cognizant that "[c]onclusive proof of efficacy is not required to show obviousness." *Hoffman-La Roche*, 748 F.3d at 1331. Nonetheless, the Federal Circuit has also indicated that reasonable expectation cannot come from a mere "hypothesis" that might form the basis for further testing. *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 647–49 (Fed. Cir. 2017) (finding prior art reference that stated the "expected" benefit of a

clinical trial did not establish a reasonable expectation of success); *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

III. ALLEGED IMPROPER REPLY MATERIALS/PATENT OWNER'S MOTION TO EXCLUDE

Pursuant to our authorization, Patent Owner filed a paper identifying allegedly improper arguments and evidence included with Petitioners' Reply. Paper 68. Specifically, Patent Owner identifies the following materials as improper: Exhibits 1043–1048, 1050, 1052, 1054, and 1055, and portions of Dr. Lipton's reply declaration (Ex. 1056) and Dr. Jusko's reply declaration (Ex. 1057) referencing those exhibits. *Id.* Patent Owner also separately filed a motion to exclude the same evidence it identifies as improper reply materials. Paper 64.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[10] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization

[10] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

to file a motion to strike." *Id.* at 17. "In most cases, the Board is capable of identifying new issues or belatedly presented evidence when weighing the evidence at the close of trial, and disregarding any new issues or belatedly presented evidence that exceeds the proper scope of reply or sur-reply." *Id.*

Nevertheless, to the extent necessary, we treat Patent Owner's Motion to Exclude and Identification of Improper New Reply Materials as a motion to strike. We have not relied upon Exhibits 1043–1048, 1050, and 1055 in rendering this decision. We have not given any weight to this evidence to support Petitioners' obviousness arguments because they have publication dates after August 27, 1999, and thus do not qualify as prior art to the '379 patent. *See* Paper 64, 7–10 (explaining why post-priority date references relied upon by Petitioners are irrelevant to obviousness determination in this proceeding). Furthermore, Exhibit 1055 has not been cited or relied upon by Petitioners in their Reply, and we decline to incorporate by reference the opinion in Dr. Jusko's reply declaration concerning that exhibit. *See* 37 C.F.R. § 42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document."). Accordingly, we dismiss as moot Patent Owner's motion to strike this evidence.

We have taken into consideration Exhibits 1052 and 1054 in our analysis, as discussed above. We determine that these exhibits and Petitioners' arguments in relation to these exhibits are proper reply evidence as they seek to respond to Patent Owner's arguments concerning the reasonableness of Dr. Jusko's pharmacokinetic analysis. Specifically, in relying upon Exhibits 1052 and 1054, and the portions of Dr. Jusko's reply declaration citing those exhibits, Petitioners seek to respond to Patent Owner's criticism that Dr. Jusko's assumptions would have overestimated

serum concentration for dose-dependent drugs such as trastuzumab. With such evidence, Petitioners seek to further support, not modify, their basis for reasonable expectation of success set forth in the Petition. We do not find that Petitioners have presented an "entirely new rationale" worthy of being excluded in their Reply. *Ericsson Inc. v. Intellectual Ventures I LLC*, No. 2017-1521, 2018 WL 4055815, *6 (Fed. Cir. Aug. 27, 2018). Although we find the new exhibits unpersuasive, that does not render them improper reply evidence. We, therefore, deny Patent Owner's motion to strike this evidence.

IV. CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that although Petitioners have shown that a skilled artisan would have been motivated to extend the dosing frequency of trastuzumab from weekly to tri-weekly, Petitioners have not met their burden to show a reasonable expectation of success with respect to such a dosing regimen. As a result, Petitioners have not shown, by a preponderance of the evidence, that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 patent would have been obvious over the combination of the Herceptin Label, Baselga '96, Pegram '98, and the knowledge of the skilled artisan.

V. ORDER

Accordingly, it is:

ORDERED that claims 1–3, 5, 7, 9–11, 16–28, and 30–40 of the '379 patent have not been shown to be unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2017-00805
Patent 7,371,379 B2

PETITIONERS:

For Hospira, Inc.:
Amanda Hollis
Stefan M. Miller
Benjamin A. Lasky
Sarah K. Tsou
Mark C. McLennan
Christopher J. Citro
KIRKLAND & ELLIS LLP
amanda.hollis@kirkland.com
stefan.miller@kirkland.com
karen.younkins@kirkland.com
benjamin.lasky@kirkland.com
sarah.tsou@kirkland.com
mark.mclennan@kirkland.com
christopher.citro@kirkland.com

For Samsung Bioepis Co., Ltd.:
Dimitrios T. Drivas
Scott T. Weingaertner
Amit H. Thakore
Eric Majchrzak
WHITE & CASE LLP
ddrivas@whitecase.com
scott.weingaertner@whitecase.com
athakore@whitecase.com
eric.majchrzak@whitecase.com

PATENT OWNER:

David L. Cavanaugh
Lauren V. Blakely
Robert J. Gunther, Jr.
Lisa J. Pirozzolo
Kevin S. Prussia

Andrew J. Danford
Robert Galvin
WILMER CUTLER PICKERING HALE AND DORR LLP
david.cavanaugh@wilmerhale.com
lauren.blakely@wilmerhale.com
robert.gunther@wilmerhale.com
lisa.pirozzolo@wilmerhale.com
kevin.prussia@wilmerhale.com
andrew.danford@wilmerhale.com
robert.galvin@wilmerhale.com

Adam R. Brausa
Daralyn J. Durie
DURIE TANGRI LLP
abrausa@durietangri.com
ddurie@durietangri.com

PROOF OF SERVICE

I hereby certify that the foregoing APPELLANT'S BRIEF was served on the 21st day of March 2019, by operation of the Court's CM/ECF system per Federal Rule of Appellate Procedure 25.

Dated: March 21, 2019

/s/ Stefan Mentzer
Stefan Mentzer
Counsel for Appellant

CERTIFICATE OF COMPLIANCE WITH RULE 32

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32(a) because this brief contains 13,027 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in a proportionally spaced serif typeface using Microsoft Office Word 2016 in 14-point Times New Roman font.

Dated: March 21, 2019

/s/ Stefan Mentzer
Stefan Mentzer
Counsel for Appellant