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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

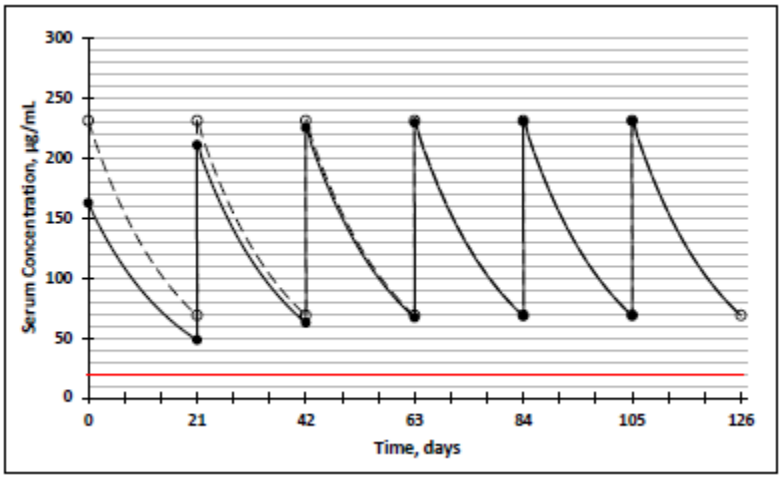
the skilled artisan would have been aware of a target trough serum concentration of 10–20 μg/mL for trastuzumab. Pet. 33, 37.

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).

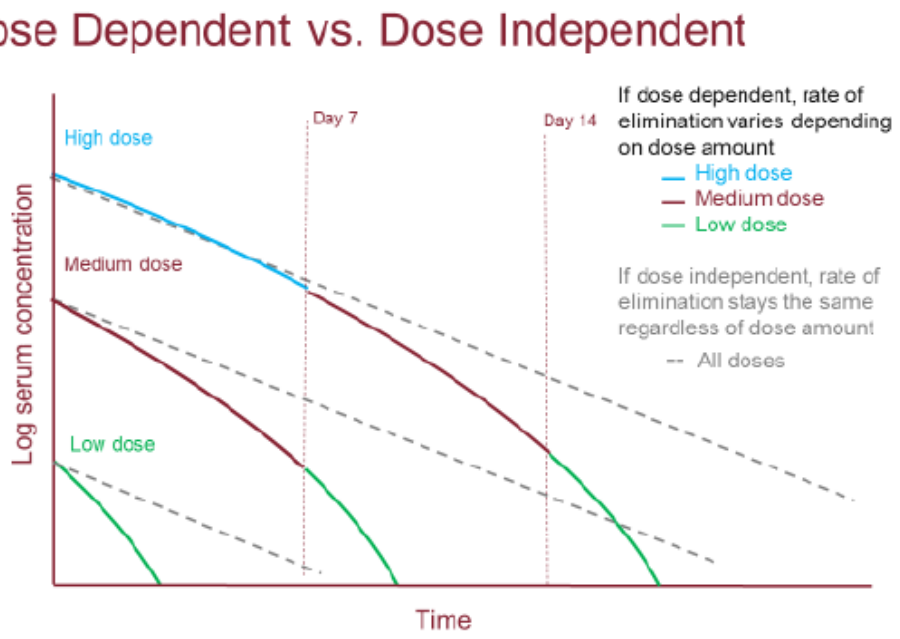
Petitioners' own prior art references highlight the uncertainty caused by the presence of shed antigens on the pharmacokinetics of trastuzumab. For instance, the Herceptin label notes that "64% of patients (287/447) had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL)," 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.



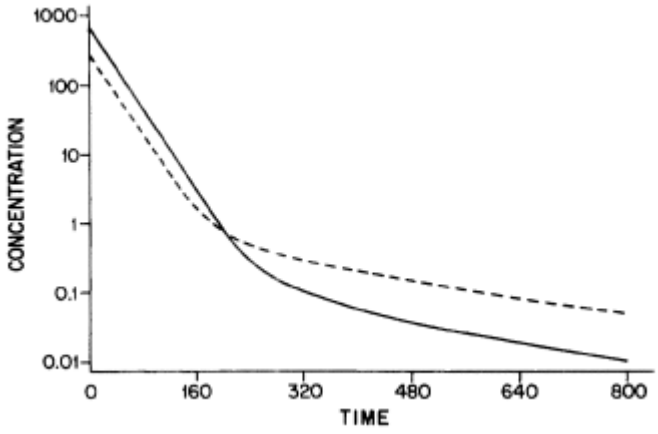
Id. ¶ 23. As shown by the solid lines in the graph above, which correspond to different dosage amounts of a dose-dependent drug, elimination increases (i.e., half-life decreases) as the drug concentration changes over time. Petitioners criticize this graph as being "made up" by Dr. Grass, as it was not 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:

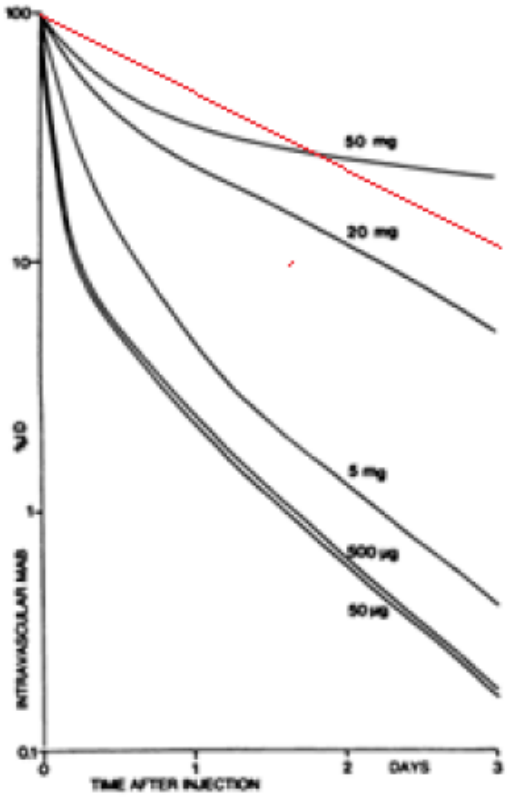


Ex. 1052, 249 (Fig. 1). The figure above shows "[t]ypical concentration-time profile in plasma *(continuous line)* and tissues *(broken line)* for a drug that is subject to high-affinity low-capacity binding in tissues." *Id.*

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.

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