UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner

Case No. IPR2017-01140
Patent No. 7,371,379

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION

As explained in the Petition, the challenged claims are obvious for the simple reason that weekly trastuzumab, in combination with chemotherapy, was already known to be safe and effective for treating metastatic breast cancer, and a person of ordinary skill in the art ("POSA") would have expected that less frequent administration of trastuzumab—administered on an every-three-week schedule to match that of the partner chemotherapy regimen—would improve convenience without sacrificing either efficacy or safety. Sifting through Patent Owner's rhetoric and mischaracterizations of Petitioner's arguments, its response comes down to two untenable positions: (1) that a POSA would not have had any motivation to improve the convenience of the prior art trastuzumab regimen; and (2) that a POSA would not have reasonably expected that administering trastuzumab on an every-three-week schedule would be effective.

The first of these arguments is as illogical as it sounds, and is expressly contradicted by the prior art, including references authored by and studies conducted by Patent Owner's own expert. The second argument relies on the unsupported presumption that a POSA would have ignored the clear implications of the prior art pharmacokinetic data due to a generalized concern over theoretical consequences of non-linear pharmacokinetics.

Neither argument has merit, and as demonstrated in the Petition, the challenged claims should have never issued, and should be cancelled for obviousness.[1]

II. ARGUMENT

A. There is no Dispute that POSAs were Motivated to Improve the Trastuzumab Dosing Regimen

Patent Owner represents the purported invention as pioneering the use of trastuzumab itself, which Patent Owner attempts to portray as a novel agent. *See* Patent Owner Reply ("POR") at 1. However, prior to the earliest possible priority date (August 27, 1999), trastuzumab was in fact widely known to, and used by, POSAs. The FDA had approved Herceptin® in September 1998, and as Patent Owner contends, POSAs had been seeking out trastuzumab for use in patients since at least 1995. Ex. 2034 at 887. Accordingly, as of the priority date, POSAs had experience administering trastuzumab, were familiar with its safety and efficacy, and its use was well-understood. Ex. 1003 at ¶9. As Patent Owner acknowledges, around the time of the purported invention, much was published about the use of the drug: "During the five years following trastuzumab's approval, ***hundreds*** of papers and abstracts were published in which researchers

[1] Patent Owner does not argue the claims separately. POR at 15-16. Accordingly, the challenged claims all stand or fall together.

explored various ways to maximize the effective use of trastuzumab." POR at 8 (emphasis added).

Patent Owner further admits that "in the late 1990s, skilled artisans were actively investigating how to combine trastuzumab with chemotherapy, including paclitaxel." *Id.* at 8, 1 (conceding that "[e]fforts to better understand and use this new therapy did not end when trastuzumab was first approved for weekly administration to treat metastatic breast cancer"). Accordingly, there is no dispute that as of the priority date, POSAs were motivated to optimize dosing regimens for trastuzumab, and were specifically looking to improve the prior art trastuzumab/chemotherapy dosing regimen. Thus, with regard to motivation, the narrow issue in dispute is whether POSAs would have only been motivated to pursue dosing regimens that improved efficacy, as Patent Owner contends, or whether POSAs would have also been motivated to pursue regimens that gave other clinical benefits, including improved patient and clinician convenience. As will be discussed, Patent Owner's assertions that convenience was not relevant to metastatic breast cancer patients is contrary to the prior art.

1. Convenience Considerations were Relevant to Cancer Treatments

One well-known way in which a dosing regimen for cancer treatment can be improved is to make it more convenient. Generally speaking, less frequent administrations are more convenient than more frequent administrations. Ex. 1101

at 3 ("The tolerance [of bi-weekly paclitaxel] is similar to the weekly schedule but bi-weekly paclitaxel may be more convenient."); Ex. 1017 at 2 (a once every three week regimen of anti-cancer drug irinotecan "has the added advantage of greater patient convenience, as it entails less frequent dosing than is required on a weekly schedule"). Pursuant to the approved Herceptin® dosing regimen, trastuzumab was administered weekly, while its chemotherapeutic partner drugs (like paclitaxel) were administered every three weeks. *See* Ex. 1008 at 1; Ex. 1005 at 5 (doxorubicin-cyclophosphamide and paclitaxel administered once every three weeks). As Dr. Ratain explained, given these different dosing schedules, a POSA would have been motivated to reduce the frequency of the trastuzumab administration to align it with the schedule for chemotherapy administration. Petition at 27 (citing Ex. 1003 at ¶¶89-90). This would have obvious convenience benefits for both the clinician and the patient, whose visits to the clinic would be reduced by two-thirds. Ex. 1123 at ¶17.

Patent Owner nevertheless disputes this seemingly irrefutable position, contending that when it comes to metastatic breast cancer, skilled artisans were singularly interested in improving efficacy of cancer treatments, to the exclusion of improving convenience. *See, e.g.*, POR at 8, 10, 27; Ex. 2028 at ¶34. This is demonstrably untrue. For example, in 1998, the FDA issued guidance directed to new uses of marketed anti-cancer drugs and biologics (like Herceptin®). Ex. 1118.

These guidelines expressly contemplated that sponsors may change dosing regimens to improve convenience:

> New dosing regimens (including changes in the range of doses administered for approved indications and ***changes in the schedule of administration) can lead to improved*** effectiveness, tolerance, or ***convenience***.

Id. at 8 (emphasis added).

Further, the literature Dr. Gelmon relies on expressly undercuts any allegation that in the 1990's POSAs were not motivated to improve the convenience of treatments for life-threatening cancer. Dr. Gelmon discusses weekly paclitaxel at length, but omits that this work was expressly undertaken to address convenience. *See, e.g.*, Ex. 2065 at 19 (noting that study of weekly paclitaxel was "***[m]otivated by*** the cytokinetic considerations of dose dense therapy, the demonstrated feasibility of 1-hour infusions and ***the considerations of convenience*** of drug administration") (emphasis added); Ex. 2016 at 3353 ("the administration of 96-hour continuous infusions of paclitaxel may impose a certain ***inconvenience*** on both the clinic and the patient") (emphasis added). Moreover, in a study Dr. Gelmon herself conducted on patients with small cell lung cancer (the most lethal type of cancer, Ex. 1104 at 20:25-21:5), she expressly identified one of the objectives of the study as "improv[ing] chemotherapy administration convenience." Ex. 1103 at 1. Additionally, a 1998 review article on which Dr.

Gelmon relies expressly states that "***[b]ecause of its convenience in the outpatient setting***, a 3-h infusion [of paclitaxel] is currently the most widely used." Ex. 2036 at 374 (emphasis added). Accordingly, Patent Owner's contention that POSAs were not motivated to improve the convenience of cancer treatments is untenable.

2. **Even in the Case of Metastatic Breast Cancer, Compliance and Convenience were Important**

Patent Owner wrongly criticizes Dr. Ratain's opinions regarding convenience as "generalized" and "untethered" to the patient population at issue, *i.e.*, patients with metastatic breast cancer.[2] *See, e.g.*¸POR at 29, 36. Patent Owner argues that given the seriousness of the disease, convenience is irrelevant,

[2] Patent Owner faults Dr. Ratain for being unable to recall the number of breast cancer patients he treated in 1999 and earlier years. POR at 29. It is not surprising that he was unable to recall specific patient numbers from twenty years ago. Indeed, Dr. Gelmon was similarly unable to recall even approximately how many patients she had treated with Herceptin® in 1998-99. Ex. 1104 at 22:17-23. Patent Owner also faults Dr. Ratain for not having a "focus" on breast cancer, but neither side proposed a POSA definition that requires such a "focus." Petition at 23; POR at 23-24. Patent Owner does not dispute that Dr. Ratain is an oncologist who qualifies as a POSA. Further, the independent challenged claims recite "cancer," not breast cancer.

as patients needed "little additional convincing in the form of convenience to take trastuzumab." POR at 36. First of all, most of the challenged claims are not limited to the treatment of metastatic breast cancer or even breast cancer. Furthermore, Patent Owner fails to cite a single published reference substantiating these allegations. Rather, it relies entirely on anecdotes from Dr. Gelmon, who contends that "compliance was not an issue for patients taking trastuzumab in 1999." Ex. 2028 at ¶41. Even though she purports to opine on missed doses for patients stemming back over 20 years ago, Dr. Gelmon testified that she did not look back at any patient records to substantiate this claim. Ex. 1104 at 20:9-22:12.

Additionally, the suggestion that due to the seriousness of their disease, metastatic breast cancer patients never miss a drug dose is contrary to the prior art, which confirms the common sense understanding that normal commitments sometimes interfere with treatment. For example, Seidman 1998 addresses "a phase II study of weekly paclitaxel therapy in women with metastatic breast cancer." Ex. 2016 at 3353. Despite the seriousness of the disease, and even in the context of a tightly controlled clinical study, patients in fact missed doses, including due to "social obligations" and other "commitments." *Id.* at 3355.

Patent Owner's assertion that no patients experienced compliance issues with anti-cancer therapies is thus both illogical and contrary to the prior art.[3]

Patent Owner points to a study which purportedly showed that adding weekly trastuzumab to an every-three-week chemotherapy regimen improved patient quality of life. POR at 27-28. But the study did not include patients who received trastuzumab every three weeks. Ex. 1104 at 82:3-24. The study is thus irrelevant to whether administering trastuzumab on the same three week schedule as chemotherapy could improve patient quality of life over requiring the patient to return each week to the hospital to get the prior art weekly trastuzumab + every-three-week chemotherapy regimen.

Despite her protestations now, Dr. Gelmon evidently believed at the relevant time that improving the convenience of trastuzumab administration through a less-frequent regimen could benefit patients. Although she did not reveal as much to the Board in her declaration, Dr. Gelmon acknowledged at deposition that beginning in "the second half of 1999," she herself conducted a clinical study on

[3] For at least this reason, Patent Owner's efforts to distinguish *Hoffmann-La Roche Inc. v. Apotex, Inc.*, 748 F.3d 1326 (Fed. Cir. 2014) on the grounds that convenience is a factor in treating osteoporosis but not cancer regimens fall flat. In *Hoffmann-La Roche*, as here, multiple prior art articles refer to patient convenience as a factor for altering cancer dosing regimens. *Id.* at 1330.

an every-three-week trastuzumab plus paclitaxel dosing regimen. Ex. 1104 at 32:3-14. That study was not designed to test whether the regimen was more efficacious or safer than the weekly trastuzumab regimen.[4] Indeed, going into the study, Dr. Gelmon had no reason to think that the every-three-week regimen would be more effective or safer than the weekly regimen, and even as of today, there have been no documented safety or efficacy advantages for the claimed regimen.[5] *Id.* at 78:16-79:7, 36:4-13. Rather, the only potential advantage of this regimen that Dr. Gelmon identified is convenience for certain patients. *Id.* at 36:14-18. And in a publication about the study, Dr. Gelmon confirmed that the reason for pursuing this regimen was that "it may improve patient convenience." Ex. 1105 at 5; *see also* Ex. 1107 ("[L]ess frequent administration may be safe, efficacious and more convenient for the patient."). As Dr. Gelmon testified, "some patients may

[4] As Dr. Gelmon testified, one needs to do a head-to-head study to determine if one regimen is more efficacious than another. Ex. 1104 at 69:11-29. The trial design for three-weekly trastuzumab lacked any testing of the weekly regimen. Ex. 1102 at 2.

[5] This is contrary to the '379 Patent's statement that the claimed regimen is purportedly "more efficacious than conventional treatments." Ex. 1001 at 4:26-31. Relatedly, it should be noted that Patent Owner has not asserted any secondary considerations of nonobviousness in this proceeding.

prefer one schedule versus the other just like some persons prefer Coke to coffee"—a statement that is as apparent to POSAs today as it was in August 1999. Ex. 1104 at 41:18-20.

Patent Owner's mischaracterizations notwithstanding, neither Petitioner nor Dr. Ratain suggested that convenience would have taken priority over efficacy such that POSAs would have adopted a more convenient regimen at the expense of effectively treating patients. However, given the expectation of equivalent efficacy, a POSA would have been motivated to pursue the more convenient, every-three-week regimen. Ex. 1123 at ¶33.

3. POSAs Were Already Extending Trastuzumab's Dosing Interval to Align it With Other Drug Intervals

In attempt to undercut motivation, Patent Owner argues that as of 1999, POSAs were not extending trastuzumab's dosing interval to match chemotherapy, but were instead doing the opposite (particularly, increasing the frequency of paclitaxel dosing to match that of trastuzumab). POR at 31. Patent Owner also points to studies involving agents other than paclitaxel, with Dr. Gelmon asserting that "skilled artisans were planning numerous trials to evaluate agents other than paclitaxel to combine with trastuzumab, and with so many different options, ***there was no intention to alter trastuzumab's dosing schedule to match any or all of these other agents***." Ex. 2028 at ¶37.

The work on weekly paclitaxel would not have undercut motivation to pursue an every-three-week regimen, and Patent Owner's contention about lack of intent to alter trastuzumab's dosing schedule to match that of other anti-cancer agents is inconsistent with the prior art.

a. The Work on Weekly Paclitaxel Would Not Have Dissuaded a POSA From Pursuing an Every-Three-Week Trastuzumab Regimen

Patent Owner contends that a POSA wanting to align the dosing schedules of trastuzumab and paclitaxel would have chosen to administer both agents weekly, as opposed to administering both every three weeks. POR at 31-33. Patent Owner's basis for this argument is that some researchers had administered paclitaxel weekly with trastuzumab. *Id.* However, simply because some researchers had pursued this regimen does not undercut a motivation to administer trastuzumab on an every-three-week schedule with paclitaxel. *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 and Dr. Gelmon also argue that POSAs would not have aligned trastuzumab to every-three-week paclitaxel because POSAs were shifting

to weekly paclitaxel.[6] *See* POR at 31-32; Ex. 2028 at ¶38, citing Ex. 2036. However, the very document Dr. Gelmon cites for this proposition states exactly the opposite, noting that for paclitaxel, "a dose of 175 mg/m^2 by 3-h infusion ***every three weeks*** appears to be very reasonable in the treatment of advanced breast cancer," and that "[t]oday, clinical studies are typically employing a 3-h infusion at a dose of 135-250 mg/m^2 ***every three weeks***." Ex. 2036 at 374, 385 (emphasis added). Furthermore, despite whatever off-label experimentation some clinicians may have engaged in, the FDA-approved dosing regimen for paclitaxel remained every three weeks as of the priority date, and remains so today. Ex. 1123 at ¶28.

b. POSAs Were Modifying the Trastuzumab Regimen to Match that of Other Drugs

Real-world evidence also refutes Patent Owner's argument that a POSA would not have considered extending trastuzumab's dosing regimen to match that of other drugs. Indeed, both Dr. Gelmon and Dr. Ratain were actively involved in such work.

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[6] Patent Owner also alleges that "by 1999, studies showed that weekly paclitaxel was more effective than a three-week regimen." POR at 9. This is simply not true. As Dr. Gelmon testified, as of the priority date, no study had shown that weekly paclitaxel was more effective than an every-three-week regimen. Ex. 1104 at 68:22-69:15.

As discussed above, although neither Patent Owner nor Dr. Gelmon acknowledged it in their submissions, in the second half of 1999, Dr. Gelmon herself studied an every-three-week trastuzumab dosing regimen. Ex. 1104 at 32:3-14. This work is completely counter to her assertion that "[a]t least because of the unfamiliarity that comes with a new class of drug, and because trastuzumab was already a very effective treatment for an aggressive disease, a clinical oncologist would not have taken chances by using the new regimen on a patient with a life-threatening disease."[7] Ex. 2028 at ¶8.

Further, as early as April 1997, Dr. Ratain was involved in a cancer clinical study that expressly extended the trastuzumab dosing regimen to match that of interleukin-2 ("IL-2"): "The biweekly schedule was tested so that trastuzumab doses would coincide with the intermediate-dose IL-2 pulses."[8] Ex. 1123 at ¶23;

[7] Dr. Gelmon also began working on changing the dosing regimen for paclitaxel for the treatment of breast cancer in 1994, the very same year it was approved for that indication, and only shortly after its initial 1992 approval. Ex. 1104 at 73:9-22; Ex. 1115 at 6156 n.3 She undertook this work despite the newness of the drug, the fact that it was a first-in-class treatment, and that it was used to treat a life-threatening disease. Ex. 1104 at 85:7-15; 46:16-48:4.

[8] The study included HER2+ breast cancer patients. Ex. 1100; Ex. 1104 at 50:22-51:1.

Ex. 1100 at 3. Dr. Gelmon testified that she did not take this study into account in preparing her declaration (Ex. 1104 at 43:3-24), leading her to incorrectly pronounce that POSAs had "no intention to alter trastuzumab's dosing schedule to match" that of other cancer drugs. Ex. 2028 at ¶37.

In view of the above, Patent Owner's litigation-inspired arguments regarding lack of motivation to extend trastuzumab's dosing interval are inconsistent with the real world and should be rejected.

4. There is No Incompatibility in Matching Trastuzumab's Dosing Interval to that of Chemotherapy

Patent Owner asserts that a POSA would not have administered trastuzumab on the same schedule as chemotherapy because it was "known that chemotherapy agents and targeted therapies like trastuzumab are dosed according to different principles." POR at 33. However, Patent Owner has not identified any reason why syncing the regimens of these two drugs would not be expected to work. Indeed, as early as May 1999, oncologists had published abstracts on clinical studies reporting the safety and efficacy of weekly co-administration of paclitaxel and Herceptin®. *See, e.g.*, Ex. 2037 at 2; Ex. 2021; *see also* Ex. 2028 at ¶38 ("There were even plans to explore the weekly co-administration of paclitaxel and trastuzumab."). That skilled artisans were already co-administering trastuzumab with chemotherapeutic agents as of the priority date undermines Patent Owner's suggestion that POSAs would not have synced dosing schedules of these agents.

B. POSAs Would Have Maintained the Same Total Dose

Patent Owner suggests that a POSA would not have selected a dosing regimen consisting of an 8 mg/kg loading dose followed by 6 mg/kg maintenance doses for an every-three-week regimen because the concept of "dose intensity" is purportedly inapplicable to targeted antibodies like trastuzumab. POR at 40. However, POSAs understood that the concept of dose intensity was applicable to a variety of oncology drugs, including targeted antibodies. Ex. 1123 at ¶36; Ex. 1126 at 4 (suggesting that low response rates may be overcome "by increasing the dose intensity of [rituximab].")

More fundamentally, whether the same dose intensity principles applicable to chemotherapeutic agents were applicable to trastuzumab is irrelevant to whether a POSA would have selected these dosage amounts. Patent Owner's misleading focus on the differences between chemotherapy and trastuzumab with respect to how maintaining dose intensity (*i.e.*, the same total dose over a given period of time) relates to overall therapeutic goals entirely misses the point. The relevant question is simply, given the known prior art trastuzumab weekly dosing regimen, what dose amount would a POSA select for an every-three-week regimen? As discussed in the Petition, the prior art trastuzumab regimen consisted of a 4 mg/kg loading dose followed by weekly 2 mg/kg maintenance doses. Petition at 19-20. This directly equates to an 8 mg/kg loading dose followed by 6 mg/kg maintenance

doses when converted to a three week regimen, and would have been the most natural starting point for the every-three-week regimen. Petition at 28-29. Contrary to Patent Owner's suggestions, this concept of maintaining dose intensity is not specific to chemotherapy. POR at 40. Rather, it is a concept that is applicable to other pharmaceutical areas as well. Ex. 1123 at ¶35.

For example, the same approach was used when reducing the administration frequency of thyroxine for the treatment of hypothyroidism from daily to once weekly. Ex. 1123 at ¶36; Ex. 1121 at 1 ("The aim of this study was to determine whether 7 times the daily dose of T_4 administered once weekly was as safe and efficacious as the usual daily dose."). The concept has also been employed with antibiotics, where, for example, aminoglycosides are administered either as a single high dose once every 24 hours, or as the same total dosage amount divided into multiple daily doses. Ex. 1123 at ¶36; Ex. 1111 at 1. The principle of maintaining the same total dosage amount over different administration schedules was also employed for ibandronate, the subject of the *Hoffmann-LaRoche* case mentioned above. Ex. 1122 at 20:28-21:19 (identifying proportionately increasing unit dose amounts for twice-weekly, once-weekly, and bi-weekly dosing).

There was nothing in the prior art about trastuzumab that would have dissuaded a POSA from using the approach of keeping the same dosage amount over time. Therefore, a POSA would have selected the claimed doses as a starting

point, not because of any similarity of trastuzumab to chemotherapy, but simply because it was a reasonable starting point.[9] Ex. 1123 at ¶37. Indeed, Patent Owner has failed to identify any alternative approach to dose selection that would have been appropriate.

C. A POSA Would Have Had a Reasonable Expectation of Success

1. A POSA Would Not Have Had Toxicity Concerns

As explained in the Petition, a POSA would have expected no undue toxicity associated with the claimed regimen. Petition at 42 (citing Ex. 1003 at ¶¶92-95). Neither Patent Owner nor its experts have challenged this conclusion. Ex. 1120 at 51:20-52:2. In fact, Dr. Gelmon confirms that "trastuzumab was exceptionally well tolerated." Ex. 2028 at ¶35.

2. A POSA Would Have Expected the Three-Week Regimen to be Effective

As explained in the Petition, the prior art taught that trastuzumab would be efficacious provided that trough serum concentrations remained above 10 μg/mL. Petition at 32-33. A POSA would have reasonably expected the every-three-week

[9] Patent Owner's reliance on Dr. Ratain having purportedly "conceded" that "the rationale that would lead [a skilled artisan] to dose chemotherapy every three weeks would not apply to dosing trastuzumab every three weeks" and that there "were not enough publications about trastuzumab for – for those [dose intensity] analyses to be presented" is thus inapposite. POR at 40-41.

trastuzumab regimen to be effective because the available pharmacokinetic data permitted a POSA to calculate that such a regimen would maintain trough serum concentrations above this threshold. Petition at 33-35. Patent Owner does not dispute that the prior art taught the 10 µg/mL threshold, but contends that a POSA would not have accepted Dr. Ratain's pharmacokinetic calculations showing that the every-three-week regimen satisfied this criteria. POR at 43.

First, Patent Owner contends that Dr. Ratain improperly assumed that the half-life of trastuzumab measured over the course of a weekly interval will remain constant over the course of a three-week interval. *Id*. Second, Patent Owner contends that Dr. Ratain impermissibly cherry-picked the data used in his calculations. *Id.* Both contentions lack merit.

a. A POSA Would Have Understood Dr. Ratain's Calculations Would Underestimate, Not Overestimate, Trough Serum Concentrations

There is no dispute that the prior art disclosed a trastuzumab half-life in excess of 7 days, or that this half-life was derived from a regimen consisting of a 250 mg loading dose followed by weekly 100 mg doses. Ex. 1003 at ¶¶98, 103; Ex. 2027 at ¶9; Ex. 1120 at 110:10-13, 113:3-20. In concluding that the every-three-week trastuzumab regimen would maintain trough serum concentrations above the threshold, Dr. Ratain utilized a 7-day half-life to determine to what extent the serum concentration would decrease three weeks after a 6 mg/kg

maintenance dose was administered. Ex. 1003 at ¶104. Patent Owner wrongly mischaracterizes Dr. Ratain's analysis as "ignoring" the prior art teachings of dose-dependent, non-linear pharmacokinetics of trastuzumab in calculating the minimum trough concentration expected for the every-three-week regimen. POR at 3; Ex. 2027 at ¶ 76. To the contrary, Dr. Ratain expressly acknowledged that the prior art taught that trastuzumab exhibited dose-dependent, non-linear kinetics, and explained that utilizing the half-life reported in the prior art would therefore ***underestimate*** trough concentrations. *See, e.g.*, Petition at 35 n.8 (citing Ex. 1003 at ¶102).

Patent Owner's suggestion that relying on the prior art half-life could lead to an overestimation of trough concentrations is based on the assumption that the rate of elimination predicted by linear kinetics would be slower than the rate of non-linear elimination. Ex. 1123 at ¶45; Ex. 2027 at ¶¶28-31. However, the rate of elimination predicted by linear kinetics would, in fact, be ***faster*** than the rate of non-linear elimination at higher concentrations. Ex. 1123 at ¶¶45-47; Ex. 1120 at 100:19-101:4. Indeed, the prior art demonstrated that the half-life of trastuzumab ***increased*** with increasing dose. Ex. 1006 at 5; Ex. 1008 at 1; Ex. 1003 at ¶102.

Importantly, the dosage amount for the three-weekly regimen is significantly higher than the dosage amount used in the prior art to calculate trastuzumab's half-life. Ex. 1123 at ¶47. A POSA would therefore have understood that by applying

the 7-day half-life derived from the low dosage amount of the prior art to analyze the pharmacokinetics of the proposed every-three-week regimen, the serum trough concentration would be underestimated, not overestimated. *Id*. Dr. Grass reaches the opposite conclusion only by ignoring the fact that the every-three-week regimen would have had a higher dosage amount than the weekly regimen. Ex. 1120 at 70:19-71:2.

Dr. Grass also ignores the available prior art data for trastuzumab's pharmacokinetics, focusing instead on hypothetical profiles that are "not based on data" and profiles of unrelated drugs that have no relevance to trastuzumab. Ex. 1120 at 53:19-54:9. For example, Dr. Grass relies upon a graph of hypothetical linear pharmacokinetic profiles that have slower rates of elimination than non-linear profiles. Ex. 2027 at ¶28. He uses this graph to suggest 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 by failing to account for the non-linear increase in elimination and corresponding decrease in the half-life that would be expected to occur as serum concentration declines." Ex. 2027 at ¶31.

First, this hypothetical graph has no basis in reality; it does not reflect any known pharmacokinetic profile of any drug, much less trastuzumab. Ex. 1123 at ¶44-45; Ex. 1120 at 52:3-53:2. Second, as discussed above, when a higher dose is

administered, as is the case in the relevant every-three-week regimen, the rate of elimination of the linear profile would be faster than the rate of elimination of the non-linear profile. *Id*. However, Dr. Grass's graph focuses exclusively on concentrations where the linear rate of elimination is slower than the non-linear rate of elimination, and is therefore clearly inapplicable to Dr. Ratain's analysis. Ex. 1123 at ¶¶45-46.

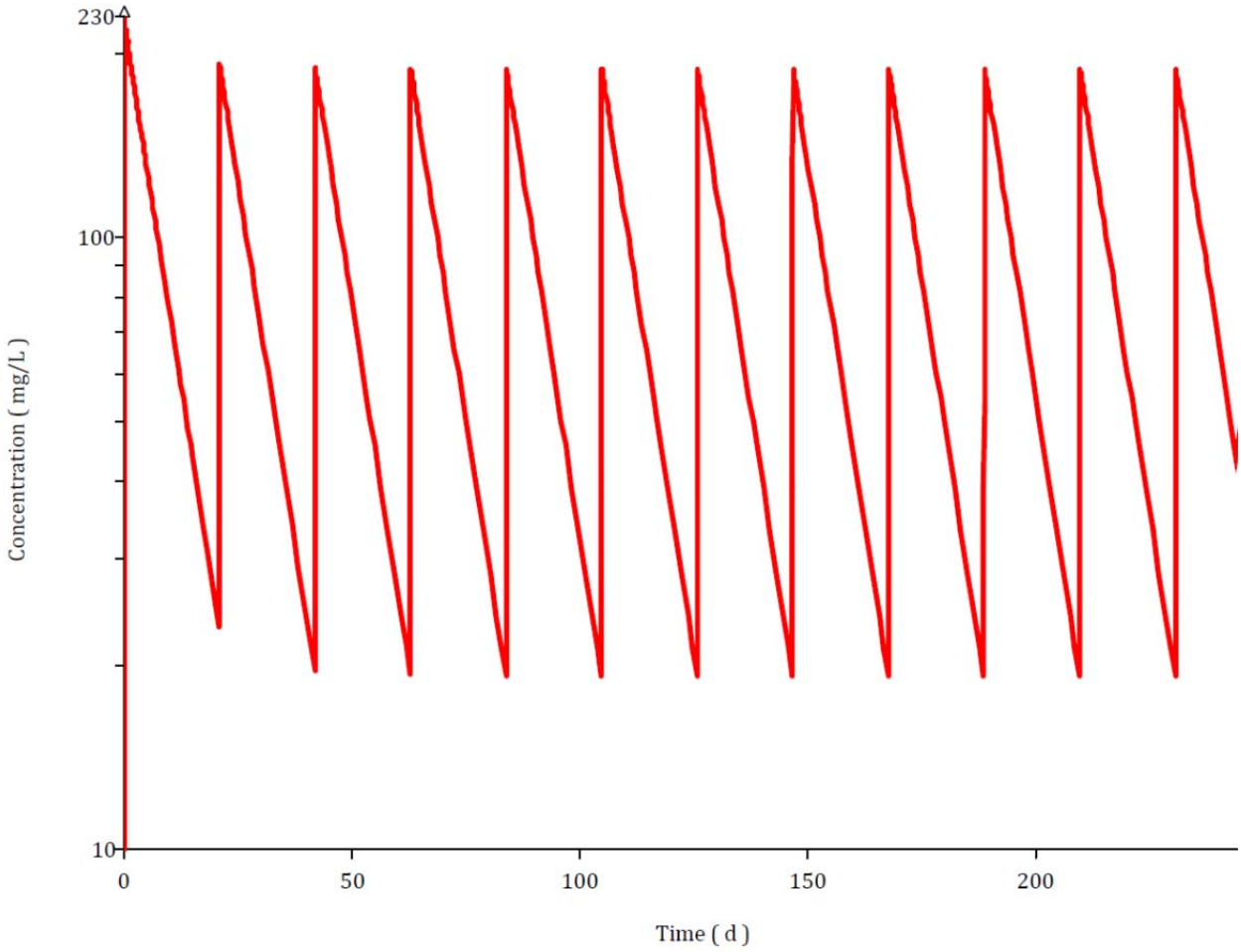
Dr. Grass further attempts to show that Dr. Ratain's calculations overestimate serum concentrations by relying on the pharmacokinetic profile of a different cancer drug, indisulam. Ex. 2027 at ¶32. But the pharmacokinetic profile of indisulam is also irrelevant. First, indisulam is a small molecule that has a terminal half-life measured in hours, not days, and works in a completely different manner than trastuzumab. Ex. 1123 at ¶49; Ex. 1120 at 79:16-20. Second, the indisulam data is from 2006, and is not prior art. Ex. 1123 at ¶50; Ex. 1120 at 80:16-81:1. Third, Dr. Grass again ignores that the every-three-week regimen employs a dosage higher than that used to determine the reference half-life. Ex. 1123 at ¶51; Ex. 1120 at 82:13-22. No conclusion can be drawn from the indisulam profile concerning what would happen if a higher dose were administered. *Id*.

In view of these deficiencies, POSAs would not have considered either of these analyses to suggest that Dr. Ratain's utilization of the prior art one-week

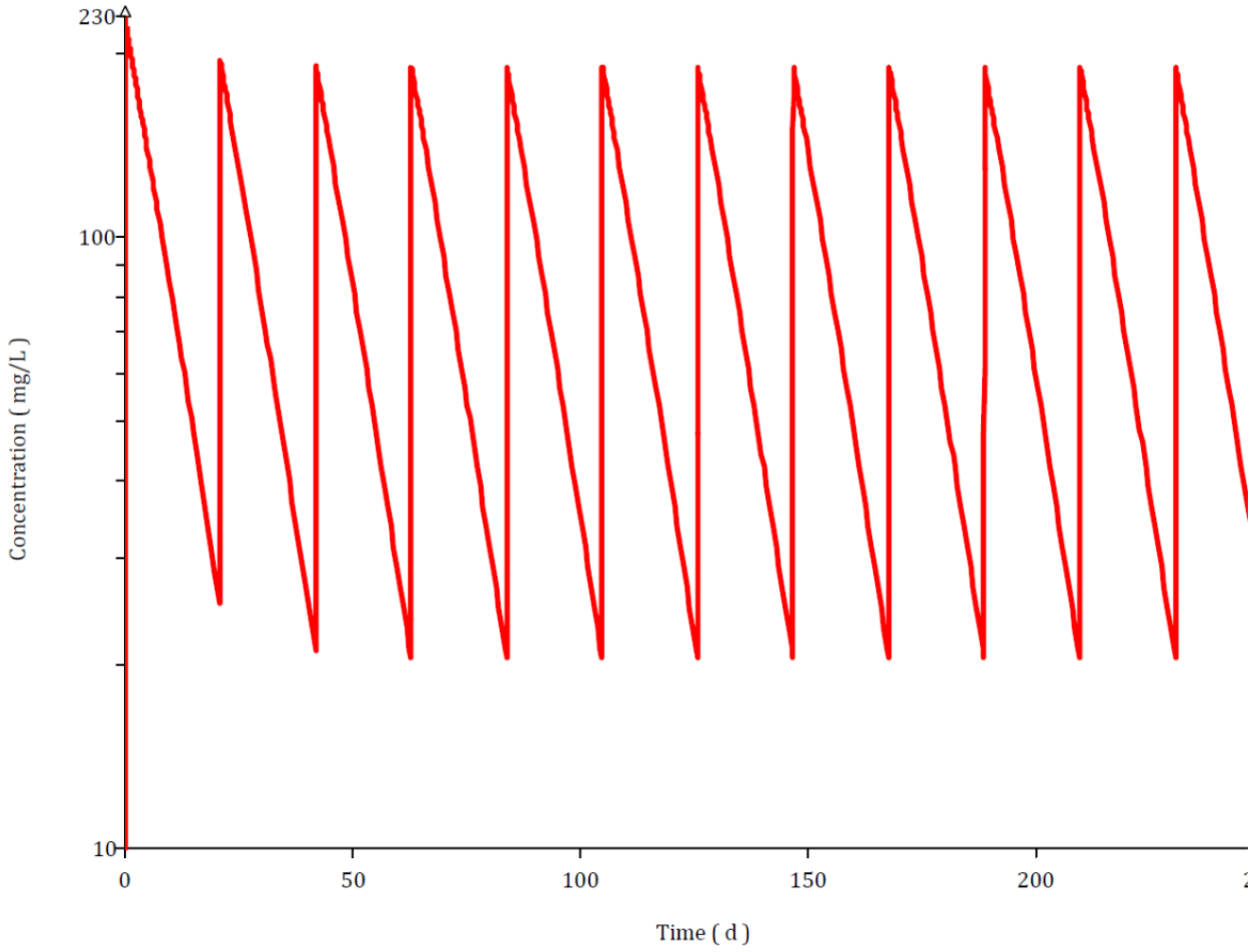
half-life would result in overestimation of the trough concentrations associated with the every-three-week regimen. To the contrary, in view of the prior art's disclosure that higher dosage amounts led to longer half-lives, a POSA would have expected that Dr. Ratain's analysis would underestimate trough serum concentrations for the higher dosage, every-three-week regimen. Petition at 35 n.8 (citing Ex. 1003 at ¶102).

Furthermore, while there was insufficient data in the prior art to derive the precise non-linear profile applicable to trastuzumab, had a POSA been concerned with overestimation of trough serum concentration as Dr. Grass argues, the prior art contained sufficient data to allow a POSA to confirm that Dr. Ratain's analysis did not result in overestimation. Ex. 1123 at ¶52. Specifically, using the pharmacokinetic data disclosed in the prior art for the weekly trastuzumab regimen—rather than focusing on hypothetical and unrelated drug profiles—a POSA could have easily determined what every non-linear model consistent with those data would look like, and compared those to the linear model to determine whether the linear model would overestimate trough serum concentrations. Ex. 1123 at ¶¶58-73.

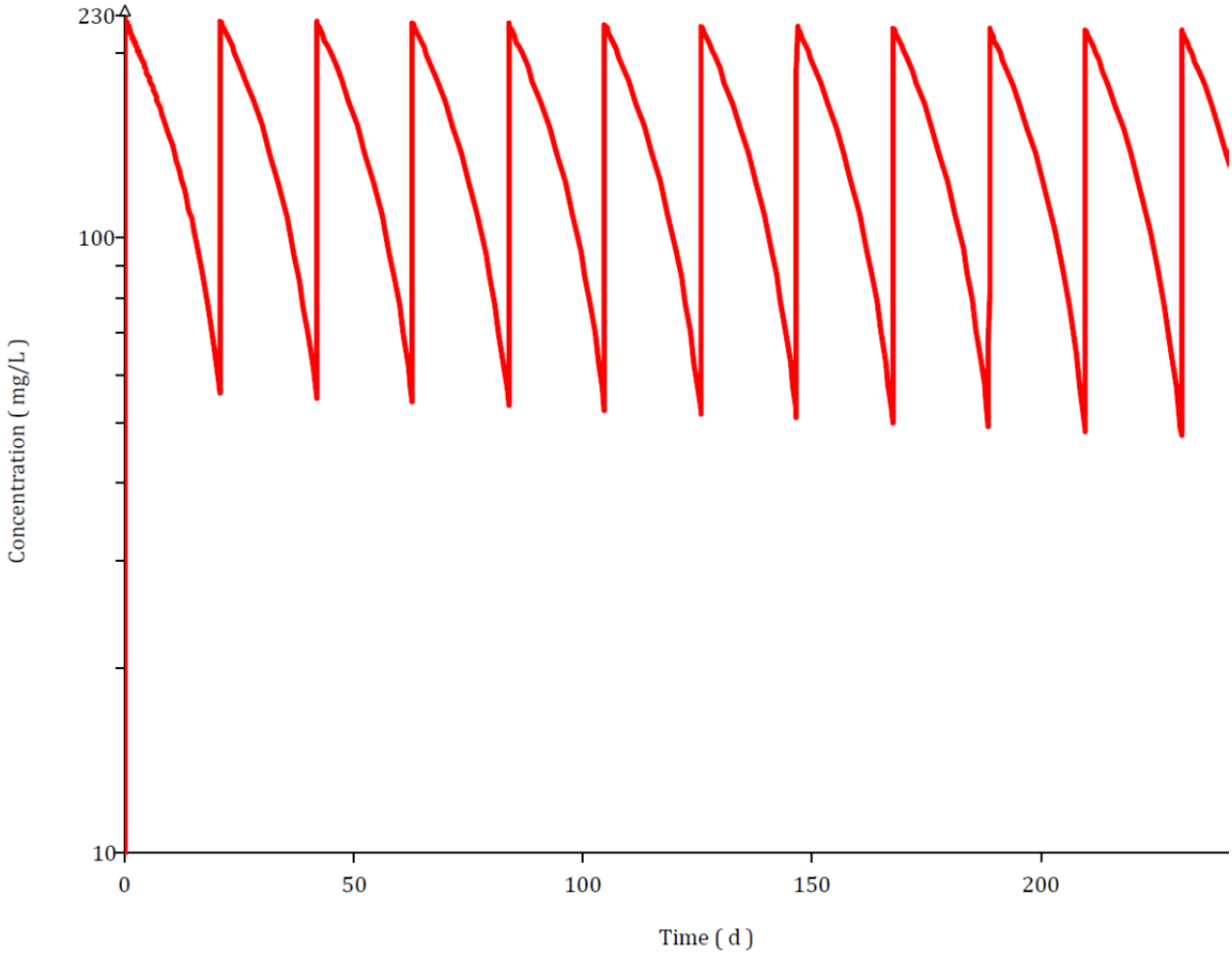
The linear model based on the pharmacokinetic data in Pegram, extrapolated to an every-three-week regimen, is illustrated below:



Ex. 1123 at ¶60. As can be readily observed, the linear model results in a trough serum concentration above 10 µg/mL. *Id.* at ¶61. Every non-linear model consistent with the Pegram data results in trough serum concentrations at least as high as those of the linear model. *Id.* at ¶71. On one extreme, the trough concentrations are essentially the same as in the linear model:



Id. at ¶66. On the other extreme, the trough concentrations are significantly higher for the non-linear model:



Id. at ¶70.

In between these two extremes, there are essentially infinite non-linear models that would fit the prior art data, and a POSA would not know which was the correct model. *Id.* at ¶71. However, every one of these models results in trough concentrations between these two extremes. *Id*. Accordingly, had a POSA been concerned, as Patent Owner argues, that applying the prior art half-life to the higher dose three-weekly regimen would overestimate trough concentrations, those

concerns would have been readily alleviated by simply considering what the plausible non-linear models could look like. *Id.* at ¶72.

b. Dr. Ratain Did Not Cherry-Pick Data

Patent Owner's suggestion that Dr. Ratain cherry-picked data is baseless. POR at 56-58. Using all of the available data from both (1) Baselga and Pegram, and (2) the 1998 Herceptin® label, Dr. Ratain independently confirmed that the every-three-week regimen would maintain target trough concentrations of at least 10 µg/mL. Petition at 33-38 (citing Ex. 1003 at ¶¶ 96-109).

Notwithstanding that the half-lives disclosed by Baselga and Pegram were 8.3 days and 9.1 days, respectively, in carrying out his analysis, Dr. Ratain used an even lower half-life of only 7 days. *Id.* at 33-34 (citing Ex. 1003 at ¶103). With regard to the Herceptin® label, Dr. Ratain used the 5.8 day half-life reported for the approved 4 mg/kg, 2 mg/kg regimen, even though the label disclosed a much longer, 12 day half-life for a 500 mg dose, which is the amount of the loading dose of the every-three-week regimen. *Id.* at 37-38 (citing Ex. 1003 at ¶¶88,107-109). Thus, far from cherry-picking data, Dr. Ratain chose the most conservative method of calculation and used the half-life data that would yield the worst-case result for trough concentrations.

Regardless, Patent Owner's experts have not demonstrated that a different result would have been obtained by using any other data.

D. Tumor-Shed ECD^{HER2} is Irrelevant

Patent Owner misleadingly emphasizes the impact of patients with detectable shed antigen levels on the expectation of efficacy for a trastuzumab regimen. POR at 38-39. Circulating levels of tumor-shed ECD^{HER2} were known to be problematic in a ***small subset of patients*** who had ***high concentrations of shed antigen***. Ex. 1123 at ¶75 (citing Ex. 1007 at 741-42). The prior art taught that for patients with circulating levels of tumor-shed ECD^{HER2} at serum concentrations > 500 ng/mL, even the weekly regimen was not effective, and did not maintain trough serum concentrations above the threshold. *Id*. In fact, "no anticancer responses were observed" in this group of patients. *Id.* The fact that these patients would not be expected to have trough serum concentrations above 10 µg/mL under an every-three-week regimen is not a negative as compared to the prior art regimen, and therefore would not be a deterrent. *Id.* at ¶76. Nevertheless, in yet another conservative approach, Dr. Ratain accounted for these patients by relying on the half-lives for the entire populations of the prior art studies, not just those with low levels of shed antigen. *Id.* at ¶77.

III. CONCLUSION

For the foregoing reason, and for the reasons discussed in the Petition, Petitioner respectfully requests that the Board cancel the challenged claims as obvious in view of the prior art.

Respectfully submitted,

Dated: March 21, 2018

/Cynthia Lambert Hardman/

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. §42.24(d), Petitioner hereby certifies, in accordance with and reliance on the word count provided by the word-processing system used to prepare this reply, that the number of words in this paper is 5,560. Pursuant to 37 C.F.R. §42.24(d), this word count excludes the table of contents, table of authorities, mandatory notices under 37 C.F.R. §42.8, certificate of service, certificate of word count, appendix of exhibits, and any claim listing.

Dated: March 21, 2018

/Daniel P. Margolis /
Daniel P. Margolis

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 21 day of March, 2018, I caused a copy of this PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE and Exhibits 1100-1130 cited therein to be served by Secure File Transfer (SFT), as previously agreed by the parties, on the lead and back up counsel for Patent Owner at the below email addresses:

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