UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.,[1]
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

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Case IPR2017-00804
Patent 6,627,196

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PETITIONERS' REPLY TO PATENT OWNER RESPONSE

[1] Pfizer, Inc. is the real-party-in-interest in IPR2017-00804. (Paper 7 at 2.) Samsung Bioepis Co. Ltd.'s IPR2017-01958 has been joined with this proceeding. (IPR2017-01958, Paper 9.)

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I. INTRODUCTION

PO's Response confirms that the Challenged Claims are untenable extensions of the now decades-old trastuzumab monopoly and should not be left to obstruct competitors from providing options to terminally ill breast cancer patients.

In PO's words, the alleged invention was the "discover[y]" that trastuzumab "could be administered on a three-week dosing regimen without compromising the safety or efficacy shown with [the prior art] weekly administration." (POR at 1.) PO's own evidence confirms the obviousness of this modification. PO concedes that POSAs were "motivated" to "co-administ[er]" trastuzumab and paclitaxel (both already FDA-approved), and ***did*** "match" trastuzumab and paclitaxel dosing schedules in ***publicized clinical trials*** that were "***well underway***."[2] (POR at 9, 31.) PO does not dispute that paclitaxel was FDA-approved only for "three-weekly treatment." (Ex. 1058 (Gelmon) at 180:22-181:1.) These undisputed teachings made the idea to extend trastuzumab dosing to three-weekly more than obvious. It was manifest.

PO responds that POSAs were co-administering paclitaxel and trastuzumab in another way—increasing paclitaxel's dose frequency to weekly to match trastuzumab's—and there was yet no publication "mentioning" extension of

[2] All emphases are added.

trastuzumab's dosing to three-weekly to match paclitaxel's. But the fact that researchers might first have studied one way of matching paclitaxel and trastuzumab dosing (weekly) does not mean the other way (three-weekly) was non-obvious. The claimed invention need not be the only, or even the preferred, option for fulfilling the established motivation. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). And obviousness would be little different from anticipation if it required prior art to "mention[]" the "claimed" dosing regimen. (POR at 3.) The three-weekly schedule ***was*** in the prior art for paclitaxel, and so were (in PO's own words) the "inspir[ation]" and "motiv[ation]" to "match" its dosing with trastuzumab. (*Id.* at 9, 31.) No more specific motivation is needed.

Given the motivation PO concedes, PO's criticisms of the other motivations Petitioner identified—convenience, compliance, quality of life, cost, etc.—fall by the wayside. But those criticisms also are wrong. PO cites only Dr. Gelmon's *ipse dixit* that "convenience and compliance were not of concern" with trastuzumab. (POR at 4.) And "convenience and compliance" are only ***some*** of the motivations Petitioner identified. In any event, Dr. Gelmon admitted that "improved patient convenience, quality of life and cost" "are factors that are ***always*** [going to] go into all of the options for treatment schedules" and that they ***did in 1999*** motivate clinical trials of the same three-weekly trastuzumab regimen the '196 patent claims. (Ex. 1058 (Gelmon) at 14:21-15:25; 73:5-75:16, 76:16-23, 328:24-329:7.)

These admissions conclusively undermine PO's motivation arguments.

That leaves PO's argument that POSAs would have had no "reasonable expectation of success" because the prior art indicated that trastuzumab exhibits "***non-linear***" pharmacokinetics. (POR at 3, 11-13, 45-48.) But the same prior art still used the ***linear*** modeling approach Petitioner's pharmacokinetics expert Dr. Jusko used to show POSAs would have expected success with the claimed dose regimen. Nor was Dr. Jusko's dose selection "arbitrary." (POR at 52.) He appropriately selected the highest dose shown to be safe and effective; choice of a lower dose to extend dosing would have made little sense. PO's complaint that "[m]ore data is needed" (POR at 12) also cannot be squared with the '196 patent's specification, which provides ***no*** data supporting its claimed regimens.

The Challenged Claims should be declared unpatentable.

II. ARGUMENT

PO asserts that there was no motivation to extend trastuzumab dosing, and that POSAs would have had no reasonable expectation that such extended dosing would be successful. PO is wrong.

A. POSAs *Were* Motivated To Extend Trastuzumab Dosing.

1. "Patient-related" factors—convenience, compliance, quality of life, and cost—motivated extended trastuzumab dosing.

The Petition identified ***multiple*** motivations in the prior art for extended trastuzumab dosing, including convenience of fewer clinic trips, lower hospital and

patient costs, better patient compliance, and better quality of life. (Petition ("PET") at 26-27; 34-36; Ex. 1002, ¶¶38-45, 63-66.) PO does not dispute these motivations existed, but asserts they are too "general," the "references upon which Petitioners rely" do not "refer[] to convenience or compliance," and POSAs were only "focused on improving efficacy." (POR at 8-10, 18, 20, 27-29, 33-36.) None of these assertions rebuts the overwhelming motivation evidence in the Petition.

First, Dr. Lipton's opinions do not reflect some "generalized convenience theory" disconnected from breast cancer treatment (POR at 29-34), but rather his extensive experience treating breast cancer patients over decades, and published literature dating back to the 1980s. Because of the "great stress and discomfort" associated with treatment (Ex. 1002, ¶¶38-42), Dr. Lipton explained that POSAs were motivated to "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*., ¶¶63, 66.) That Dr. Gelmon might not have personally seen patients inconvenienced by frequent clinic visits (POR at 35) does not negate this motivation, particularly given her admission that those patients existed. (Ex. 1058 at 46:12-47:5, 65:11-15, 66:4-68:20.)

Published literature and Dr. Gelmon's testimony corroborate Dr. Lipton's opinions. (Ex. 1002, ¶44 (citing Exs. 1019 (Coates *et al.*, 1997); 1020 (Aaronsen

et al., 1993) and 1021 (Ferrell, 1996).) Indeed, these considerations had long been identified as important. For example, a 1983 study analyzed "patient perception of the side-effects of cancer chemotherapy," finding certain non-physical "side-effects" (*e.g.*, time taken for treatment, worry about needles, impact on work/home duties) had a more severe perceived impact on quality of life than physical side-effects (*e.g.*, nausea, vomiting). (Exs. 1042 (Coates '83); 1056, ¶24.) Dr. Gelmon acknowledged that many of these non-physical "side effects" were correlated with treatment frequency. (Ex. 1058 (Gelmon) at 94:5-101:10.) Another study found that mean "non-medical costs" during breast cancer treatment weeks were approximately 40% higher than in non-treatment weeks, while reducing treatment frequency "could be projected to [save] approximately $143,000,000 yearly on a national level." (Exs. 1041 (Houts '84); 1056, ¶24.)

Notably, Dr. Gelmon ***admitted*** 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"; "improved patient convenience, quality of life and cost" "are factors that are ***always*** [going to] go into all of the options for treatment schedules"; and those same motivations ***did***, in fact, motivate her own clinical trial of three-weekly trastuzumab using the same scheme as in the '196 patent claims ***within months of the '196 patent priority date in 1999***. (Ex. 1058 (Gelmon) at 73:19-75:16, 328:24-

329:7.)[3]

Far from being too "generalized" or "untethered to the specific patient population in the claims" (POR at 37), this evidence, including testimony of ***PO's own expert***, belies PO's assertions that "convenience and compliance were not of concern to women with HER2-positive breast cancer or their physicians" (POR at 4), and confirms that the motivation to extend dosing existed and applied to the very combination chemotherapy treatments (with paclitaxel as well as doxorubicin) to which the '196 patent was directed. *Cf. Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014) ("A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance.").

Second, PO's argument that the cited prior art must "refer" to the identified motivation is at odds with governing precedent, and confuses obviousness with anticipation. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[T]he

[3] This motivation was independent of the '196 patent. The decision was made at a meeting in Toronto, Canada at which the named inventors of the '196 patent were not present, before they had even added their ***prophetic*** three-weekly regimen (Example 6) to their patent application in 2000 (*see* Ex. 1051), and potentially before August 1999 (Ex. 1058 (Gelmon) at 16:1-16, 323:18-324:9).

[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 [POSA] would employ."); *Novartis AG v. Noven Pharm. Inc.*, 853 F.3d 1289, 1295-96 (Fed. Cir. 2017)("Second, Novartis alleges that Sasaki 'does not ***mention*** rivastigmine' or otherwise disclose that rivastigmine is susceptible to oxidative degradation … Novartis predicates its argument on the belief that the prior art must expressly disclose a motivation to combine; however, a 'motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art.'"). The Board already correctly rejected this argument (Paper 13 at 12-13), and PO has given no reason to revisit it.

Third, PO's argument that POSAs were "focused on improving efficacy" and "safety" (POR at 28) is smoke and mirrors. PO points to no evidence that POSAs believed trastuzumab would be ineffective or unsafe at less frequent (*e.g.*, three-weekly) doses, instead citing irrelevant articles about life expectancy of "untreated patients" (*id.* at 28) and work on increasing chemotherapy efficacy (*id.* at 29). That POSAs "discuss[ed] safety and efficacy" or improvements thereto does not mean they were ***not*** motivated to extend trastuzumab dosing by patient convenience, quality of life and cost concerns that undisputedly factored into dosing decisions—including trastuzumab's—at the relevant time. PO's own expert's testimony shows that any focus on safety or efficacy would not have made

trastuzumab dosing immune to these motivations.[4]

PO's cited cases are inapposite. No motivation to make the claimed high-conductivity steel was found in *Rovalma, S.A. v. Böhler-Edelstahl GmbH & Co. KG* because "prior art disclosures of the general desirability of ***high*** thermal conductivity" did not establish "that a [POSA] would have been ***motivated to increase*** thermal conductivities beyond levels previously achieved." 856 F.3d 1019, 1025–26 (Fed. Cir. 2017); *Böhler-Edelstahl GmbH & Co. KG. v. Rovalma, S.A.*, IPR2015-00150, Paper 51 at 12-13 (Dec. 6, 2017). Here, the motivations to decrease trastuzumab dose frequency from the "seemingly 'inconvenient'" weekly dosing to three-weekly for convenience, quality-of-life and cost reasons are well-evidenced.

In *Depomed, Inc. v. Actavis Elizabeth LLC*, the court held that, although "there may have existed a general motivation to create a once-daily gabapentin formulation to improve compliance and possibly reduce side effects, certain unique

[4] The Osoba reference merely "found that treatment with weekly trastuzumab could improve patient quality of life ***in comparison to treatment with chemotherapy regimens alone***" and "never compared health-related quality of life of a weekly Herceptin regimen with that of a three-weekly regimen" (Ex. 1058 (Gelmon) at 207:8-11).

characteristics of gabapentin," such as instability in the stomach, "may have dissuaded a POSA from attempting to develop an effective extended release gabapentin formulation and weigh against a finding of reasonable expectation of success." No. 12-1358 JAP, 2014 WL 4215435, at *48 (D.N.J. Aug. 25, 2014). No such "unique characteristics" exist here, and PO identifies none.

Finally, in *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008), the challenger's expert listed prior art and concluded with a stock phrase that "would not have been helpful to a lay jury in avoiding the pitfalls of hindsight," and in *Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017), the challenger provided "no explanation or reasoning for concluding that [a POSA] would have combined [the cited] references to produce the claimed invention." Here, Dr. Lipton presented detailed testimony explaining the motivations for three-weekly trastuzumab by reference to his own experience and published literature specific to breast cancer treatment. (Ex. 1002, ¶¶41-45, 62-66.) ***PO's own expert Dr. Gelmon*** further confirmed these motivations and their applicability to trastuzumab. (Ex. 1058 at 73:19-75:16, 328:24-329:7.)

PO's attempt to distinguish *Hoffman-La Roche v. Apotex* fails. (POR at 38-40.) Just as the Federal Circuit held that relatively infrequent dosing had "long been viewed as a potential solution to the problem of patent compliance stemming from the inconvenience of oral bisphosphonate regimens," so too had it long been

viewed as a potential solution to the convenience, compliance and cost problems stemming from i.v. cancer treatments. That patients "need little additional convincing in the form of convenience to take trastuzumab" at risk of death (POR at 40) might explain why PO sought to fast-track approval of Herceptin® with a "seemingly 'inconvenient'" regimen, but does not establish that later optimization motivated by well-established considerations was somehow inventive.

2. PO concedes that POSAs were motivated to "match" trastuzumab and chemotherapy dosing.

PO's own Response also admits of another motivation, *i.e.*, that "in the late 1990s, skilled artisans were actively investigating how to combine trastuzumab with chemotherapy, including paclitaxel" and that they were "[i]nspired" and "motivate[ed]" by the Herceptin® Label "to match" paclitaxel and trastuzumab schedules. (POR at 9-10.) PO identifies research published by August 1999 where the drugs were administered on the same schedule. (*Id.*)

The motivation PO acknowledges—matching trastuzumab and paclitaxel dosing—is itself a motivation to extend trastuzumab's dosing to match paclitaxel's. At the time, paclitaxel had been FDA-approved as safe and effective only for three-weekly dosing. (Ex. 1058 (Gelmon) at 180:22-181:1.) To "match" dosing with trastuzumab's, there were only three options: (1) dose paclitaxel less frequently to match trastuzumab's weekly regimen; (2) dose trastuzumab more

frequently to match paclitaxel's three-weekly regimen; or (3) dose both on a completely new regimen. Neither side contends a POSA would have equally considered changing ***both*** drugs' schedules, leaving just two options.

PO focuses on the first—weekly dosing—which it concedes was "seemingly 'inconvenient,'" but toward which it asserts there was a "trend." (POR at 9, 29.) As of August 1999, however, "there was no scientific data published showing which was superior between weekly and three-weekly paclitaxel," and no study had been published that even attempted to make the comparison. (Ex. 1058 (Gelmon) at 159:12-21, 165:23-174:14.) In any event, that POSAs tried weekly first does not show three-weekly was nonobvious. Obviousness does not require the claimed regimen to be the only or best choice, nor may a patentee defeat obviousness simply by identifying an already-tried alternative. *In re Fulton*, 391 F.3d at 1200; *see also Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (that the prior art teaches "a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art.").[5]

[5] PO's assertions that "[t]he biologic mechanisms of trastuzumab differed from traditional anti-cancer treatment" and POSAs "thus would not have expected them to be dosed on the same intervals" make no sense, given its own

(continued…)

3. PO raises no genuine dispute that POSAs would have chosen 500mg maintenance and 712mg loading doses.

PO does not dispute that the prior art described trastuzumab as tolerable and safe in a range of doses, up to 500mg weekly. (PET at 31; Exs. 1008 at 1; 1003, ¶28; 1059 (Grass) at 132:25-133:6.) Nor does PO argue that the prior art taught that higher doses would be intolerable or unsafe. On the contrary, the prior art stated trastuzumab was not known to be toxic at "any dose level." (Ex. 1015 at 5.)

PO nevertheless asserts there was no "plausible rationale for why a [POSA] would select" 500mg as a maintenance dose and use it to calculate a loading dose. (POR at 24.) As Dr. Jusko explained, however, to extend trastuzumab's dosing schedule, POSAs naturally would have chosen the highest-known tolerable dose with the highest-reported half-life to give the best chance of achieving the target serum concentrations needed for efficacy. (Exs. 1003, ¶48; 1057, ¶29.) POSAs also would have known that, since ***weekly*** 500mg doses were tolerable, less-frequent doses also would be tolerable. (*Id.*) Not only is there a "plausible" scientific rationale for choosing 500mg, that approach made the most sense. (*Id.*)

After that, the 712mg loading dose is simply the result of a straightforward

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arguments that POSAs ***were*** in fact motivated to co-administer paclitaxel and trastuzumab, and had done so in the prior art. (POR at 5-8, 32.)

calculation that PO does not dispute POSAs would have known to apply. (Ex. 1003, ¶¶59-63.) Herceptin® was tested and FDA-approved with a loading dose, as described in the prior art (Exs. 1008; 1059 (Grass) at 80:17-81:15), and PO offers no reason why a POSA would deviate from that approach in a less frequent dosage regimen. Nor does—or could—PO argue that a 712mg dose (equivalent to 10.2 mg/kg for a 70 kg patient) would have been expected to be unsafe or intolerable. The prior art taught that trastuzumab "has no substantial toxicity at any dose level" (Ex. 1015 at 5), and an 8 mg/kg loading dose followed by weekly 4 mg/kg doses was "well-tolerated" (Exs. 1016; 1003, ¶¶55, 60).

PO's Response also is noticeably silent about what if anything a POSA supposedly would have done differently, or what if anything the named inventors supposedly did differently. PO asks the Board to believe that a POSA would consider trastuzumab dosing not "predictable" and simply not "select [] untested doses…to devise a new dosing regimen with trastuzumab." (POR at 24-26.) But that fatalistic view is unsupported, and ignores the level of skill and creativity of researchers in the field. Work did not simply stop once Herceptin® was approved. PO itself says that, following trastuzumab's approval, "hundreds of papers and abstracts were published in which researchers explored various ways to maximize the effective use of trastuzumab" (POR at 2, 9), and as discussed above, that included investigation of new, less frequent dosage regimens.

4. Contemporaneous literature confirms that POSAs were motivated by "patient-related factors" to investigate three-weekly dosing of trastuzumab.

Myriad publications—***including some authored by PO's expert***—directly refute PO's assertion that patient-related factors did not apply to trastuzumab.

First, within months of the '196 patent's priority date, Dr. Brian Leyland-Jones (McGill University) reported that his group had administered Herceptin® "as an 8mg/kg i.v. initial dose followed by a 6mg/kg i.v. dose administered once every 3 weeks." (Ex. 1043 at 17.) He predicted success from the knowledge that "Herceptin® demonstrates dose-dependent, non-linear pharmacokinetics" which "means that higher doses of the drug can be administered less frequently." (*Id.*) He subsequently expanded on his motivations, *i.e.*, that "[e]xtending the time between Herceptin doses is attractive, particularly in the adjuvant setting where the burden of therapy becomes more of an issue." (Ex. 1044 at 3; *id.* at 5)(three-weekly trastuzumab "would facilitate a ***more convenient regimen for combination therapies*** and would be attractive to patients, especially in the adjuvant setting.").)

Dr. Gelmon herself acknowledged in publications co-authored with Dr. Leyland-Jones and others that three-weekly trastuzumab "would have advantages for patients and medical staff in terms of ***acceptability, ease of administration and, potentially, cost-effectiveness***." (Ex. 1045 at 1; *id.* at 46 ("As administration and nursing costs form a major component of the total cost of i.v. chemotherapy, less

frequent administration and/or a switch to s.c. administration may have implications for the cost-effectiveness of trastuzumab.").) She further acknowledged that "[p]atient convenience, quality of life, and cost considerations are ***important*** when therapy for patients with cancer is being selected" and "***[t]hese factors*** provide[d] additional support to the continued evaluation of [three-weekly trastuzumab] in patients with primary breast cancer and MBC." (Ex. 1047 at 7; Exs. 1050 at 11-12 ("The patient-related convenience of a regimen can have a ***significant impact*** on a patient's quality of life, especially when patients live at a distance or have limited support networks."); 1046 at 4 ("less frequent administration [of trastuzumab] may be safe, efficacious and more convenient for the patient, especially in the adjuvant setting or during long term therapy").) Another POSA stated that "[i]ncreasing the dose interval of herceptin would ***obviously*** be more convenient, would increase patient compliance and would render more feasible studies of herceptin in the adjuvant setting." (Ex. 1048 at 4.)

While these references might have been published after the priority date, they describe and cite events and publications from at or before the priority date in describing these motivations, and there is no indication that any post-priority date development prompted any relevant revelations. *Cf. Disney Enters., Inc. v. Kappos*, 923 F. Supp. 2d 788, 801 (E.D. Va. 2013)("Publications published after the date of invention have long been allowed 'as evidence of the state of the art existing on the

filing date of an application.'")(collecting cases).

Notably, the only benefit of an extended dosing regimen described in the '196 patent is that it "mak[es] the treatment regimens of the invention convenient and cost-effective for the patient and medical professionals administering the antibody." (Ex. 1001 at 43:52-57.) There is no suggestion that this result was in any way unexpected. On the contrary, Dr. Gelmon admitted 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 (Gelmon) at 328:24-329:7.)

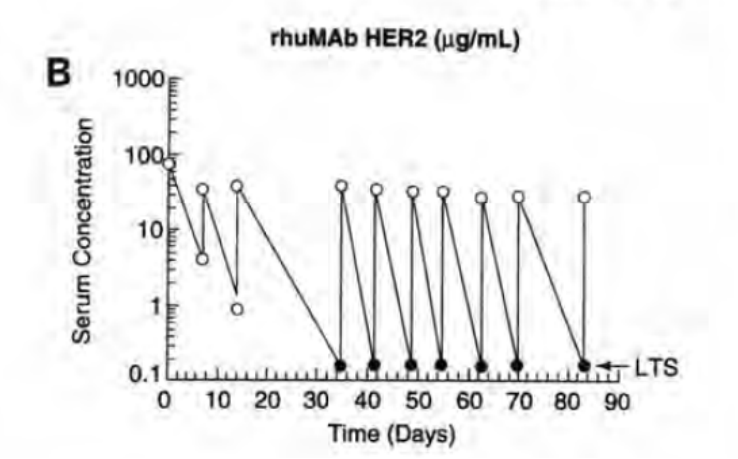
B. POSAs Had Reasonable Expectations Of Success.

1. Dr. Jusko demonstrated that three-weekly trastuzumab dosing would have been expected to be safe and effective.

In his opening declaration, Dr. Jusko applied a set of widely-known pharmacokinetic equations (a linear, one-compartment model) to data available in the prior art to demonstrate that, at three weeks after dosing, the serum concentration of trastuzumab would have been expected to be above the target level for effectiveness. (Ex. 1003.) PO does not dispute that, by August 1999, the model Dr. Jusko applied was a textbook approach routinely used by POSAs, and that trastuzumab efficacy could be predicted if serum concentrations were maintained above the prior art 10-20μg/mL target level that Dr. Jusko applied.

(POR at 8; PET at 28, 37; Exs. 1003, ¶51; 1058 (Gelmon) at 213:5-14; 1059 (Grass) at 37:22-38:3.) PO criticizes Dr. Jusko for applying a "one-compartment linear" model, however, asserting that "trastuzumab had demonstrated non-linear kinetics" and the linear model would "overestimate" serum trough concentrations. (POR at 43-57; Ex. 2039 (Grass Decl.).)

As explained in the Petition, however, ***Dr. Jusko applied the very same model that PO and its collaborators did in the prior art***. Baselga '96 states that "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a ***one-compartment model***," and includes figures showing linear pharmacokinetics after dosing:



(Exs. 1013 at 10, 12; 1003, ¶¶33-34; 2037 at 88:8-14, 120:8-121:14; PET at 36-37.) Similarly, PO's Herceptin® Label reported a single half-life for trastuzumab at each dosage level, suggesting use of a one-compartment model. (*Id.*; Exs. 1008 at 1; 1003, ¶34.) Although PO attempts to raise doubts based on the labels of ***other***

drugs (POR at 47-48), it presents no contrary evidence for Herceptin®.[6] PO also ignores that Baselga '96 applied a one-compartment model despite ***expressly acknowledging*** trastuzumab's non-linear pharmacokinetics. Faced with the same information PO highlights, POSAs used the same model Dr. Jusko used.

2. Dr. Jusko's analysis would at worst have *underestimated*, not "overestimated," serum trough concentrations.

Contrary to PO's assertion, Dr. Jusko's analysis if anything would have ***underestimated***, not "overestimated" (POR at 56) trough serum concentrations at three weeks. As Dr. Jusko described, prior to the '196 patent priority date, POSAs knew that "the metabolism of antibodies is relatively uniform across most antibodies within a given class" and that "humanized antibodies were expected to behave similarly to IgG." (Ex. 1003, ¶71 (citing Ex. 1029, King '98 at 77).) The King reference cited by Dr. Jusko surveyed known chimeric and humanized antibodies, showing they followed a common linear profile, with initial quick clearance and short half-life ($t_{½}\alpha$), followed by slower clearance and longer half-life ($t_{½}\beta$). (*Id.*) Dr. Grass acknowledged that King showed that *all* characterized antibodies followed this same profile. (Ex. (Grass) 1059 at 187:17-190:6.) As Dr.

[6] PO's expert Dr. Grass admitted he did not even ask PO whether a one-compartment model was used. (Ex. 1059 at 126:5-129:21.)

Jusko explains, this "dose-dependent, non-linear" profile is referred to as "receptor-mediated" or "target-mediated" drug disposition whereby, as serum concentration decreases after dosing, clearance ***decreases*** and half-life ***increases*** from an "initial phase" with a short half-life to a "terminal phase" with a long half-life. (Ex. 1057, ¶¶14–15, 18, 32.) This is shown in the following exemplary figure:

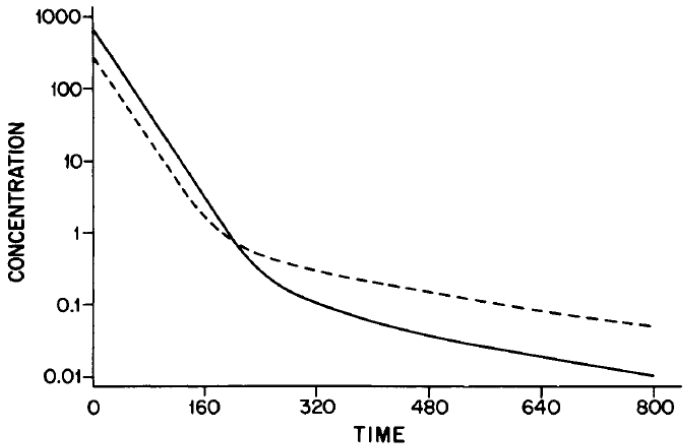


Fig. 1. Typical concentration-time profile in plasma *(continuous line)* and tissues *(broken line)* for a drug that is subject to high-affinity low-capacity binding in tissues. Distribution of drug from plasma to tissues was assumed to be practically instantaneous.

(Exs. 1052 at 4; 1057, ¶15; *see also* Exs. 1003, ¶28; 1008 at 1; 1059 (Grass) at 54:10-25, 57:1-10, 63:19-69:12, 170:16-24.) Other references similarly showed that monoclonal antibodies follow this profile type, including in cancer patients:

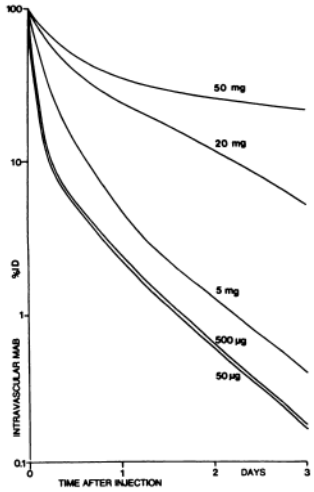
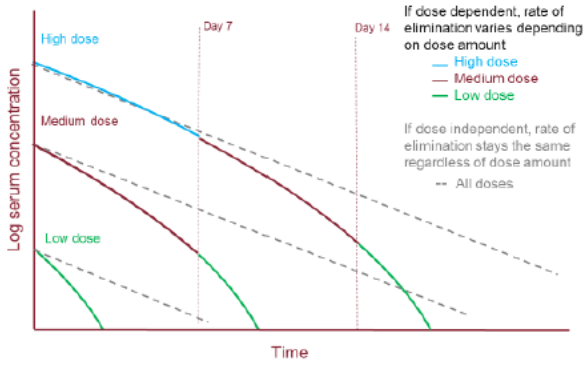


FIGURE 8
Model simulated curves for intravascular MAb reflecting effect of different amount of injected MAb on blood clearance of MAb. Clearance rate of larger injection amount is decreased

(Exs. 1054 at 10; 1057, ¶16; 1059 at 191:5-195:19.)

In stark contrast, PO and Dr. Grass present a profile that is the ***opposite*** of that in the published literature regarding antibodies:



(POR at 49-50; Ex. 2039, ¶¶22, 26.) Notably, however, Dr. Grass acknowledged that he "made that up" and it is "not in any document [he] cited." (Ex. 1059 at 116:16-21.) Indeed, the only document he identified as purportedly supporting the figure is a paper from ***2006***, seven years ***after*** the '196 patent priority date, that describes pharmacokinetics of a "***small molecule,***" which Dr. Grass conceded were

known to behave differently from antibodies in a number of significant ways. (Ex. 2039, ¶26; 1059 (Grass) at 73:21-75:16, 116:24-118:17.) And Dr. Grass could not identify "***any*** paper that shows the pharmacokinetic profile of an antibody drug follows the shape of the graph for nonlinear pharmacokinetics" he presented in his declaration, and on which PO relies in its Response. (*Id.* at 118:23-119:18.) Notably, Dr. Gelmon testified that she "would have had concerns about extrapolating from a small molecule to an antibody" (which Dr. Grass did) and "would have expected that a pharmacokineticist would have taken what was known in the field about antibodies into consideration" (which Dr. Grass did not). (Ex. 1058 (Gelmon) at 120:19-121:18.)

As Dr. Jusko explains, his linear model if anything would been expected to ***underestimate***, not "overestimate," serum trough concentration at three weeks, as shown in the following exemplary figure, which shows that, 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:

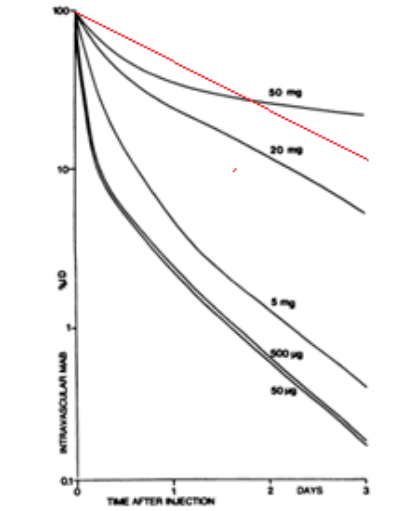


FIGURE 8
Model simulated curves for intravascular MAb reflecting effect of different amount of injected MAb on blood clearance of MAb. Clearance rate of larger injection amount is decreased

(Exs. 1054 at 10 (annotations added); 1057, ¶37.) That is because, while the linear model assumes clearance will be constant at the rate predicted by the mean half-life (and therefore correspond to a lower predicted serum level), by contrast dose-dependence according to the non-linear profile known to be associated with antibodies means the half-life ***increases*** and clearance ***decreases*** (such that the actual serum concentrations would be higher than predicted). (Ex. 1057, ¶¶14–15, 18, 32.) This would have given POSAs even ***more*** confidence that three-week trastuzumab dosing, as calculated by a linear model, would be effective. (Ex. 1056, ¶63.)

Notably, PO's contrary theories are flatly contradicted by published literature stating that trastuzumab's prior art Phase I and II pharmacokinetic data indicated "that higher doses of the drug can be administered less frequently." (Ex.

1043 at 17; *see also* Exs. 1044 at 5; 1045 at 2 (describing the Phase I dose-dependent data as "important because it indicated that it may be possible to administer trastuzumab for longer intervals while maintaining serum concentrations above the minimum required for therapeutic activity.").)

3. Dr. Jusko's use of the 12-day half-life was appropriate.

PO criticizes Dr. Jusko's use of the 12-day half-life as "arbitrary" but, as discussed above, his reliance on data from the highest tested dose—here 500mg and 12 days as set forth in the Label—was appropriate. (*See* §A.3, *supra*.) PO misrepresents Dr. Jusko's "core assumption." Dr. Jusko did ***not*** assume "that trastuzumab's half-life remains constant regardless of the dose amount." (POR at 51.) Rather, he acknowledged that trastuzumab's mean half-life increased with ***dose*** (as shown in the Label), but assumed that clearance and half-life remained constant ***as serum concentration decreased at any given dose level***, which is different. (Exs. 1003, ¶¶33-35; 1057, ¶33.) This made sense, as PO had similarly assumed linear clearance in the prior art despite trastuzumab's dose-dependence, and it was known that, if anything, this would ***underestimate*** serum concentrations at three weeks. It also made sense to rely on the highest reported dose to assess feasibility of three-week dosing, and to use the half-life reported for that dose that was being simulated. There is no inconsistency. (*Contra* POR at 51-53.)

PO points out that the half-life of trastuzumab was reported to be dependent

on shed antigen levels. (POR at 12-13.) But such an effect was only described as potentially significant in the small percentage of patients for which shed antigen reached "high levels," *i.e.*, greater than about 0.5µg/mL. (Exs. 1013 at 11; 1014 at 14-15; 2038 at 250:3-252:1.) For the remaining vast majority of patients, no impact on serum trough levels or efficacy was predicted. (*Id.*; 1057, ¶46.) Indeed, Dr. Gelmon testified with respect to shed antigen at the '196 patent priority date that "[t]here was no science to say that it -- that we should not investigate three-weekly Herceptin." (Ex. 1058 (Gelmon) at 62:20-65:6.) And, the '196 patent makes no mention of any impact of shed antigen or patient-to-patient variability on feasibility of three-weekly dosing, suggesting these are made-up concerns. (Exs. 1001, *generally*; 2038 at 256:14-20.)

Endo Pharm. Inc. v. Depomed, Inc., IPR2014-00654, Paper 69 at 26-27 (PTAB Sept. 21, 2015) is inapposite. In that case, an expert sought to piece together components of controlled-release formulations without considering their impact on properties the same expert admitted would affect drug release, admitted such formulation would be "very difficult," and did not address why a POSA would believe the prior art formulation could be modified. *Id.* Nothing of the sort happened here. PO criticizes Dr. Jusko for "picking" trastuzumab's highest tested dose and its associated half-life but identifies no other reasonable alternative, no associated difficulty, and no unconsidered factors. Dr. Jusko's approach is what

POSAs in the field would have done based on the same data. (Ex. 1043 at 17.)

4. There was sufficient data in the prior art to reasonably predict that the claimed regimen would work.

PO cites one paper, published in the fall of 1999, stating that antibody dosing generally "at the time of the invention" was "a 'complicated task.'" (POR at 26.) But that comment does not say anything about whether the ***claimed dosage regimen*** was complicated or non-obvious in light of the knowledge in the art, including trastuzumab's known safety at 500mg weekly doses, known efficacy at 4mg/kg followed by 2mg/kg weekly doses and known dose-dependence. As explained by the Pegram '98 reference, prior art Phase I studies "showed that the pharmacokinetics of rhuMAb HER2 were predictable." (Ex. 1014 at 9.) PO's references (POR at 41, 50-51) do not indicate otherwise.

PO also ignores that, by the time the article upon which it relies was published, ***three-weekly trastuzumab was already being publicly tested in clinical studies***, and success was predicted based on the knowledge that "Herceptin® demonstrates dose-dependent, non-linear pharmacokinetics." (Ex. 1043 at 17.) Events at the time of the alleged invention thus confirm that POSAs were motivated to investigate less frequent dosing of trastuzumab as of the priority date of the '196 patent ***and*** had reasonable expectation of success in doing so.

PO's arguments also are contradicted by the '196 patent's specification.

While PO now argues that there was a "concern" that "failure to reach therapeutic serum trough concentrations would reduce efficacy" (POR at 22)[7], that cannot be accurate if the patent is enabled, as the '196 patent specification does nothing to resolve that purported "concern." As PO's experts admitted, the specification provides no explanation for why the claimed dosing regimens were selected, or why they would reach serum trough concentrations and maintain efficacy. (Exs. 1059 (Grass) at 195:20-201:18; 1058 (Gelmon) at 273:16-282:1.) Nor can PO's assertion that the claimed dosing regimens "could not have [been] reliably predicted" based on "serum concentration data from weekly administration of different dose amounts" (POR at 55-56) be accurate, as such data is all that the '196 patent presents. (Exs. 1059 (Grass) at 195:20-201:18; 1001, *generally*.)

Were PO correct that trastuzumab dosing was so "unpredictable" and "complicated" that a POSA could not "accurately predict whether a three-week dosing regimen would be clinically effective" (POR at 26, 55-56), the '196 patent surely should have provided more data and explanation. *Cf. Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005) ("The '329 patent sets forth no human clinical or laboratory data showing the safety and tolerability of the

[7] PO asserts the "concern" was "well-documented," but cites nothing documenting it. (POR at 22.)

treatment methods claimed by the patent. …So while the district court may be correct in finding the [prior art] may have invited skepticism based on concerns for dose-related GI problems, the claimed invention adds nothing beyond the teachings of those articles. Thus, the district court clearly erred in finding any difference between the claimed invention and the [prior art] on this point.").

C. Secondary Considerations Do Not Support Nonobviousness.

PO does not even argue, much less show, that ***any*** secondary considerations support non-obviousness of the Challenged Claims. The only purported "result" of the claimed invention—a dosing regimen that is "convenient and cost-effective for the patient and medical professional administering the antibody" (Ex. 1001 at 31)—was in no way "unexpected." Nor has PO established a long-felt need for the claimed dosing regimen; indeed, PO asserts that "convenience and compliance were not of concern to women with HER2-positive breast cancer or their physicians." (POR at 4; *see also* Ex. 1058 (Gelmon) at 232:5-16 (asserting there was no "need" for three-weekly trastuzumab).)

D. These Proceedings Are Constitutional.

According to current precedent, these proceedings are constitutional. *MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1288-93 (Fed. Cir. 2015), *cert. denied*, 137 S. Ct. 292 (2016).

III. CONCLUSION

The Challenged Claims should be found invalid as obvious.

* * *

Date: March 21, 2018

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This Reply complies with the type-volume limitations as mandated in 37 C.F.R § 42.24, totaling 5,591 words. Counsel has relied upon the word count feature provided by Microsoft Word.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Reply to Patent Owner Response was served on March 21, 2018, via electronic service on lead and back-up counsel:

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