No. 2019-1263

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

GENENTECH, INC.,

Appellant,

v.

ANDREI IANCU, Director, U.S. Patent and Trademark Office,

Intervenor.

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2017-00731

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October 15, 2019

CERTIFICATE OF INTEREST

Counsel for Appellant Genentech, Inc. certifies the following:

1. The full name of every party or *amicus* represented by me is:

Genentech, Inc.

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

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Genentech, Inc. is a wholly-owned subsidiary of Roche Holdings Inc. Roche Holdings Inc.'s ultimate parent, Roche Holdings Ltd, is a publicly held Swiss corporation traded on the Swiss Stock Exchange. Upon information and belief, more than 10% of Roche Holdings Ltd's voting shares are held either directly or indirectly by Novartis AG, a publicly held Swiss corporation.

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

WILMER CUTLER PICKERING HALE AND DORR LLP: Owen K. Allen (former), Lauren V. Blakely, David L. Cavanaugh, Lisa J. Pirozzolo, Kevin S. Prussia, Rebecca A. Whitfield (former)

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

Genentech, Inc. et al. v. Amgen Inc., No. 1:18-cv-00924 (D. Del.)
Genentech, Inc. v. Iancu, No. 19-1265 (Fed. Cir.)
Genentech, Inc. v. Iancu, No. 19-1267 (Fed. Cir.)
Genentech, Inc. v. Iancu, No. 19-1270 (Fed. Cir.)

Dated: October 15, 2019

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INTRODUCTION

It is undisputed that when Genentech created the claimed drug combination, using drugs never before combined to treat humans, its invention revolutionized breast cancer treatment and became the first antibody-based first-line therapy for treatment of solid tumors ever approved by the FDA. The Board's decision denied Genentech any claims to that novel combination, no matter how narrowly drawn. But the Board's decision was flawed from start to finish, and the government's efforts to backfill on appeal cannot save it.

The government's brief is most notable for what it does not say. In arguing that Genentech had no statutory right to offer a new claim amendment after the Board instituted on a new ground, the government never seriously grapples with the text of 35 U.S.C. § 316(d)(1) and this Court's interpretation of parallel language in *Shaw Industries Group, Inc. v. Automated Creel Systems, Inc.*, 817 F.3d 1293, 1300 (Fed. Cir. 2016). In defending the Board's entry of a partial adverse judgment, the government does not seriously contend that the Board's action was consistent with 37 C.F.R. § 42.73(a)-(b); it instead seeks to justify the extraordinary step of *waiving* that requirement, based on flawed reasons that were not articulated by the Board. And in arguing that Genentech lacked good cause to offer a new amendment, the government relies on an incorrect "could have" test and ignores how Genentech's motion, which was offered as a non-contingent

amendment, could have streamlined the proceedings by eliminating the need to consider other issues.

The same pattern of omission permeates the government's discussion of Genentech's original claims. The government does not identify any language in the claims or specification that would support the Board's claim construction. It also does not dispute that the Board's construction—which compares the claimed combination to a patient left entirely untreated—makes no practical sense. The government instead relies on a single statement from the prosecution history, while disregarding the citations embedded in that statement and the subsequent amendment of the claims, both of which inform how a person of skill in the art would view the claims.

Similarly, in defending the Board's ruling that the claims are obvious under the correct construction, the government does not dispute that the Board's holding depends on a faulty measure of efficacy that "excludes patients with no response [to treatment] … potentially skewing the results upward." PTO Br. 42. The government's contention that Genentech somehow waived this argument ignores that the petitioner never raised the issue in its petition and Genentech identified the reference's shortcomings at its first opportunity after the argument was eventually made. The government also fails to plug the holes in the Board's reasoning on the

safety element in the claims and does not dispute that the Board relied on the inventor's own path to support its finding of obviousness.

The Board's numerous errors deprived Genentech of protection for its foundational discovery. The Board's decision should be reversed or, at a minimum, vacated and remanded for correction of these errors.

ARGUMENT

I. THE BOARD'S DECISION TO PROHIBIT GENENTECH FROM FILING A NON-CONTINGENT MOTION TO AMEND SHOULD BE REVERSED

As Genentech's opening brief explained (at 25-35), the Board committed three independent errors in refusing to allow Genentech to file a new amendment after the Board instituted on a new ground. Each requires reversal.

A. The Plain Text Of § 316(d)(1) Grants Genentech A Statutory Right To Amend

Section 316(d)(1)'s plain language affords a patent owner the right to amend the underlying patent when the Board institutes on a new ground. *See* Genentech Br. 26-28. *First*, the statute gives patent owners the right to amend their patents once "***during*** an inter partes review instituted under this chapter." 35 U.S.C. § 316(d)(1).[1] This Court has held that the analogous phrase "during [an] inter partes review" refers to the period after institution and only to the grounds on which IPR was actually instituted. *Shaw Indus. Grp., Inc. v. Automated Creel Sys.*,

[1] All emphasis added unless otherwise indicated.

817 F.3d 1293, 1300 (Fed. Cir. 2016). Specifically, *Shaw* held that a ground on which the Board denied institution was not subject to estoppel under § 315(e) because it was not a ground raised "*during*" the *inter partes* review. *Id.* As this Court explained, "Shaw raised its Payne-based ground in its petition for IPR, the PTO denied the petition as to that ground, [and] thus no IPR was instituted on that ground." *Id.* "The plain language of the statute prohibits the application of estoppel under these circumstances" because an "IPR does not begin until it is instituted" and "Shaw did not raise—nor could it have reasonably raised—the Payne-based ground *during* the IPR." *Id.* (emphasis in original).

Under *Shaw*'s "plain language" interpretation of the parallel phrase "during … inter partes review," Genentech's right to amend in response to Ground 1 under § 316(d)(1) was not triggered until the Board instituted on Ground 1, because until then, Genentech had no opportunity to file its amendment "during" the proceeding that included Ground 1. The government notably does not even cite *Shaw*, much less address its impact on this case. This silent concession speaks volumes.

Second, the statute states that patent owners have the right to amend their patents "during an inter partes review ***instituted*** under this chapter," tying the amendment right to the institution decision. 35 U.S.C. § 316(d)(1). Absent institution, the right to amend has not been triggered. Indeed, it would lead to absurd results if—as in this case—a party was denied the opportunity to amend

where the Board completed the act of institution and changed the scope of the IPR proceedings after both its initial institution decision and an initial motion to amend had been filed. It is fundamentally inequitable to force a patentee like Genentech to rely on the Board's discretion to exercise an "important" statutory right—the right to amend the patent—that Congress saw fit to place beyond the bounds of agency discretion. *Aqua Products, Inc. v. Matal*, 872 F.3d 1290, 1299 (Fed. Cir. 2017) (en banc). The text of § 316(d)(1) compelled the Board to permit an amendment as of right following institution of Ground 1.

The government responds (at 23-24) that the Board framed its institution decision on Ground 1 as a "modific[ation]" of the existing *inter partes* review rather than as a new institution decision. *See also* Appx13081. But the Board's ruling on Ground 1 clearly stated that it was "institut[ing]" review. Appx13081 ("We hereby modify our institution decision to ***institute on … all of the grounds*** presented in the Petition."). Ground 1 had not previously been instituted and was not part of the prior proceedings. The Board thus made a new decision to institute review (to include Ground 1), which in turn triggered a new amendment as of right. Indeed, the original act of "institution" solely on Ground 2—in violation of *SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348 (2018)—was necessarily incomplete without a ruling on Ground 1. It was only when the Board took that missing step and decided to institute on both grounds, rather than cancel the proceeding, that

Genentech's statutory right to amend "*during* an inter partes review *instituted* under this chapter" fully matured.

The government's argument that this new act of institution did not reset other deadlines is unavailing. Those provisions stand on a different footing, and none uses the same language as § 316(d)(1). The time bar on filing a petition, for example, asks whether "the ***petition*** requesting the proceeding is filed more than 1 year after the date" a complaint is filed. 35 U.S.C. § 315(b). Because the deadline is keyed to filing the petition rather than events "during" the "instituted" IPR, there is no inconsistency between applying it as written and honoring Genentech's statutory right to amend after the Board's new institution decision. Nor is there any conflict with the joinder provision, which not only uses different phrasing than § 316(d)(1), but, as a regulation, does not provide a relevant point of comparison indicating *congressional* intent. 37 C.F.R. § 42.122(b) (joinder request "must be filed … no later than one month after the institution date").

On both joinder and the one-year deadline to issue a final written decision, moreover, the government simply assumes those deadlines do not reset upon a new institution decision, but never explains why that would be the case. For example, the deadline for a final written decision expires "1 year after the date on which the Director *notices the institution of a review*." 35 U.S.C. § 316(a)(11). It would be eminently reasonable to have that deadline—which runs from "institution"—start

anew for any ground that is the subject of a new institution decision. To be clear, this Court need not decide this or any other related issue. The point is simply that the government comes nowhere close to identifying any statutory inconsistency with Genentech's approach, and certainly not one of a magnitude sufficient to require deviation from § 316(d)(1)'s plain text granting Genentech the right to amend.

The belated institution decision on Ground 1, moreover, occurred only because ***the Board initially violated the law*** by instituting on Ground 2 alone in contravention of 35 U.S.C. § 318(a). *SAS*, 138 S. Ct. at 1352-1353. The Board could have fixed its error by dismissing the petition in its entirety. Instead, by deciding to institute on Ground 1 as well, the Board completed its initial act of institution and triggered Genentech's statutory right to amend under § 316(d)(1).

B. The Board's Decision To Grant Partial Adverse Judgment Is Contrary To Its Own Regulations

The Board also erred by granting the petitioner's request for a ***partial*** adverse judgment on Ground 1. Genentech Br. 28-30. The Board's own regulation governing "adverse judgment" defines judgment as a ruling that "disposes of ***all*** issues"—not just some. 37 C.F.R § 42.73(a)-(b).

Tellingly, the government does not explain how the Board's ruling can be squared with § 42.73's plain text. PTO Br. 29-31. Instead, it argues that the Board exercised its authority under 37 C.F.R. § 42.5(b) to waive the normal requirements

of the adverse judgment regulation. *Id.* The Board's decision to unilaterally overrule its regulation, however, cannot be reconciled with basic administrative law. It is well-established that, "in order to permit meaningful judicial review," an agency must at a minimum "disclose the basis of its action." *Department of Commerce v. New York*, 139 S. Ct. 2551, 2573 (2019); *see also FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) (agency "must show … good reasons for" "depart[ing] from a prior policy"). The Board provided no explanation for its decision to rely on § 42.5(b). Appx22. Accordingly, its ruling cannot stand.[2]

The government attempts to fill this gap with its own explanations for invoking § 42.5(b). *See* PTO Br. 30-31. But this Court may uphold agency action only "on the basis articulated by the agency itself" and not based on the post hoc arguments of government attorneys. *See Motor Vehicles Mfrs. Ass'n of U.S. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 50 (1983); *accord Doty v. United States*, 53 F.3d 1244, 1251 (Fed. Cir. 1995) (same).

Moreover, the government's post hoc arguments are flawed. The government first contends (at 30) that Genentech suffered no prejudice when the

[2] The government argues (at 30) that Genentech waived this argument because its opening brief did not cite § 42.5(b) by name. This ignores Genentech's lengthy argument regarding the underlying substantive point—the Board failed to provide a meaningful explanation for its decision. *See* Genentech Br. 29-30 (noting the "Board did not grapple with any" of the policy failings of its ruling).

Board disregarded § 42.73 because the petitioner could have accomplished the same result by "simply conceding" its Ground 1 argument. The government does not, however, identify a single authority suggesting that this tactic can be used to unilaterally cut off further proceedings, including the patent owner's right to amend. Indeed, the government's approach would render superfluous the procedures under § 42.73 for *requesting* an adverse judgment from the Board.

The government also contends (at 30-31) that gamesmanship is not a serious concern in this context because the petitioner will suffer some "negative effects" by voluntarily dropping part of its argument. But the mere existence of some trade-offs to receiving partial adverse judgment does not mean that gamesmanship will not come into play. That is clear from this very case, where the petitioner made a calculated, tactical decision that, despite having pressed to have Ground 1 instituted, it was better off dropping Ground 1 to try to avoid Genentech's new, non-contingent amendment. *See* Genentech Br. 29.

C. At A Minimum, The Board Abused Its Discretion By Finding That Genentech's Request To Amend Was Not Supported By Good Cause

Even assuming that Genentech was not entitled to amend as of right, the Board abused its discretion in finding there was not good cause to amend. Genentech Br. 30-35; 37 C.F.R. § 42.121(c). *First*, when Genentech filed its initial motion to amend, it could not have anticipated that the Board would later institute

on Ground 1. *Second*, the Board's guidance on amendment practice became significantly less restrictive after Genentech filed its first motion. *Third*, Genentech's new motion to amend would not have unduly delayed the proceedings. To the contrary, it would have significantly simplified the matter by cancelling all issued claims and replacing them with a single claim.

The government's primary response (at 25) is that Genentech "could have proposed" its second, non-contingent amendment in its initial motion to amend. *See also* PTO Br. 2, 16. But that is not the correct standard. Because the underlying patent in an IPR remains the same throughout the proceeding, the contents of a second motion to amend *always* "could"—with sufficient foresight—have been proposed earlier. So, on the government's theory, a patentee would never be able to show good cause.

Indeed, it is difficult to reconcile the government's "could have" standard with the PTO's own statements in the Federal Register. In announcing a pilot program allowing patent owners to offer new motions to amend in response to feedback from the Board on their original motions, the Board did not propose any changes to the "good cause" standard in 37 C.F.R. § 42.121(c). Rather, it stated that, under the ***existing*** good cause standard, a ruling "addressing the initial [motion to amend] and/or a petitioner's opposition to the initial MTA provides 'good cause' to file a revised" motion to amend. 84 Fed. Reg. 9,497, 9,501 (Mar.

15, 2019). That is true even though the documents merely "present information relevant to whether an MTA meets statutory and regulatory requirements and/or whether proposed substitute claims meet the patentability requirements." *Id.* This interpretation of the existing "good cause" standard demonstrates that the "good cause" inquiry cannot be reduced to a "could have" filed test. The salient question is not whether a patent owner might have foreseen a need to amend at an earlier time, but whether the patent owner has a sufficient reason to want to amend at the present time.

Genentech had just such a good reason in this case. Institution on Ground 1 changed the playing field because Ground 1 was primarily based on Baselga '97, whereas Ground 2 was mainly based on Baselga '96. Genentech Br. 31. The government incorrectly asserts (at 25) that there was no meaningful difference between the two references. But even the Board acknowledged that Ground 1 and Ground 2 were hardly "identical." *See* Appx6; *see also* PTO Br. 26 (recognizing that Baselga '97 included a "unique disclosure" not at issue in the other references).

Baselga '96 vaguely notes that "clinical trials are … currently in progress," with no additional detail regarding (1) how they are to be conducted, (2) whether they specifically involve a combination of rhuMab HER2 and paclitaxel, or (3) what clinical endpoint would be measured. Appx1080 (Baselga '96). In stark

contrast, Baselga '97 (1) disclosed the design of a Phase III study specifically testing the interaction between rhuMab HER2 and paclitaxel, (2) stated for the first time that the combination of rhuMab HER2 and paclitaxel would be tested in humans, and (3) disclosed that the "main goal" was to determine whether the combination "increases the time to disease progression." Appx1096. And although Genentech had antedated Baselga '97 during prosecution and in the IPR, its return in the newly instituted ground reopened the question. The institution of Ground 1 thus provided good cause to amend because it materially changed the scope of the IPR.

The government argues (at 26) that Genentech's motion was not exclusively directed to Baselga '97 but instead designed to simplify the entire proceeding. *See also* Genentech Br. 2. This kind of simplifying amendment, however, is precisely what Congress envisioned. "The possibility of amendment" was intended to be "*the* central feature of the IPR process," as it would help "preserve 'the merited benefits of patent claims better than the win-all or lose-all validity contests in district court.'" *Aqua Products*, 872 F.3d at 1298, 1304, 1312. Indeed, the PTO's own guidance has lauded amendments as a method of "'producing clear and defensible patents at the lowest cost point in the system.'" *Id.* at 1299 (quoting Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,764 (Aug. 14, 2012)).

The government contends (at 27-28) that Genentech should have made those changes earlier, downplaying the change in the law from *Idle Free* to *Western Digital* on the ground that Genentech's initial motion to amend advocated the standard subsequently adopted in *Western Digital*. But this argument misses the point. Genentech's foresight in advocating for the *Western Digital* standard does not mean that this standard indeed governed at the time. It should not be forgotten that the PTAB was notoriously hostile to motions to amend for years. *Aqua Products*, 872 F.3d at 1299-1300. Had *Western Digital* undisputedly been governing law, Genentech would have felt more leeway to draft a "picture claim" directly keyed to one particular disclosure in its specification, as it later did in its non-contingent motion to amend. Genentech Br. 33-34.

Finally, the government's argument that Genentech's motion would have unduly delayed proceedings makes no sense. The non-contingent amendment would have narrowed the issues and led to a speedy resolution by cancelling the originally issued claims in favor of a single amended claim. Genentech Br. 35. Most of the Board's subsequent final written decision was unnecessary and could have been dispensed with—as could all of the remaining issues in this appeal—if the Board had not been so resistant to Genentech's efforts to amend. That resistance was fueled by legal error and should be reversed.

II. THE GOVERNMENT'S ATTEMPT TO DEFEND THE BOARD'S CLAIM CONSTRUCTION FAILS

The government identifies *no* language in the original claims or specification that supports comparing the claimed combination of an anti-ErbB2 antibody (e.g., rhuMAb HER2) and a taxoid (e.g., paclitaxel) to a patient receiving no treatment whatsoever. To the contrary, both the claims and specification make clear that the proper comparison is to a patient who—although "untreated" with the claimed combination—is administered a drug, specifically a taxoid. The government's claim construction argument thus depends on a theory of disclaimer—i.e., that a single sentence from the prosecution history unmistakably overrides the plain meaning of the claims and specification. Viewed in context, that single sentence does not meet the demanding standard for establishing a disclaimer.

The plain language of the claims makes clear that the relevant comparison cannot be to a patient receiving no treatment at all. The claims state that the claimed combination must "extend the time to disease progression … without increase in overall severe ***adverse events***." Appx225(33:52-54). The government does not dispute that an adverse event is "[a]n unexpected medical problem that happens ***during treatment with a drug or other therapy***." Appx11205; *see also* Appx12391; Genentech Br. 38. The plain language of the claims thus requires a comparison of (1) any severe medical problems that occur "during treatment" with the claimed combination to (2) the severe medical problems that occur "during

treatment" with another drug.[3] To be sure, a patient left untreated would experience medical problems as the breast cancer progresses, but those are not "adverse events" within the meaning of the claims. The point is to measure the side-effects of the treatment itself.

The specification drives home that the proper comparator is treatment with a taxoid alone. The specification does not disclose a single instance of the extension of time to disease progression (TTP) being measured relative to a patient receiving no treatment. Indeed, the government does not dispute that a patient would never be provided no treatment because it would be unethical to do so. Genentech Br. 37 Appx9632(¶141). Breast cancer is a life-threatening disease for which there were already therapies approved by the FDA. A skilled artisan thus would have readily appreciated the illogic of interpreting the claims, as the Board did, to require a comparison to no treatment at all. Appx9632. The government responds (at 34) that the claims "are not limited to an FDA-approved clinical study requiring that all patients be treated." But that is no answer. The issue is not just whether the FDA would approve a study, but whether any physician would undertake such a comparison—and the government does not dispute that the answer is "no."

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[3] The government argues (at 36) that Genentech could have added a "different comparator for its new safety limitation." But arguing that the claims could be ***rewritten*** does nothing to defend the Board's construction of the claims ***as drafted***. The claims provide no indication that they refer to two different comparators.

The specification instead makes clear that the proper comparison for measuring the extension of TTP is between the claimed combination and a control arm of paclitaxel alone. Appx223(29:9-30:25) (comparing "T+H" (i.e., Taxol and Herceptin) to "T" (i.e., Taxol)). Reading the claims in light of that disclosure is not, as the government alleges (at 35), an attempt to import limitations from the specification into the claims. By their plain terms, the claims require the comparator to be a form of treatment. The specification further "informs the proper construction of the claims," *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc), by confirming that the comparator is a taxoid—the standalone treatment to which the specification compares the claimed combination.[4]

The government also argues (at 37) that comparing the claimed combination to a taxoid alone would add new matter, and that Genentech somehow conceded that its construction of the original claims lacked written description support. But this Court has "certainly not endorsed a regime in which validity analysis is a regular component of claim construction." *Phillips*, 415 F.3d at 1327. In any

[4] The government tries to muddy the waters by arguing (at 35-36) that anthracycline/cyclophosphamide might serve as a comparator even though "the claims exclude anthracycline therapy," based on "increased cardiac side-effects," Appx223(30:20-21). But in determining the comparator for the treatment that succeeded, an ordinary artisan would have naturally looked to the control in that same arm of the study (i.e., a taxoid alone), not the control in the arm that failed.

event, Genentech has made no such concession; the original claims are different from the proposed amendment the Board analyzed. Appx75. Moreover, the percentages cited by the government compare "adverse events" (i.e., "AE") rather than "severe adverse events." PTO Br. 37; Appx223(29:9-30:12). And the specification supports the claims by showing no more than a negligible difference—i.e., no "overall" increase—in severe myocardial dysfunction. Appx223(29:13-16).

Unable to find support for its construction in the claims or specification, the government rests its argument on a statement in the prosecution history that "the expression[] 'extend the time to disease progression'" is "clear from the specification (see, in particular, page 15, lines 15-17; and pages 42-43)" and means "extend the time to disease progression relative to an untreated patient." Appx2082. But when that statement is read in the context of the prosecution history as a whole, and the patent specification to which it refers, it is not sufficiently "clear and unmistakable" to meet the demanding standard for establishing a disclaimer. *SanDisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1287 (Fed. Cir. 2005).

First, the government improperly discounts the citations embedded in the very same statement on which it relies. The alleged disclaimer said that the comparator for extending TTP is "clear from the specification (see, in particular,

page 15, lines 15-17; and pages 42-43)." Appx2082. The government (at 34) dismisses these cross-references as "additional citations to descriptions of TTP." But the referenced "pages 42-43" explicitly disclose the results of Genentech's clinical trials in which the claimed combination ("T+H") was ***compared to a taxoid alone ("T")***, with no mention whatsoever of patients receiving no treatment. Appx1372-1373. Thus, even at the moment of the alleged disclaimer, the prosecution history was pointing to the comparison with a taxoid as indicative of the meaning of the claims, signaling that "untreated patient" meant untreated ***with the claimed combination***. *See also* Appx8709 (petitioner's expert: "There's frequently a control which I guess you could say is untreated."). Moreover, the designated portion of the specification disclosing a taxoid as the comparator provided a "specific definition of the comparator," PTO Br. 33, sufficient to resolve any definiteness concerns.

Second, the government cannot get around the fact that the claims were amended ***after*** the alleged disclaimer to add the "serious adverse events" limitation, which, as explained above, is incompatible with comparing the claimed combination to a patient receiving no treatment. The government argues that "[r]ather than dispel ambiguity, the amendment created it" because it did not expressly "provide a different comparator" or "revisit its prior selection." PTO Br. 36. But the government's assessment that the amendment ***created ambiguity***

hardly helps the government. "Where the alleged disavowal is ambiguous, or even amenable to multiple reasonable interpretations," this Court has "declined to find prosecution disclaimer." *Massachusetts Inst. of Tech. v. Shire Pharms., Inc*., 839 F.3d 1111, 1119 (Fed. Cir. 2016) (internal quotation marks omitted). And "[e]ven if an isolated statement appears to disclaim subject matter, the prosecution history as a whole may demonstrate that the patentee committed no clear and unmistakable disclaimer." *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1342-1343 (Fed. Cir. 2009).[5] That is the case here.

Finally, the government implies that the prosecution history could be "'relevant as reinforcing the evident meaning of the claim language at issue, whether or not it would meet standards for disclaimer or disavowal.'" PTO Br. 32-33 (quoting *D'Agostino v. MasterCard Int'l Inc*., 844 F.3d 945, 949 (Fed. Cir. 2016)). Given that the government seeks to use the prosecution history to override rather than "reinforc[e]" the language of the claims and specification, however, the demanding standard for disclaimer is the relevant standard here.

[5] The government's citation (at 36) of *Amgen Inc. v. Coherus BioSciences Inc.*, 931 F.3d 1154 (Fed. Cir. 2019) is not to the contrary. *Amgen* rejected a bright-line rule limiting prosecution disclaimer to "arguments made in the most recent submission before allowance." *Id*. at 1161. Mere failure to repeat a disclaimer is easily distinguished from amending claims in a manner inconsistent with the alleged disclaimer.

Even if that were not the case, the prosecution history does not control. Prosecution history is often "less useful for claim construction purposes" than the specification "because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation." *Phillips*, 415 F.3d at 1317. Nor does the government's invocation of the broadest reasonable interpretation standard help it. The government never explains how choosing one comparator over another would make the claims broader or narrower. The choice here is not between a broad or narrow construction, but between a comparator unsupported by anything other than an isolated statement early in the prosecution history (the Board's construction) or a comparator supported by the claims and specification (the correct construction).

III. UNDER A PROPER CONSTRUCTION, THE BOARD'S OBVIOUSNESS RULING CANNOT STAND

The claimed combination is now the standard of care but, in 1997, rhuMAb HER2 offered a completely new approach to treating breast cancer using a human-engineered antibody. Such treatment of solid tumors had never before been approved by the FDA, there were no other clinical trials testing the combination of rhuMAb HER2 and paclitaxel, and measurement of TTP for the combination had never been reported in *any* model, not even a preclinical model. With this minimal data on a fundamentally new therapy, and well aware of the high failure rate of oncology drugs in clinical trials, an ordinary artisan simply did not have enough

information to form a reasonable expectation of success about the efficacy and safety of combining rhuMAb HER2 and a taxoid in human patients.

As Genentech's opening brief explained, there are three critical defects in the Board's determination that Genentech's groundbreaking claims would have been obvious even under the correct claim construction. *First*, the Board erred in finding that an ordinary artisan would have reasonably expected the claimed ***efficacy***—extension of time to disease progression in human patients, compared to a taxoid alone—achieved by the combination of rhuMAb HER2 and a taxoid. *Second*, the Board erred in finding that an ordinary artisan would have reasonably expected the claimed ***safety***—without increase in overall serve adverse events—that was also achieved. *Third*, the Board improperly relied on the ***inventor's own path*** in finding the claims obvious. In response, the government admits that the Board relied on skewed data and repeats many of the Board's same errors.

A. The Board's Decision On Efficacy Was Based On Results That The Government Concedes Were "Skew[ed]"

Genentech's opening brief showed that the Board's key determination regarding extension of TTP rested on a simple, fundamental error: The Board compared apples to oranges. The Board read Baselga '96 to disclose that the TTP for patients treated with rhuMAb HER2 alone was 5.1 months. It compared that to the Physician's Desk Reference's statement that the TTP for a taxoid (paclitaxel) was 3 or 4.2 months. It then concluded that, because the TTP for rhuMAb HER2

appeared to be greater than the TTP for paclitaxel, combining rhuMAb HER2 with paclitaxel would necessarily result in a longer TTP than paclitaxel alone.

The problem is that Baselga '96 and the Desk Reference reported TTP figures calculated in very different ways. The Desk Reference reported the median TTP for paclitaxel based on ***every*** patient treated in a 471-patient study, including the 338 patients who did not respond to treatment. Appx10054. Baselga '96, by contrast, reported median TTP for rhuMAb HER2 based on ***only 16 of the 43*** assessable patients in the study, excluding 22 patients who did not respond to treatment and showed disease progression. Appx65-67; Appx1077.

The government acknowledges the Board's critical mistake. It concedes (at 42) that Baselga '96 "excludes patients with no response … ***potentially skewing the results upward***." This admission should end this Court's analysis. There is simply no way of telling from these partial, admittedly "skew[ed]" results what rhuMAb HER2's actual effect on extension of disease progression was likely to be compared to treatment with a taxoid alone.

The government's attempts to argue around this clear flaw in the Board's decision fail. The government's first contention (at 41-43) is that Genentech waived the argument by not raising it in the Patent Owner Response and "accept[ing] 5.1 months as Herceptin's TTP." PTO Br. 41-43. But there was no waiver because the petitioner never suggested comparing those TTPs in its petition

or any of its papers. *See* Appx12001-12075; Appx12321-12336; Appx12793. To be sure, the petition described Baselga '96 and mentioned that it reported a 5.1-month TTP. But it nowhere suggested that this TTP could or should be compared to the TTP for paclitaxel disclosed in the Desk Reference to establish a reasonable expectation of success. *See generally* Appx12001-12075. Indeed, the petition itself acknowledged that Baselga's TTP figure included only those patients with "[m]inor responses" and "stable disease[s]." Appx12058. Nor did the Board suggest this reasoning in its Institution Decision, which was based on its erroneous claim construction requiring comparison to patients who received *no treatment*. Appx12390-12391. Genentech could not rebut an argument in its Patent Owner Response that was not made in the first place. *See, e.g.*, *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1080 (Fed. Cir. 2015); *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc*., 859 F.3d 1341, 1348-1349 (Fed. Cir. 2017); *In re NuVasive, Inc*., 841 F.3d 966, 971-973 (Fed. Cir. 2016).

The government also misses the mark when it argues that Genentech failed to show that Baselga '96's exclusion of patients without any tumor response in the calculation of TTP would matter because Baselga '96 also excluded patients in remission, possibly skewing the results in the opposite direction. PTO Br. 42-43. This argument fails for at least three reasons.

First, the record contains no evidence that would permit anyone to draw a reliable conclusion based on the government's unsupported speculation that multiple omissions in Baselga '96 might have cancelled each other out. *See In re Kao*, 639 F.3d 1057, 1067 (Fed. Cir. 2011) ("conjecture does not supply the requisite substantial evidence"). This absence of proof is a shortcoming in petitioners' case, not Genentech's, and means that the Board's decision is not based on substantial evidence.

Second, the government cannot shift the burden to Genentech to establish the actual TTP for rhuMAb HER2. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1377-1379 (Fed. Cir. 2016) (reversing final written decision because the Board shifted the burden of proof on obviousness from the petitioner to the patent owner); *see also Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. de C.V.*, 865 F.3d 1348, 1355-1356 (Fed. Cir. 2017) ("In an *inter partes* reexamination involving obviousness, the standard is not whether the patent owner can persuasively show that one of ordinary skill would have expected failure. Rather, the burden is on the Examiner to show that one of ordinary skill would have had a motivation to combine the references with a reasonable expectation of success."). Genentech has demonstrated that the Board's decision depended on a comparison from which no reliable conclusion can be drawn. Genentech does not

have an *additional* burden to produce evidence showing what the result of a study with a comparable calculation would have been.

Third, the government cannot defend the Board's decision based on a factual rationale the Board did not adopt. Nowhere did the Board address the defects with Baselga '96's TTP calculation or endorse the speculative reasoning the government now advances. This kind of backfilling is legally impermissible: "The Board's judgment must be reviewed on the grounds upon which the Board actually relied." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1294 (Fed. Cir. 2012) (citing *SEC v. Chenery Corp.*, 332 U.S. 194, 196 (1947), and *In re Lee*, 277 F.3d 1338, 1345-1346 (Fed. Cir. 2002)).

Where the only reference relied on by the Board as establishing the claimed efficacy in fact provided an incomplete calculation of TTP, an ordinary artisan could not conclude that rhuMAb HER2 in combination with a taxoid would extend TTP as compared to a taxoid alone. On this basis alone, the Board's decision should be reversed or, at a minimum, vacated and remanded.

B. The Board Erred In Finding The Claimed Safety Obvious

The government also fails to rehabilitate the Board's holding that the claimed level of safety was obvious. The Board concluded that an ordinary artisan would reasonably expect the combination of rhuMAb HER2 and paclitaxel not to increase severe adverse events compared to a taxoid alone. Genentech's opening

brief outlined the lack of substantial evidence supporting this conclusion: None of the prior art described any testing of the combination of rhuMAb HER2 and paclitaxel in humans, and safety results of each therapy alone and data regarding the combination from xenograft preclinical models was insufficient to establish a reasonable expectation that the combination would not increase severe adverse events in humans. Genentech Br. 45. Instead of addressing Genentech's argument, the government largely repeats the Board's hindsight-driven analysis.

The prior art must be read from the perspective of an ordinary artisan in 1997, not with the benefit of knowing the extraordinary success that Herceptin became. A new combination's toxicity cannot be predicted simply by adding together the adverse events of each drug alone. Genentech Br. 45-47. "Even where each drug in a combination therapy is tested separately, a clinician cannot predict the results of combining them." Appx9656(¶192); *see also United States v. Hiland*, 909 F.2d 1114, 1133 n.29 (8th Cir. 1990) ("[E]ven if the component parts of a drug are generally recognized as safe, the combination of those parts may not be safe.").

Further, the only testing of the combination in the record was Baselga '94's preclinical xenograft studies, which although helpful in identifying promising avenues for experimentation in humans, do not provide a reliable prediction of a particular result in human patients, especially on safety issues. Genentech Br. 46.

Indeed, Baselga 94's only statement on toxicity was that trastuzumab "did not increase toxicity of paclitaxel or doxorubicin in animals as determined by animal survival and weight loss." Appx1085. This says nothing about what adverse effects may occur in humans, and the study itself was not designed to offer such prediction. *See* Genentech Br. 46 (citing Appx10626-10628). The government's argument conflates what an ordinary artisan might ***hope*** with what an ordinary artisan would ***reasonably expect***. *OSI Pharms., Inc. v. Apotex Inc.*, No. 2018-1925, __ F.3d __, 2019 WL 4892078, at *8 (Fed. Cir. Oct. 4, 2019) ("hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art").

Beyond blanket assertions regarding the predictive value of preclinical studies, the government argues that Genentech itself relied on Baselga '94's mouse studies in applying for approval of its proposed Phase III studies, and that the purpose of Baselga '94 was "to look at trying to predict what can be helpful in patients." PTO Br. 44-46. As an initial matter, "trying to predict what can be helpful in patients" is very different from forming a reasonable expectation of achieving a particular result. Further, to accept the government's argument would lead to the untenable conclusion that any time an inventor relies on a certain reference to propose a trial before the FDA, and the trial is ultimately successful, such reference has necessarily provided a reasonable expectation of success.

Unless the inventions underlying every successful clinical trial are obvious in view of the references submitted to justify the clinical trial, this clearly cannot be correct. *See Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1060-1062 (Fed. Cir. 2019) (phase I data did not provide a reasonable expectation of success).

Finally, the government argues that the Board properly disregarded Baselga '94's failure to predict that rhuMAb HER2 and doxorubicin increased toxicity because Genentech characterized these results as "unexpected." PTO Br. 45. However characterized, these results show that an ordinary artisan could not reliably predict the toxicity of any combination of rhuMAb HER2 and another drug from the study without more data. For these reasons, this Court should reverse on this basis as well.

C. The Board Failed To Offer A Proper Basis For Its Reliance On The Inventors' Path In Its Obviousness Determination

The government does not dispute that the Board relied on the inventors' path to support its obviousness determination. On the claimed efficacy limitation, the Board cited the inventors' FDA communications to support its conclusion that "an ordinary artisan would have had a reasonable expectation that adding rhuMAb HER2 [to paclitaxel] would achieve an extension of TTP over paclitaxel alone." Appx65-67. The very next sentence reads, "[o]ur conclusion is further supported by the representations Patent Owner made in its submission to the FDA." *Id.* On

the claimed safety limitation, the Board strung together a series of inferences—that Genentech cited Baselga '94 to support its proposed phase III trial, that the FDA must have found Genentech's planned phase III trial "reasonable," and therefore that an ordinary artisan would have reasonably expected that the proposed combination would not increase overall severe adverse events. Appx67. This reliance on the inventors' path infected the Board's decision with impermissible hindsight.

That the inventors sought, and the FDA approved, a Phase III clinical trial ***testing*** the later-claimed combination does not mean that an ordinary artisan would have reasonably expected success in obtaining the specific result recited in the claims. Indeed, the lack of data on the combination in humans is significant in light of the highly unpredictable nature of cancer treatments, as shown by the high failure rate of drugs entering Phase III trials (almost 60%). Appx9605; *see also OSI Pharms.*, 2019 WL 4892078, at *7 (reversing obviousness determination that relied on fact of Phase II trials, and noting the high failure rate of drugs in clinical trials).

The government argues that this information is relevant as "additional evidence" to show that Genentech has allegedly taken inconsistent positions regarding Baselga '94. PTO Br. 47. But that confuses what the inventor, who possessed extraordinary skill and extensive information about taxoids, believed

appropriate to propose to the FDA, with whether an ordinary artisan would reasonably expect the claimed results. Genentech Br. 49; Appx8935; Appx8941. The inventors' path is simply not a proper basis for an obviousness finding. *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1363 (Fed. Cir. 2009) (inventor's personal expectations do not demonstrate expectation of success of a POSA); *see also Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]he inventors' reliance on the [prior art] and the motivations that they derived from it have no bearing on the issue of patentability.").

CONCLUSION

The Board's decision should be vacated and remanded for further proceedings on Genentech's non-contingent motion to amend. In the alternative, the Board's decision on the original claims should be reversed or, at a minimum, vacated.

Respectfully submitted,

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October 15, 2019

CERTIFICATE OF SERVICE

I hereby certify that, on this 15th day of October, 2019, I filed the foregoing Reply Brief for Appellant Genentech, Inc. with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system, which will send notice of such filing to all registered CM/ECF users.

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CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(g), the undersigned hereby certifies that this brief complies with the type-volume limitation of Federal Circuit Rule 32(a).

1. Exclusive of the exempted portions of the brief, as provided in Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b), the brief contains 7,000 words.

2. The brief has been prepared in proportionally spaced typeface using Microsoft Word 2016 in 14-point Times New Roman font. As permitted by Fed. R. App. P. 32(g), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

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