Review article

Patenting antibody combination therapies

Li Feng*, Lin Chen[†], Amanda Murphy[†], Jeffrey Jacobstein[†] and Stacy Lewis[†]

Finnegan, Henderson, Farabow, Garrett & Dunner LLP., 901 New York Avenue, NW, Washington, DC 20001-4413, USA

Abstract

There is emerging, intense interest in antibody combination therapies. However, antibody combination therapies pose unique intellectual property challenges. In some instances, it may be difficult to obtain patents with claims that provide innovators with adequate protection for such inventions. Patent examiners often regard claims to a composition or use of an antibody in combination with another therapeutic agent as obvious if the individual components of the combination were both known and well-studied in the field for use in treating similar indications. Nevertheless, even if the individual components of a combination were known and generally effective, the combination therapy may not be obvious if there would not have been a motivation to specifically combine the individual components or if there was no reasonable expectation of success in combining the components. Antibody combination therapies may also offer fertile grounds for demonstrating objective evidence of nonobviousness for a particular combination, such as through unexpected results, if a sufficient nexus can be established across the scope of the claims and if the superior results constitute a significant improvement.

> **Statement of Significance:** Even if the individual components of an antibody combination therapy were known and generally effective, the combination therapy may still be patentable. This article highlights valuable obviousness considerations regarding obtaining patent protection of antibody combination therapies.

KEYWORDS: Combination therapy; Patent; ADC; Invention; Obviousness

INTRODUCTION

Over the last two decades, antibody-based therapies have grown exponentially in value for treating various diseases. The estimated global market value of monoclonal antibody therapeutics was US$115B in 2018 and was expected to reach US$300B by 2025.[1] In 2019, 8 of the top 10 top-selling prescription drugs in the USA were antibodies.[2] There is emerging, intense interest in combination therapies comprising an antibody, including: combinations of monoclonal antibodies (e.g., for targeting multiple checkpoint inhibitors); multispecific antibodies (e.g., an antibody that simultaneously binds to two unique antigens or different epitopes on the same antigen); antibody-drug conjugates ("ADCs," typically a combination of a targeting antibody conjugated to a small molecule cytotoxic "payload"); antibody-cytokine fusion proteins; antibody-RNA combinations; and antibody-vaccine combinations.

However, such antibody combination therapies pose unique intellectual property (IP) challenges. In our experience, it may be difficult in some instances to obtain patents with claims that provide innovators with adequate protection for such inventions. For example, patent examiners often regard claims to a composition or use of an antibody in combination with another therapeutic agent as obvious, if the individual components of the combination were both known and well-studied in the field for use in

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*To whom correspondence should be addressed: Li Feng, Finnegan, Henderson, Farabow, Garrett & Dunner LLP., 901 New York Avenue, NW, Washington, DC 20001-4413. Email: li.feng@finnegan.com

[†]Lin Chen, Amanda Murphy, Jeffrey Jacobstein and Stacy Lewis are coauthors.

treating similar indications. There may also be data support issues with respect to antibody combination therapy claims. For example, claims broadly reciting the benefits of targeting two pathways—but without describing the specific inhibitors used to target each pathway—may face examiner rejections for lack of written description support and/or lack of enablement in the patent specification. In addition, other players in the field may have already created a maze of IP rights in their own patents that could be difficult to circumvent. Indeed, any developer wishing to market its antibody combination therapy may need to avoid not only third-party patents that cover each individual product, but also any patents embracing the combination. In this article, we focus on obviousness issues inventors must account for when seeking patent protection for this promising class of therapy.

LEGAL STANDARD OF OBVIOUSNESS

A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. The determination of obviousness under 35 U.S.C. § 103 depends on at least four underlying factual issues set forth by the US Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966), and confirmed in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 399 (2007):

> (1) the scope and content of the prior art;
> (2) differences between the prior art and the claims at issue;
> (3) the level of ordinary skill in the pertinent art; and
> (4) evaluation of any relevant secondary considerations.

The test for obviousness is often articulated as whether "a skilled artisan would have had *reason to combine* the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had *a reasonable expectation of success* from doing so."[3] (emphasis added). Under the first three factors above, if the art was unpredictable and if there was no motivation to combine the teachings of the prior art with a reasonable expectation of success of arriving at the claimed invention, the courts have typically upheld claims as nonobvious, even if all elements of the claimed invention were disclosed in one or more prior art references.[4]

Under factor four above, evidence pertaining to secondary considerations of nonobviousness (also known as objective evidence), such as unexpected results, commercial success, long-felt but unmet need, and copying by competitors, must be taken into account if submitted. However, when there is a strong motivation to combine known prior art elements with predictable results, weak evidence of secondary considerations may not preclude a finding of obviousness.[5] Finally, secondary considerations must have a nexus to the claimed invention (i.e., a causal relationship between the evidence and the claimed invention) in order to have any bearing on the determination of nonobviousness.[6]

PTAB CASES ON ANTIBODY COMBINATION THERAPIES

We are not aware of much case law arising from federal district court litigations directly commenting on obviousness issues regarding antibody combination therapies. However, the Patent Trial and Appeal Board (PTAB) at the United States Patent and Trademark Office has evaluated the patentability of such therapies. We therefore review several PTAB cases (from post grant proceedings and *ex parte* appeals) to illustrate how obviousness is analyzed for claims directed to antibody combination therapies.

Post grant proceedings at the PTAB generally include *inter partes* review (IPR) and post grant review (PGR). In a typical IPR or PGR proceeding, a Petitioner first files a petition to the PTAB requesting review of one or more claims of a granted patent. If the PTAB agrees to review the patent to reassess patentability of the issued claims, it "institutes" the review. Next, the Patent Owner and the Petitioner present evidence and arguments to support their respective positions. The PTAB then issues a final written decision determining whether the challenged claim(s) is patentable (i.e., whether the claim survives the challenge). Such a decision can be appealed to the Court of Appeals for the Federal Circuit. So far, IPR and PGR challenges to antibody combination therapy patents have been instituted just about as frequently as for challenges to other types of biotech patents or patents overall, but there is a noticeably higher claim survival rate for antibody combination therapy claims compared to other technologies (see Fig. 1). As further illustrated below in several representative IPR cases, it appears that, while antibody combination therapy patents are vulnerable to obviousness attacks when they bring together known monotherapies that were already published in the art, a Patent Owner may successfully defend such patents by relying on a showing that the prior art taught away from the claimed combination, or by arguing a lack of reasonable expectation of success due to the "unpredictability" recognized in the art, and/or by pointing to unexpectedly surprising results from the claimed combination.

IPR2017-01121, 02063, and 00731

We turn first to three IPRs that challenged US Patent No. 7,846,441 ("the '441 patent"), which claimed cancer treatment methods using an ADC of an anti-ErbB2 antibody that binds to epitope 4D5 (e.g., HERCEPTIN®) and a taxoid compound. No claims of the '441 patent survived the IPR challenges, and the Court of Appeals for the Federal Circuit affirmed the PTAB's determination that the claims were unpatentable as obvious.[7]

Claim 1 of the '441 patent is representative and recited:

> A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative, to the human patient in an amount effective
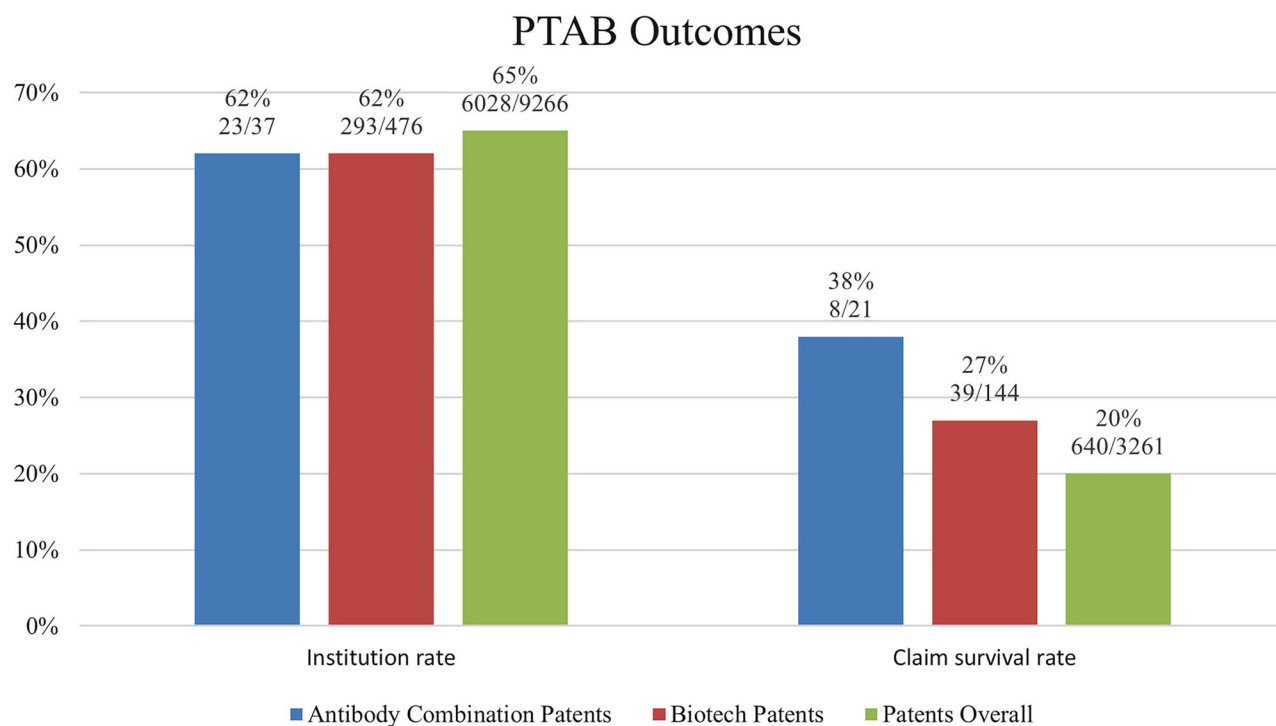
PTAB Outcomes

Figure 1. Antibody combination therapy patent statistics and biotech patent statistics, based on Finnegan research, 16 September 2012 to 5 August 2020; United States Patent and Trademark Office (USPTO), 16 September 2012 to 30 June 2020, https://www.uspto.gov/patents-application-process/patent-trial-and-appealboard/statistics. Institution rate = petitions granted/(petitions granted + petitions denied). Claim survival rate only includes Final Written Decisions in which all challenged claims were held not unpatentable. It does not include mixed outcomes in which at least one claim was held unpatentable and at least one claim was held not unpatentable. Such mixed outcomes account for about 10% of antibody combination therapy patents (2/21), about 13% of biotech patents (18/144), and about 18% of patents overall (588/3,261). It should be noted that the sample size for antibody combination therapy patents is small and, therefore, the statistics are more volatile than for larger sample groups.

to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

The PTAB found that the prior art references cited in the petitions "show 'apparent synergy' between rhuMAb HER2 [an anti-ErbB2 antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence] and paclitaxel [a taxoid]" in a mouse model of cancer.[8] The PTAB further noted that the mouse studies in the prior art were "a reliable predictor of success in humans."[9] Interestingly, the PTAB also considered Patent Owner's statements to the FDA as support for showing obviousness because, there, Patent Owner relied on one of the asserted prior art references to show expected efficacy when requesting approval to test the combination of trastuzumab and paclitaxel.[10] This highlights another potential challenge patent owners sometimes face in the tension between seeking protection for an antibody combination therapy at the Patent Office (which may require the patent owner to argue unpredictability), and seeking regulatory approval from the FDA (which may require the reference-product sponsor to argue predictability).

The Patent Owner presented objective evidence of nonobviousness in the form of commercial success, unexpected results, and long-felt-but-unmet need, but the evidence was rejected as lacking sufficient nexus to the claimed invention.[11] For instance, with respect to

commercial success based on the Herceptin sales, the PTAB noted that the challenged claim "requires the combination of an anti-HER2 antibody and a taxoid. Herceptin, however, was also approved for single-agent use."[12] Thus, the PTAB found that the Patent Owner "has not shown what portion of the sales of Herceptin is attributable to the claimed combination, and not the single-agent use."[13] And because the Patent Owner had not established a nexus between the objective evidence of nonobviousness and the claimed invention, the PTAB concluded that the evidence was not sufficient to overcome the strong case of obviousness established by the prior art.

Phigenix, Inc. v. Genentech, Inc., **IPR2014-00842**

In IPR2014–00842, Petitioner challenged the claims of U.S. Patent No. 7,575,748 ("the ′748 patent"), which protects Genentech's ado-trastuzumab emtansine product sold under the trade name Kadcyla®. The ′748 patent describes immunoconjugates comprising an anti-ErbB antibody, such as the humanized anti-ErbB2 antibody known as HERCEPTIN® (huMAb4D5–8), linked to a maytansinoid toxin.

Claim 1 of the ′748 patent is representative and reads:

> A method for the treatment of a tumor in a mammal, comprising the steps of

1. identifying said tumor as being characterized by overexpression of an ErbB2 receptor and as being *a tumor that does not respond, or responds poorly, to treatment with an anti-ErbB antibody*, and
2. intravenously administering to the mammal a therapeutically effective amount of a conjugate of a humanized antibody huMab 4D5-8 covalently linked via a thioether linking group with a maytansinoid DM1 having the structure
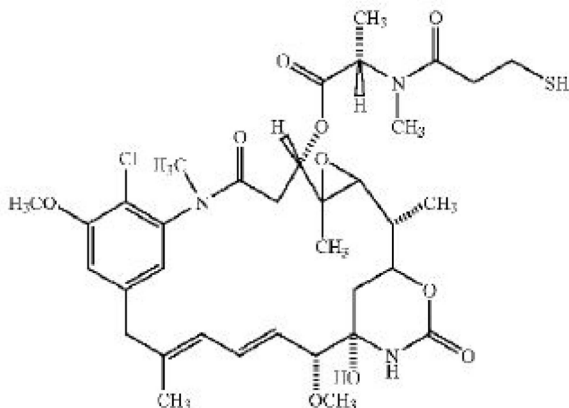
at a dose of between about 0.2 mg/kg and about 10 mg/kg (antibody-maytansinoid conjugate weight/-body weight) and at a frequency of dosing selected from the group of dosing frequencies consisting of bolus, less than about one time per week, one time per week, two times per week, more than two times per week, and continuous infusion, whereby said tumor characterized by overexpression of an ErbB2 receptor and that does not respond, or responds poorly, to treatment with an anti-ErbB antibody, is treated.

The asserted prior art references included the HERCEPTIN® label as well as other art disclosing immunoconjugates comprising the maytansinoid toxin, DM1, chemically coupled to a mouse antibody targeting ErbB2 receptor, which is known to be expressed at high levels on human breast tumor cells. According to Petitioner, while the cited art on maytansinoid conjugates does not expressly teach using huMAB4D5–8 as the antibody portion of the ADC, the HERCEPTIN® label "describes the use of huMAB4D5-8 (i.e., HERCEPTIN®) for the treatment of human patients with metastatic breast cancer, and specifically tumors characterized by overexpression of an ErbB2 receptor."[14]

The primary dispute centered on the claim limitation requiring the identifying and treating of a tumor that "does not respond, or responds poorly, to treatment with an anti-ErbB antibody."[15] Petitioner asserted that "the HERCEPTIN® Label discloses the 'identifying' such a tumor, and an ordinary artisan would have been motivated to treat such a tumor using a HERCEPTIN® conjugate."[16] The PTAB rejected the Petitioner's argument because, to the extent the HERCEPTIN® label identified patients that do not respond (or respond poorly) to a particular type of therapy, it does not suggest whether or how to treat these patients.[17] Specifically, the PTAB stated:

> We are not persuaded, however, that the Petition has advanced sufficient reasoning, based on a rational underpinning, to support its contention that the Label (alone or in combination with Chari 1992) discloses or suggests that patients unresponsive to HERCEPTIN® would respond to the HERCEPTIN® antibody, if administered with chemotherapy.[18]

The PTAB also responded favorably to Patent Owner's evidence that one of ordinary skill in the art would have thought HERCEPTIN® was in fact a poor choice because the patients in question likely had HERCEPTIN® resistance.[19]

Since all of the asserted grounds principally relied upon the HERCEPTIN® label, and none of the other art remedied its deficiency, the PTAB denied the IPR petition and all challenged claims survived.[20]

Phigenix, Inc. v. Immunogen, Inc., IPR2014-00676

In IPR2014-00676, Petitioner challenged the claims of US Patent No. 8,337,856 ("the ′856 patent") as obvious. The ′856 patent is in the same patent family as the ′748 patent challenged in IPR2014-00842, discussed above. The asserted grounds in IPR2014-00676 were based on some of the same references submitted in IPR2014-00842, including the HERCEPTIN® label.

Claim 1 of the ′856 patent is representative and reads:

> An immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid, wherein the antibody is huMAb4D5–8.

Petitioner relied on a prior art reference teaching immunoconjugates comprising an anti-ErbB2 mouse antibody chemically coupled to the maytansinoid toxin, DM1, and argued that this reference met all the limitations of claim 1 "except that it does not disclose huMAB4D5-8."[21] According to Petitioner, it would have been obvious to the ordinarily skilled artisan to substitute the mouse anti-ErbB2 antibody of the prior art immunoconjugates with the humanized mAb huMAB4D5-8 disclosed in the HERCEPTIN® label to reduce immunogenicity in humans, based on "the general knowledge in the art at that time."[22]

Patent Owner countered that, at the time the ′856 patent was filed, HERCEPTIN®-maytansinoid immunoconjugates "would have been expected to exhibit unacceptable levels of antigen-dependent toxicity in normal human liver tissue in patients."[23] In view of Patent Owner's arguments and evidence, the PTAB concluded that Petitioner had not carried its burden of establishing that the asserted references would have motivated one of ordinary skill in the art to arrive at the claimed immunoconjugates with a

reasonable expectation of success in view of the general understanding of "unacceptable" toxicity.[24]

Interestingly, the PTAB provided additional analysis regarding dependent claims 6 and 8 of the '856 patent. Both claims differ from claim 1 in that they further recite a specific noncleavable linker. Claim 8 additionally requires that the maytansinoid be DM1, and the claim is therefore directed specifically to Kadcyla®. The PTAB noted that Patent Owner's "substantial" objective evidence of nonobviousness, including unexpected superior results as compared to the closest prior art compositions, fulfilling a long-felt and unmet need, praise in the field, and commercial success, supported a finding of nonobviousness.[25] In addition, a sufficient nexus was also found because Patent Owner tied the objective evidence to the claimed invention:

> Patent Owner sufficiently establishes that it is the exact combination of those components recited in claim 8, rather than different components previously combined in the prior art, that provided the unexpected results at issue, and led to praise and commercial success.[26]

As a result, all of the claims of the '856 patent survived the IPR challenge.

Ex Parte Minh Diem Vu, App. No. 14/783,775, Appeal No. 2018-008737 (P.T.A.B. November 25, 2019)

In addition to third-party challenges to granted patents, the PTAB has also addressed combination antibody claims in an appeal of a patent application rejected by an examiner at the USPTO. The *Ex Parte Minh Diem Vu* case involved an appeal from an examiner's final rejection during prosecution of a patent application. Claim 18 was representatives and read:

> 18. A method of treating an ROR1-positive hematological malignancy comprising[:]
>
> administering a trivalent bispecific antibody which specifically binds human CD3ε (CD3) and the extracellular domain of human ROR1 (ROR1), wherein the antibody comprises ROR1 Fab-Fc-CD3 Fab-ROR1 Fab (Fig. 1(1)), to a subject in need thereof,
>
> wherein the ROR1-positive hematological malignancy is selected from the group consisting of: chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), diffuse large B cell lymphoma (DLBCL), multiple myeloma (MM), and follicular lymphoma (FL).

The cited prior art taught each of the components that had been brought together in the claimed trivalent, bispecific antibody. Specifically, the two references cited by the Examiner and reviewed on appeal taught an anti-CD3 fragment and an anti-ROR1 fragment, respectively, and both references stated that bispecific embodiments comprising their respective antibody fragments may be beneficial in treating hematological malignancy, as claimed. The Examiner found the claim obvious over the prior art combination, arguing that a "skilled artisan would have been motivated to combine the [prior art] antibody constructs for advantages in cancer treatment, and … could have reasonably expected to successfully combine the references for such a purpose because each reference indicates that its molecules could be fabricated and provided as therapy by no more than routine, well-known techniques in the art."[27]

The Applicant argued that there would have been many options for a person of ordinary skill in the art to choose from ("seven hundred possible antibody fragment combinations"), the prior art did not provide sufficient guidance as to which one would work, and the field of treating cancer is complex and unpredictable.[28]

However, the Board agreed with the Examiner, relying heavily on the holding of the Supreme Court case *KSR* that "the combination of familiar elements or steps according to known methods is likely to be obvious when it does no more than yield predictable results." In particular, the Board noted that although treating cancer is somewhat unpredictable in general, both prior art references disclose that their antibody fragments target blood cancer cells for effective therapeutic treatment and the references were presumed enabled.[29] In addition, the Board noted:

> There is a universal, strong motivation in the therapeutic arts to develop cancer treatments and there would be logical motivation to combine cancer therapies in routine ways that have been identified as useful for a common purpose.[30]

The Board also stated that "conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."[31]

Finally, the Board rejected the Applicant's objective evidence of unexpected results. In particular, the Board noted that "[a]lthough Appellant has presented some evidence of improvements with an embodiment appearing to fall within the scope of the invention over comparative examples, the evidence does not clearly compare the results achieved in the invention with the closest prior art and does not clearly show an improvement in kind versus a mere improvement by degree so as to be particularly persuasive."[32] In addition, the Board noted that "there is no evidence" other than "Attorneys' argument" that the results shown in the specification were unexpected.[33] After receiving the Board's decision, the Applicant reopened prosecution and is currently pursuing claims reciting antibodies identified by specific complementarity-determining region sequences.

CONCLUSION

As can be seen from the early case law that is emerging at the PTAB, antibody combination therapies produce a unique set of obviousness considerations. The main battleground for obviousness challenges seems to be whether there is a reasonable motivation to modify and/or combine the prior art, particularly where components of the combination

were separately disclosed in the literature. Winning this argument will depend heavily on expert testimony as to what an ordinary person of skill in the art would understand from the patent and from the prior art.

Several observations emerge from the case review. First, even if the individual components of a combination were known and generally effective (either as stand-alone therapies or with other active agents), there still may not have been a motivation to specifically combine the claimed elements if, for example, the general state of the art taught away from the particular combination (e.g., expected unacceptable toxicity). Second, there may also be no reasonable expectation of success in combining the products if the art established significant "unpredictability" in doing so, which may often be the case in combinations targeting indications such as cancer. Third, antibody combination therapies offer fertile grounds for demonstrating objective evidence of nonobviousness for a particular combination, such as through unexpected results (e.g., unexpected superior efficacy and/or tolerability compared to the closest prior art, either through expert testimony or through comparative testing), if a sufficient nexus can be established across the scope of the claims and if the superior results constitute a significant improvement (i.e., a difference in kind and not merely in degree).[34] Even though the objective evidence may not always be sufficient to outweigh a strong case of obviousness (e.g., when the prior art teaches a strong motivation to combine with predictable results), the Patent Owner nonetheless should strive to marshal all possible secondary evidence of nonobviousness to tip the balance.

Lastly, obtaining data (e.g., clinical trial results to show superiority) is important and likely necessary to support antibody combination therapy patents. If the patents are filed too late, publications (e.g., on clinicaltrials.gov) might become prior art and/or motivate third parties to file patents covering the space. On the other hand, if the patents are filed too early, the developer may not have the data needed to support the combination claims. Thus, a developer of antibody combination therapies should carefully balance (1) the need to file patent applications before too much information on the clinical trial design emerges against (2) the need to generate data in support of the claimed combination.

ACKNOWLEDGEMENT AND DISCLAIMER

Notes

1. Lu, R., Hwang, Y., Liu, I. *et al.*, "Development of therapeutic antibodies for the treatment of diseases." *J Biomed Sci* 27, 1 (2020). https://doi.org/10.1186/s12929-019-0592-z
2. https://www.pharmaceutical-technology.com/features/top-selling-prescription-drugs/
3. *Par Pharm. Inc. v. TWI Pharms. Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014)
4. *See, e.g., Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1366–67 (Fed. Cir. 2012).
5. *See, e.g., Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).
6. *See, e.g., Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 305 (Fed. Cir. 1985).
7. *See Celltrion Inc. v. Genentech, Inc.*, IPR2017–01121, *Pfizer v. Genentech, Inc.*, IPR2017–02063, *Hospira v. Genentech, Inc.*, IPR2017-00731, and *Genentech v. Iancu*, 809 Fed. Appx. 781 (Fed. Cir. 2020).
8. *Hospira v. Genentech*, IPR2017–00731, Paper 120, at *23 (P.T.A.B. Oct. 3, 2018).
9. *Same* at *26.
10. *Same* at *27–28.
11. *Same* at *40–43.
12. *Same* at *40.
13. *Same* at *41.
14. *Phigenix, Inc. v. Genentech, Inc.*, IPR2014–00842, Paper 10, at *12 (P.T.A.B. Dec. 9, 2014).
15. *Same.*
16. *Same.*
17. *Same* at *13.
18. *Same* at *15–16.
19. *Same* at *16–17.
20. *Same* at *18–20.
21. *Phigenix, Inc. v. Immunogen, Inc.*, IPR2014–00676, Paper 39, *11 (P.T.A.B. Oct. 27, 2015).
22. *Same* at *12.
23. *Same* at *16.
24. *Same* at *16–21.
25. *Same* at *23–25.
26. *Same* at *25.
27. *Ex Parte Minh Diem Vu*, App. No. 14/783,775, Appeal No. 2018–008737, at 15 (P.T.A.B. Nov. 25, 2019).
28. *Same* at *15–16.
29. *Same* at *16.
30. *Same* at *18–19.
31. *Same* at *24.
32. *Same* at *28.
33. *Same.*
34. See *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) ("Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time."); *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015) (The court found a difference in kind because "the record shows that the claimed amounts of the two different ingredients could and did materially and unpredictably alter the property of the claimed formulation.").