United States Court of Appeals for the Federal Circuit

2009-1270
(Serial No. 09/719,045)

IN RE ANDREW P. CHAPMAN and DAVID J. KING

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Appealed from: United States Patent and Trademark Office
Board of Patent Appeals and Interferences

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Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences.

DECIDED: February 24, 2010

Before GAJARSA, CLEVENGER, and DYK, Circuit Judges.

DYK, Circuit Judge.

Andrew Paul Chapman and David John King (collectively, "Chapman") appeal from a final decision of the United States Patent and Trademark Office, Board of Patent Appeals and Interferences ("Board"). The Board found claims 1-10 and 12-15 of Chapman's Application Serial No. 09/719,045 unpatentable as obvious. Ex Parte Chapman, No. 2008-0454 (B.P.A.I. May 27, 2008) ("Initial Decision"); (B.P.A.I. Dec. 11, 2008) ("Final Decision"). For the reasons set forth below, we vacate and remand for further proceedings.

BACKGROUND

The technology in this appeal concerns divalent antibody fragments. Antibodies are proteins made of amino acids and bind to antigens to inactivate them as a part of an

immune response. The basic functional units of antibodies are “Y”-shaped and have two identical light chains and two identical heavy chains.

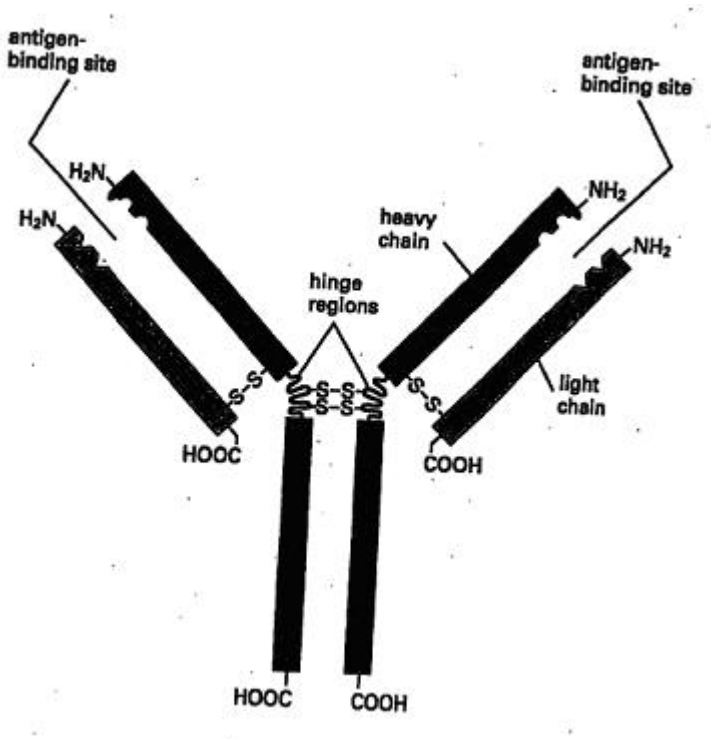

Figure 1.

Appellee’s Br. 1-Reverse. As denoted above, each arm of the Y-shape is formed by one light chain and one heavy chain. The two chains are linked by a chemical bond known as a disulphide bridge. The two “arms” of the Y-shape are also linked by disulphide bridges. Disulphide bridges (denoted above as S-S) are formed by a covalent bond between two sulphur atoms from the thiol (-SH) groups in the amino acid cysteine on each chain. At the upper end of each branch of the “Y” are the variable regions of the antibody, which are the locations at which the antibody binds to antigens, i.e., the antigen-binding sites.

Whole antibodies are less than ideal for certain diagnostic and therapeutic uses due to their size, which inhibits distribution to the tissue. In addition, their long half-lives in the body can affect diagnostic sensitivity and cause toxicity. Antibody fragments are preferable to whole antibodies for these uses as they are distributed more rapidly from the blood to tissues than whole antibodies. Antibody fragments may also be preferable to whole antibodies because they are cleared more rapidly from the circulation, i.e., they have a shorter circulating half-life.

Antibody fragments are produced by digesting antibodies using specific enzymes. When an antibody is digested by the enzyme pepsin, the enzyme cleaves the antibody below the “arms” of the “Y,” removing the “stem” of the “Y” to generate a $F(ab')_2$ fragment. This is shown in the following figure.

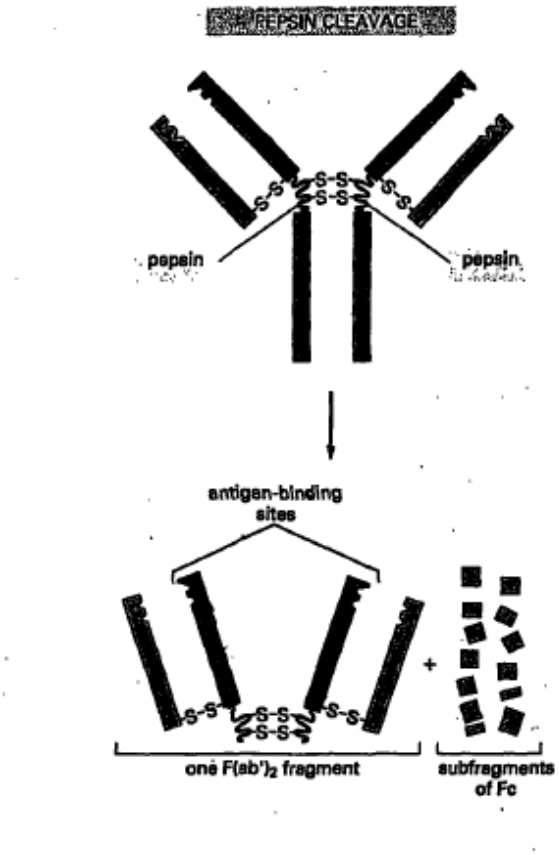

Figure 2.

Appellee's Br. 2-Reverse. A $F(ab')_2$ fragment is comprised of two Fab' fragments, linked at the hinge regions, and is dumbbell-shaped. It is also described as "divalent," because it has two antigen binding sites, one at the end of each arm.[1] A Fab fragment is designated as Fab' when it has at least one cysteine residue in the hinge region of the fragment (see Figure 1 for the hinge region). A Fab' fragment is denoted as Fab'-SH when the cysteine residue(s) have a free thiol (-SH) group.

[1] A single Fab fragment is "monovalent" because it only has one antigen binding site.

When a $F(ab')_2$ antibody fragment is digested by the enzyme papain, the disulphide bridges between the two "arms" are broken, and two separate Fab' fragments are formed.

Chapman's application is directed to divalent antibody fragments comprising two antibody heavy chains and at least one polymer molecule attached to the heavy chains in a site-specific manner on each chain. Among other things, Chapman teaches combining two separate Fab' fragments (with their light chains removed) using an interchain bridge that contains at least one covalently linked polymer. This interchain bridge indirectly links the sulphur atom of a cysteine residue in one heavy chain to the sulphur atom of a cysteine residue in the other heavy chain via the intervening polymer, rather than having the chains be linked through disulphide bridges. Claim 1, below, is representative; all other claims depend from claim 1.[2]

> 1. A divalent antibody fragment comprising
>
> [a] two antibody heavy chains and
> [b] at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage,
> [c] each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain, said cysteine residues being located outside of the variable region domain of each chain, characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.

[2] The Board noted that claims 2-10, 12, 13, and 15 "fall with claim 1" because separate reasons for their patentability were not provided. Initial Decision, slip op. at 10 (citing 37 C.F.R. § 41.37(c)(1)(vii)). For that reason, only claim 1 is discussed on appeal.

(brackets added). The intervening polymer is characterized as "effective for increasing the circulating half-life" of the antibody fragment. Initial Decision, slip op. at 1-2. Chapman's invention involves joining together two fragments with an interchain bridge containing a polymer, thus achieving a circulating half-life that is intermediate between that of an individual fragment and a whole antibody. Chapman does not dispute the examiner's characterization of Chapman's claimed antibody fragment as being "dumbbell-shaped." See Appellant's Br. 20-23.

U.S. Patent No. 6,025,158 ("Gonzalez") is prior art to Chapman's application. Gonzalez describes linking antibody fragments to a polymer to increase an antibody's circulating half-life for therapeutic purposes. Gonzalez Abstract; id. col.1 ll.13-19; id. col.13 ll.15-24; id. col.15 ll.32-36. Gonzalez notes that the prior art established that a particular polymer, polyethylene glycol ("PEG"), "attached to a sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule." Id. col.1 ll.38-42. Gonzalez discloses, among other things, a single antibody fragment linked to a polymer(s); a "dumbbell-shaped" structure made up of two antibody fragments joined by a polymer; and a "rosette" or other shaped structure composed of more than two antibody fragments joined by a polymer(s). Id. col.35 ll.38-57. Gonzalez also teaches the preparation of antibody fragment-polymer conjugates. It identifies Fab, Fab', Fab'-SH, $F(ab')_2$, scF_v, and F_v as possible choices for the antibody fragment, id. col.21 ll.33-35, and identifies PEG as a potential polymer, id. col.26 ll.39-40. Gonzalez teaches how to attach the polymer to a particular amino acid residue or a particular region; in some embodiments, it teaches doing so without using a disulphide bond.

Gonzalez col.19 ll.35-43. Gonzalez teaches a preference for the cysteine residue as an attachment point. Gonzalez specifically teaches a preference for the cysteine residue in the hinge region of the antibody fragment. See, e.g., id. col.19 ll.62-65. Gonzalez discloses, in its only complete working example, linking PEG to the hinge cysteine of a Fab' heavy chain to make a Fab'-PEG conjugate. Id. cols. 120-23. Like Chapman, Gonzalez discloses that attaching a polymer to an antibody fragment achieves a clearance rate intermediate to that of a whole antibody and that of an individual fragment without an attached polymer. See id. col.1 ll.38-42. U.S. Patent No. 5,436,154 ("Barbanti") is also prior art to Chapman's application. Barbanti describes the use of antibodies for in vivo therapy.

The examiner rejected claims 1-10, 12, 13 and 15 of Chapman's application under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over, Gonzalez. Initial Decision, slip op. at 3. The examiner also rejected claims 1, 13, and 14 under 35 U.S.C. § 103(a) as obvious over Gonzalez and Barbanti. Id. Chapman appealed to the Board.

In analyzing the examiner's rejections, the Board took claims 1, 13 and 14 as representative. Id. The examiner made, and the Board adopted, a number of fact findings ("FFs") concerning the scope of Gonzalez. Relevant for the purposes of this appeal are FFs 3, 7, 8, and 12, which are set out below.

> [FF] 3. The antibody can be a monovalent Fab fragment, a monovalent Fab' fragment which includes one or more cysteine residues in the constant region, or an $F(ab')_2$ antibody fragment which has a hinge cysteine between the Fab' fragments (Gonzalez, at col. 11, ll. 57-66; Ans. 5).

> . . . .
> [FF]7. Gonzalez also describes conjugates containing a F(ab')$_2$ antibody fragment in which the polymer is attached between the disulphide bridge that would ordinarily link the heavy and lights [sic] chains (Gonzalez, at col. 21, 50-59). In this embodiment, the polymer is attached to a cysteine in the light or heavy chain; the cysteine in the opposite chain is replaced with another amino acid to avoid forming a disulphide bond between the chains (id.).
>
> [FF]8. In another embodiment, Gonzalez describes antibody conjugates in which 'a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure . . . [sic] Such structures can be made by using a polymer molecule derivatized with multiple functional groups permitting the direct attachment, or the attachment by means of bi- or multi-functional linkers, of two or more antibody fragments to the polymer backbone.' (Gonzalez, at col. 35, ll. 45-57; at col. 41, ll. 41-43; see Ans. 5).
> . . . .
> [FF]12. In regard to the obviousness of the claimed structure, the Examiner states there are explicit teachings of a dumbbell-shaped structure (FF 8) and a Fab' conjugated to PEG in the hinge region via a cysteine residue (FF 6).

Initial Decision, slip op. at 4-6.

The Board reversed the examiner's anticipation rejection over Gonzalez because

> although Gonzalez suggests the antibody structure of claim 1, too much in the way of mental gymnastics would have been necessary for persons of ordinary skill to have 'at once envisage[d]' the claimed antibody structure among the different structures described in the Gonzalez patent . . . . [P]icking and choosing would have been necessary to have arrived at the antibody structure of claim 1.

Id. at 12-13. However, the Board affirmed the examiner's findings and legal conclusion that Chapman's claims 1-10, 12, 13, and 15 would have been obvious over Gonzalez. Id. at 1-10. The Board also affirmed the examiner's rejection of claims 1, 13, and 14 as obvious over Gonzalez in view of Barbanti. Id. at 14-16.

With respect to obviousness over Gonzalez, the Board observed that Gonzalez teaches linking two antibody fragments with a polymer to form a "dumbbell-shaped" structure. Id. at 8-9. The Board also noted that Gonzalez teaches a Fab molecule with a PEG linked to the hinge cysteine of the heavy chain. Id. at 8. The Board then concluded that "the only issue—as recognized by the Examiner—is whether persons of skill in the art would have had reason to join the [Fab'] fragments together using a polymer linked to the hinge cysteine residue." Id. at 8. (citation omitted).

The Board ultimately agreed with the examiner that Gonzalez would have led a skilled artisan to utilize the claimed hinge cysteine because of Gonzalez's preference for linking a polymer there. Id. In particular, the Board observed that Gonzalez refers to prior art that establishes that linking a PEG to the "hinge region of a Fab fragment reduced clearance compared to the parental Fab' molecule . . . ." Id. In addition, the Board emphasized that Gonzalez discloses a complete working example in which a polymer is attached to the hinge cysteine of the heavy chain. Id. at 8-9. Based on these disclosures, the Board found that

> Gonzalez's teaching of the dumbbell-shaped structure, without more guidance in how to make it, together with the disclosure of stable Fab' fragments with a polymer conjugated to a cysteine of the hinge region . . . would have suggested to the ordinary skilled person that such Fab' fragments could be readily linked polymer to polymer using a bifunctional linker, as explicitly stated by Gonzalez when characterizing the dumbbell-shaped antibody structure (FF8).

Id. at 9. By linking the Fab' fragments together at the hinge cysteines using PEG as a linker, a skilled artisan would arrive at Chapman's invention. Id. The Board rejected Chapman's argument that Gonzalez "teaches away" from Chapman's claimed molecule

and also rejected Chapman's argument that the examiner used impermissible hindsight in arriving at Chapman's claimed invention. Id. at 7, 9. With respect to Barbanti, the Board concluded that a person skilled in the art would have had reason to modify Barbanti's claimed antibody fragment with PEG in order to extend its serum half-life (reduce its clearance time) thereby increasing its therapeutic efficacy. Id. at 15. Chapman requested rehearing, and on rehearing, the Board sustained the finding of obviousness. This appeal followed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. § 141.

DISCUSSION

The Patent and Trademark Office ("PTO") is governed by the Administrative Procedure Act ("APA"), and PTO decisions are reviewed under the APA standard. Dickinson v. Zurko, 527 U.S. 150, 152 (1999). Thus, we review Board's legal conclusions without deference, and review its findings of fact to determine if they are supported by substantial evidence. See Hitzeman v. Rutter, 243 F.3d 1345, 1353-54 (Fed. Cir. 2001); see also 5 U.S.C. § 706(2).

On appeal, Chapman contends that the Board erred as a matter of law in finding representative claims 1, 3, and 14 obvious alone over Gonzalez or in view of Barbanti. Both parties agree that the sole question on appeal is the accuracy of the Board's description of Gonzalez, the primary reference.

Whether an invention would have been obvious is a legal question based on underlying findings of fact, including (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention

and the prior art; and (4) objective evidence of nonobviousness. In re Gartside, 203 F.3d 1305, 1319 (Fed. Cir. 2000) (citing, ultimately, Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)).

At the outset, Chapman urges that we should reverse the Board's decision finding Chapman's application obvious and conclude that the subject matter of Chapman's invention is non-obvious as a matter of law. Chapman argues that "Gonzalez describes two antibody fragments linked together by polymer molecules to form a dumbbell-shaped structure, but does not specify how and where the antibody molecules are linked by the polymer molecules, or what fragments are to be used." Appellant's Br. 5. To the extent that Chapman argues that there is no motivation to modify Gonzalez to arrive at Chapman's claimed invention, we think that this issue is best addressed in the remand that we order below to correct certain errors in the Board's decision.

Chapman's argument for reversal also rests on his claim that Gonzalez "teaches away" from Chapman's claimed invention as a matter of law. A finding that a reference teaches away can preclude a finding that the reference renders a claim obvious. See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."). Whether or not a reference teaches away from a claimed invention is a question of fact. See In re Napier, 55 F.3d 610, 613 (Fed. Cir. 1995).

Chapman argues that Gonzalez teaches away from Chapman's claimed invention because Gonzalez teaches the existence of multiple locations on an antibody fragment to which a polymer molecule, or multiple polymer molecules, can be attached. Chapman's apparent theory is that even though Gonzalez shows a preference for attachment at a hinge cysteine residue, the fact that Gonzalez teaches other attachment points "teaches away" from using the hinge cysteine as an attachment point for the polymer. However, Gonzalez specifically discloses a preference for the hinge cysteine as an attachment point for a polymer. See, e.g., Gonzalez, col.19 ll.56-65, col.19 ll.40-46, cols.102-123. Moreover, Gonzalez offers this teaching to solve the very problem that Chapman was trying to solve here—increasing the circulating half-life of the antibody fragment. Id. col.15 ll.15-24. Therefore, Gonzalez does not teach away from using the hinge cysteine as an attachment for a polymer. Further, Chapman argues that while Gonzalez teaches attaching a polymer to a $F(ab')_2$ fragment, Gonzalez does not teach using the polymer as a bridge. While it may be correct that Gonzalez does not explicitly teach using the polymer as a bridge between the two fragments, Gonzalez does not teach away from doing so.

Alternatively, Chapman argues that three of the Board's factual findings concerning the scope and content of Gonzalez are not supported by substantial evidence and that a reversal is required. As discussed below, the government agrees that the Board's opinion includes three erroneous statements, but the government urges that the three errors in the Board's opinion are harmless. The judicial review provision of the APA includes a harmless error rule. See 5 U.S.C. § 706 ("[D]ue account shall be

taken of the rule of prejudicial error"). We have noted that "the harmless error rule applies to appeals from the Board just as it does in cases originating from district courts." In re Watts, 354 F.3d 1362, 1369 (Fed. Cir. 2004) (citing In re McDaniel, 293 F.3d 1379, 1385-86 (Fed. Cir. 2002); Gechter v. Davidson, 116 F.3d 1454, 1457 (Fed. Cir. 1997)). We have said that

> to prevail the appellant must not only show the existence of error, but also show that the error was in fact harmful because it affected the decision below. See Munoz v. Strahm Farms, Inc., 69 F.3d 501, 504 (Fed. Cir. 1995) ("The correction of an error must yield a different result in order for that error to have been harmful and thus prejudice a substantial right of a party."); see also Palmer v. Hoffman, 318 U.S. 109, 116 (1943) ("He who seeks to have a judgment set aside because of an erroneous ruling carries the burden of showing that prejudice resulted.").

Id. The Supreme Court has recently reaffirmed that "review of ordinary administrative proceedings" is like "review of civil cases in this respect. Consequently, it is clear that the burden of showing that the error is harmful normally falls upon the party attacking the agency's determination." Shinseki v. Sanders, 129 S. Ct. 1696, 1706 (2009) (citations omitted). In the light of this standard, we proceed to consider the three errors, and whether they were harmless.

First, Chapman takes issue with the Board's statement that "the Examiner finds Gonzalez teaches a dumbbell-shaped antibody structure comprised of two monovalent Fab' fragments (FF 8, 12) and describes linking them via a polymer molecule." Initial Decision, slip op. at 7. On appeal, the government agrees that Gonzalez does not teach linking "two monovalent Fab' fragments . . . via a polymer." Indeed, the examiner's fact findings 8 and 12, relied on by the Board, do not suggest otherwise, as

the government concedes. See Oral Arg. at 18:07-18:19 ("I think that in the first instance, they conflate two correct fact findings, and the way they conflate them is not correct, so that sentence is in error, but the two fact findings are not in error . . . ."). The government contends that this error is harmless as the Board did not base its obviousness rejection on this particular statement but was simply (erroneously) describing a position taken by the examiner. We agree with the government that that Board's decision on rehearing makes clear that the Board is not relying on any such explicit disclosures in Gonzalez.

As to the second alleged error, the Board stated that "Gonzalez describes a divalent antibody in which the polymer is linked between light and heavy chains and only one cysteine residue is present." Initial Decision, slip op. at 8 (citing FF 7; Appellant's Br. 6) (emphasis added). Citing column 21, lines 50-59 of Gonzalez, the examiner's FF 7 states that Gonzalez describes conjugates containing an "$F(ab')_2$ antibody fragment in which the polymer is attached between the disulphide bridge that would ordinarily link the light and heavy chains." Id. at 4 (emphasis added). Chapman argues that both the examiner and the Board misunderstand the relevant disclosure in Gonzalez, which reads as follows:

> In yet another preferred embodiment, the conjugate contains a $F(ab')_2$ antibody fragment attached to no more than about 2 polymer molecules, wherein every polymer molecule is attached to a cysteine residue in the light or heavy chain of the antibody fragment that would ordinarily form the disulfide bridge linking the light and heavy chains, wherein the disulfide bridge is avoided by substituting another amino acid, such a serine, for the corresponding cysteine residue in the opposite chain.

Gonzalez, col.21 ll.51-59. Chapman argues that the examiner and the Board misinterpreted this passage and that in this embodiment, the polymer is not serving as a link between the light and heavy chain; it is attached to either the light or the heavy chain. The government conceded at oral argument that Chapman's reading of this passage is correct. See Oral Arg. at 24:40-24:47 ("[I]n Gonzalez . . . the polymer is attached to either the light or the heavy chain; it's not linking the light and heavy chains.").

The third alleged error concerns FF 3, wherein the Board stated that "[t]he antibody can be a monovalent Fab fragment, a monovalent Fab' fragment which includes one or more cysteine residues in the constant region, or an $F(ab')_2$ antibody fragment which has a hinge cysteine between the Fab' fragments." Initial Decision, slip op. at 4 (citing Gonzalez col.11 ll.57-66; Answer 5). However, it is clear that, as the government concedes, Gonzalez teaches six different possible antibody fragments: F(ab), F(ab'), F(ab')-SH, $F(ab')_2$, scF_v, and F_v. Gonzalez, col.21 ll.33-41; Oral Arg. at 27:58-28:00 ("There are more than three [antibody fragments] disclosed [in Gonzalez]."). FF 3 is incorrect as both parties agree that Gonzalez discloses more than three choices for an antibody fragment.[3]

The government argues that these errors are harmless, but we conclude that these errors are harmful because they increase the likelihood that Chapman was

[3] Chapman points out that the Board's rehearing decision can be read even more restrictively, i.e., to suggest that in Gonzalez, only the Fab' fragments and not even the Fab or $F(ab')_2$ fragments can be formed into a dumbbell-shaped structure. See Final Decision, slip op. at 4.

erroneously denied a patent on grounds of obviousness. If the Board based its decision on a misunderstanding of Gonzalez, its conclusions regarding obviousness are called into question. With respect to the second error, the Board was mistaken as to whether Gonzalez teaches the use of a polymer to link the light and heavy chains in a $F(ab')_2$ fragment in the cited embodiment. Therefore, Chapman's use of a polymer to link together two F(ab') fragments may be less likely to be obvious. Further, as to the third error, if the Board did not appreciate the full scope of antibody fragments disclosed in Gonzalez, we cannot be confident about its ultimate conclusion that the selection of one of them to form Chapman's molecule is obvious, as it appears that there are more possibilities from which to choose. Because we cannot say with confidence that the Board would have reached the same conclusion in the absence of these errors, we are persuaded they are indeed harmful. See Kotteakos v. United States, 328 U.S. 750, 765 (1946) ("[I]f one cannot say, with fair assurance, . . . that the judgment was not substantially swayed by the error, it is impossible to conclude that substantial rights were not affected." This is not a situation where "an agency's path, though convoluted, can be discerned." In re Huston, 308 F.3d 1267, 1281 (Fed. Cir. 2002) (quotation and citation omitted).

On remand, the Board need only revisit its conclusion of obviousness in light of a corrected understanding of Gonzalez. The Board is in no way precluded from, and indeed may be correct in, finding the claims to be obvious, particularly in the light of Gonzalez's disclosure of joining two antibody fragments together with a polymer to make a dumbbell-shaped structure.

VACATED and REMANDED

COSTS

No costs.