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Paper 16
Entered: February 12, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-02020
Patent 9,249,218 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

FRANKLIN, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Pfizer, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1 and 5–7 of U.S. Patent No. 9,249,218 B2 (Ex. 1001, "the '218 patent"). Paper 2 ("Pet."). Genentech, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 10 ("Prelim. Resp.").

We have authority under 35 U.S.C. § 314 to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); *see also* 37 C.F.R. § 42.4(a). Upon considering the Petition and the Preliminary Response, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 1 and 5–7. Accordingly, we institute an *inter partes* review with respect to those claims.

A. Related Proceedings

Petitioner and Patent Owner provide notice that Petitioner has concurrently filed a petition for *inter partes* review of certain claims of U.S. Patent No. 6,339,142 B1 (IPR2017-02019). Pet. 2; Paper 4, 3. Petitioner notes also that a "European counterpart" to the '218 patent has been the subject of several proceedings in Europe. *See* Pet. 2–3.

B. The '218 Patent

The '218 patent relates to "a method for purifying a polypeptide (e.g., an antibody) from a composition comprising the polypeptide and at least one contaminant using the method of ion exchange chromatography." Ex. 1001, 1:23–27. The contaminant is a material that is different from the desired polypeptide product, and may be a variant of the desired polypeptide. *Id*. at 5:29–31. Further, the invention provides a composition comprising a mixture of anti-HER2 antibody and one or more acidic variants thereof,

wherein the amount of the acidic variant(s) is less than about 25%. *Id*. at 3:49–53.

The Specification explains that an "acidic variant" is "a variant of a polypeptide of interest which is more acidic (e.g. as determined by cation exchange chromatography) than the polypeptide of interest." *Id*. at 5:60–62. According to the Specification, an example of an acidic variant is a deamidated variant. *Id*. at 5:62–63. The Specification states that "[i]t has been found, for example, that in preparations of anti-HER2 antibody obtained from recombinant expression, as much as about 25% of the anti-HER2 antibody is deamidated." *Id*. at 6:15–18.

The Specification explains that the term "humMAb4D5-8" refers to humanized anti-HER2 antibody comprising the light chain amino acid sequence of SEQ ID NO:1 and the heavy chain amino acid sequence of SEQ ID NO:2, or amino acid sequence variants thereof which retain the ability to bind HER2 and inhibit growth of tumor cells which overexpress HER2. *Id*. at 13:65–14:5. When referring to the rhuMAb HER2 antibody in an example, the Specification identifies parenthetically "humAb4D5-8." *Id*. at 8:14–15; 20:39–40 (Example 1). Deamidated humMAb4D5 antibody from Example 1 in the Specification has Asn30 in CDR1 (complementarity determining region) of either or both of the V_L (light chain variable domain) regions thereof converted to aspartate. *Id*. at 6:1–3; 7:67–8:1.

Additionally, the composition optionally comprises a pharmaceutically acceptable carrier. *Id*. at 3:54–55; 19:30–53. According to the Specification, "[t]he humMAb4D5-8 antibody of particular interest herein may be prepared as a lyophilized formulation, e.g. as described in [Andya]; expressly incorporated herein by reference. *Id*. at 19:54–57. The

Specification states that "[t]he polypeptide purified as disclosed herein or the composition comprising the polypeptide and pharmaceutically acceptable carrier is then used for various diagnostic, therapeutic or other uses known for such polypeptides and compositions." *Id*. at 20:25–29.

C. Claims

Independent claim 1 is representative of the challenged claims and is reproduced below:

> 1. A therapeutic composition comprising a mixture of anti-HER2 antibody and one or more acidic variants thereof,
> wherein the amount of the acidic variant(s) is less than about 25%,
> and wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated,
> and wherein the anti-HER2 antibody is humMAb4D5-8,
> and wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate,
> and a pharmaceutically acceptable carrier.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1 and 5–7 of the '218 patent on the following grounds:

Claim(s)	Basis	References
1 and 5–7	pre-AIA § 102(b), § 103(a)	Andya[1]
1 and 5–7	pre-AIA § 103(a)	Waterside[2]
1 and 5–7	pre-AIA § 103(a)	Harris[3]

Petitioner also relies upon the Declarations of Carl Scandella, Ph.D. (Ex. 1003) and Richard Buick, Ph.D. (Ex. 1042).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with

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[1] International PCT Application No. WO 97/04801 published on Feb. 13, 1997 (Ex. 1004).
[2] Harris, *Chromatographic Techniques for the Characterization of Human MAbs (slides presented at the Waterside Monoclonal Conference held at the Omni Waterside Hotel in Harborside-Norfolk, Virginia on Apr. 22–25. 1996)*(Ex. 1006).
[3] Harris, *Processing of C-terminal Lysine and Arginine Residues of Proteins Isolated from Mammalian Cell Culture*, 705 J. CHROMATOGRAPHY A 129 (1995) (Ex. 1005).

reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner asserts that the preamble of each claim, "[a] therapeutic composition" is not limiting because it merely "gives a descriptive name" to the claimed elements without adding structural limitations to those in the body of the claim. Pet. 33.

Patent Owner asserts that the phrase should be construed to mean "a composition containing a therapeutically effective amount of a polypeptide." Prelim. Resp. 17. According to Patent Owner, this construction is supported by the Specification statement that "[t]he polypeptide as disclosed herein . . . is then used for various diagnostic, *therapeutic* or other uses . . . . For example, the polypeptide may be used to treat a disorder in a mammal by administering *therapeutically effective amount* of the polypeptide to the mammal." *Id*. at 18 (quoting Ex. 1001, 20:25–31) (emphasis added by Patent Owner). Patent Owner asserts also that the Specification describes one purpose of the invention is to overcome the challenge of separating the desired protein from the mixture of compounds to a purity "sufficient for use as a human therapeutic." *Id*. at 19 (quoting Ex. 1001, 1:38–41). Thus, according to Patent Owner, the preamble "breathes life and meaning into the claims and, hence, is a necessary limitation to them." *Id*. (citing *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 866 (Fed. Cir. 1985)).

Preamble language that merely states the purpose or intended use of an invention is generally not treated as limiting the scope of the claim. *See Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp*., 320 F.3d 1339, 1345, (Fed. Cir. 2003). If the body of the claim "sets out the complete invention," the preamble is not ordinarily treated as limiting the scope of the

claim. *Schumer v. Lab. Computer Sys., Inc*., 308 F.3d 1304, 1310 (Fed. Cir. 2002). "When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention." *Eaton Corp. v. Rockwell Int'l Corp*., 323 F.3d 1332, 1339 (Fed.Cir.2003); *see also C.R. Bard, Inc. v. M3 Sys., Inc*., 157 F.3d 1340, 1350 (Fed.Cir.1998) ("[A] preamble usually does not limit the scope of the claim unless the preamble provides antecedents for ensuing claim terms and limits the claim accordingly.").

Based on the current record, we determine that the preamble reciting a "therapeutic composition" is not limiting. The term is not required to provide antecedent basis for the subsequent claim language. Indeed, the subsequent claim language sets forth, on its own, the complete structure of the invention, i.e., the elements of the composition. As evidenced by the portions of the Specification cited by Patent Owner, *see* Prelim. Resp. 18–19, the preamble term "therapeutic" merely recites a context in which the invention may be used. *See Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002). Thus, we decline to interpret the preamble to require that the composition is actually effective for this purpose.

Petitioner asserts also that the phrase "pharmaceutically acceptable carrier" means "a non-toxic carrier to recipients at the dosages and concentrations employed, and may include the carriers, excipients, and stabilizers identified in the specification." Pet. 35. Patent Owner asserts that the term need not be construed, but that it does not contest Petitioner's proposed construction. Prelim. Resp. at 19–20. In view of our analysis, we determine that construction of this, or any other, claim term is not necessary for purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g*,

Inc., 200 F.3d 795, 803 (Fed. Cir. 1999) (only terms that are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

According to Petitioner, a person of ordinary skill in the art at the time of the invention would have been "a person or a team of persons with a Ph.D. in chemistry, biochemistry, or a closely related field or the equivalent knowledge gained through, for example, an M.S. in chemistry, biochemistry, or a closely related field and 3–5 years of relevant work experience." Pet. 9 (citing Ex. 1003 ¶ 16). Additionally, Petitioner asserts that the person of ordinary skill in the art would have had "knowledge of and experience regarding protein analysis and protein chemistry, including protein preparation and purification, and formulation of therapeutic proteins for human use." *Id.* Patent Owner proposes a similar definition, except that Patent Owner (a) includes chemical engineering as an additional option for the Ph.D. or equivalent knowledge, and (b) specifies that the person would have three to five years of experience with protein chemistry. Prelim. Resp. 17.

At this stage in the proceeding, we determine that Petitioner's broader description of the level of ordinary skill in the art is sufficiently supported by the current record. Moreover, we have reviewed the credentials of Drs.

Scandella (Ex. 1003) and Buick (Ex. 1042) and, at this stage in the proceeding, we consider them to be qualified to provide their opinion on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention. We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

C. Discretionary Denial under 35 U.S.C. § 325(d)

Patent Owner asserts that we should exercise our discretion to deny the Petition 35 U.S.C. § 325(d) because each of the asserted grounds rely upon the same prior art previously considered by the Office during the prosecution of the '218 patent. Prelim. Resp. 63–64 (citing Ex. 1002,[4] 121–22, 302, and *Cultec, Inc. v. Stormtech LLC*, IPR2017-00777, Paper 7, 8 (Aug. 22, 2017) (informative) (denying institution where the same, or substantially the same prior art was considered by the examiner during prosecution)).

We have considered Patent Owner's arguments, but decline to exercise our discretion under § 325(d). Petitioner has identified three earlier applications directed to similar claims, wherein a different examiner rejected the claims over Andya. Pet. 28–32. Thus, it is unclear to us whether the examiner considered each reference regarding the instant claims sufficiently. Under these circumstances, we decline to exercise our discretion under § 325(d) to deny any ground.

[4] Ex. 1002, prosecution history of the '218 patent.

D. Anticipation by or Obviousness over Andya

Petitioner asserts that claims 1 and 5–7 are anticipated by Andya, or in the alternative, would have been obvious over Andya. Pet. 38–48.

1. Andya

Andya is an International PCT Application filed by Genentech, Inc. and published on February 13, 1997. Ex. 1004. Andya discloses a stable lyophilized protein composition which can be reconstituted with a suitable diluent to generate an isotonic, high protein concentration formulation suitable for subcutaneous administration. *Id*. at 1, 3.[5] In particular, Andya explains that a "therapeutically effective amount" of its disclosed reconstituted formulation may be administered to a mammal, "wherein the mammal has a disorder requiring treatment with the protein in the formulation." *Id*. at 5. Andya sets forth in Example 1 the development of a lyophilized anti-HER2 formulation comprising full length humanized antibody huMAb4D5-8. *Id*. at 20–21. Andya explains that overexpression of the HER2 proto-oncogene product ($p185^{HER2}$) has been associated with a variety of aggressive human malignancies. *Id*. at 20. The murine monoclonal antibody, known as muMAb4D5, is directed against the extracellular domain of $p185^{HER2}$. *Id*. Andya explains that the molecule has been humanized to improve its clinical efficacy by reducing immunogenicity and allowing it to support human effector functions. *Id*. at 20–21.

Andya states that "[i]n early screening studies, the stability of several lyophilized recombinant humanized anti-HER2 antibody (rhuMAb HER2) formulations was investigated after incubation at 5º C (proposed storage

[5] Page numbers refer to those added to the exhibit by Petitioner.

condition) and 40º C (accelerated stability condition). *Id*. at 21. Andya explains that "[i]n the liquid state, rhuMAb HER2 was observed to degrade by deamidation (30Asn of light chain) and isoaspartate formation via a cyclic imide intermediate, succinimide (102Asp of heavy chain)." *Id*.

Also in Example 1, Andya analyzed the loss of native protein due to deamidation and succinimide formation for four reconstituted rhuMAb HER2 formulations using cation exchange chromatography to measure the recovery of intact native protein. *Id*. at 26–27 (referring to Figures 5–8). The loss of native protein is depicted in Figures 5-8. The results indicate that the four formulations provide an acceptable rate of degradation under refrigerated storage conditions for thirty days after reconstitution with bacteriostatic water for injection (BWFI). *Id*.

Andya Figures 5–8 are set forth below:

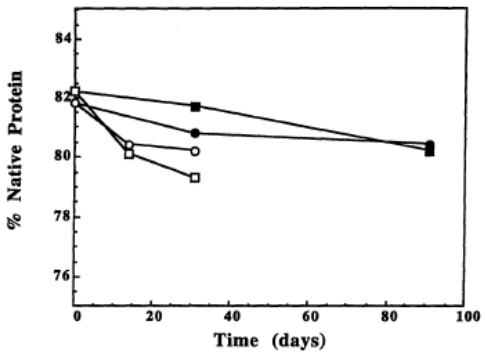

FIG. 5

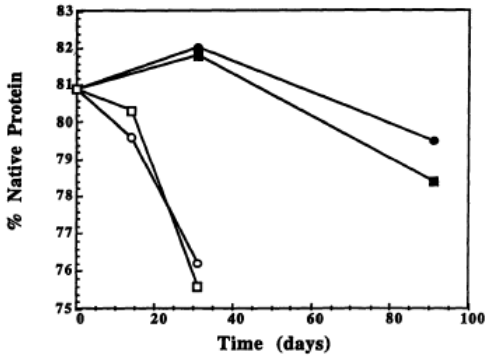

FIG. 7

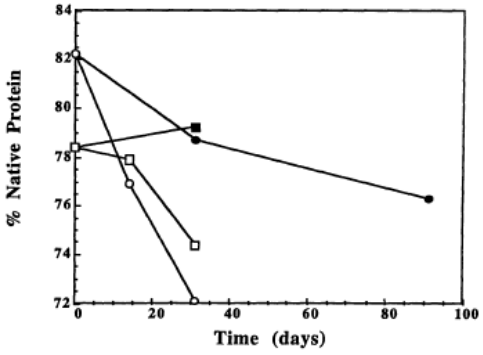

FIG. 6

SUBSTITUTE SHEET (RULE 26)

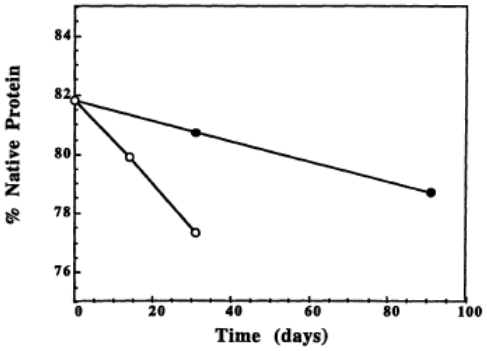

FIG. 8

SUBSTITUTE SHEET (RULE 26)

Andya explains that Figures 5–8, Ex. 1004, 39–40, illustrate the stability of reconstituted lyophilized rhuMAb HER2, *id*. at 6. "The % native protein was defined as the peak area of the native (not degraded) protein relative to the total peak area as measured by cation exchange chromatography." *Id.* Although Andya does not precisely quantitate the amount deamidation and succinimide variants in Figures 5–8, it notes that

> deamidation was minimized at pH 5.0 resulting in degradation primarily at the succinimide. At pH 6.0, slightly greater deamidation was observed in the liquid protein formulation. The lyophilized formulations were therefore studied with: (a) 5 or 10 mM succinate buffer, pH 5.0 or (b) 5 or 10 mM histidine buffer, pH 6.0.

Id. at 19. As explained on page 4 of Andya, the experiments in Figures 5 and 8 were conducted with sodium succinate buffers at pH 5.0, and those in Figures 6 and 7 with histidine buffers at pH 6.0.

2. Analysis

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id*. at 417.

Petitioner asserts that Andya discloses each element of independent claim 1. Pet. 38–46. In particular, Petitioner asserts that, although the preamble is not limiting, Andya discloses that the invention is suitable for human administration and therapeutic uses. *Id*. at 38 (citing Ex. 1004, 3). Petitioner asserts also that in Example 1, Andya discloses an anti-HER2 composition comprising full length humanized antibody huMAb4D5-8. *Id*. at 38–39, 43 (citing Ex. 1004, 20–22). Petitioner asserts that the composition also comprises acidic variant(s) of the antibody. *Id*. at 39. In support of that assertion, Petitioner relies upon Andya's disclosure in Example 1 that "[i]n the liquid state, rhuMAb HER2 was observed to degrade by deamidation (30 Asn of light chain) and isoaspartate formation via a cyclic imide intermediate, succinimide (102 Asp of heavy chain)." *Id*. (citing Ex. 1004, 21). Additionally, Petitioner relies on Andya's disclosure

that it assessed the loss of native protein due to deamidation or succinimide formation for reconstituted humMAb4D5-8 compositions using cation-exchange chromatography. *Id*. (citing Ex. 1004, 28 and Figures 5–8).

Petitioner and its declarant, Dr. Scandella, assert that Figures 5–8 show the percentage of native (not degraded) protein is 78–82% and the percentage of degraded protein is 18–22%. *Id*. at 23–24, 39; Ex. 1003 ¶¶ 76–82. According to Petitioner and Dr. Scandella, a person of skill in the art would have understood that the degraded protein includes deamidated variants because Andya teaches that a major degradation route for rhuMAb HER2 is deamidation. *Id*. at 39 (citing Ex. 1004, 28). Further, Petitioner and Dr. Scandella explain that a person of ordinary skill in the art would have considered such deamidated variants to be acidic variants. *Id*.; Ex. 1003 ¶ 88. Moreover, Dr. Scandella notes that the Specification of the '218 patent defines "acidic variant" as including deamidated variants. Ex. 1003 ¶ 42 (citing Ex. 1001, 6:14–19). Thus, Petitioner asserts that Andya's Figures 5–8 disclose that the reconstituted anti-HER2 antibody formulations described in Example 1 comprise a mixture of both native protein, i.e., anti-HER2 antibody, and one or more acidic variants thereof. Pet. 39–40.

Petitioner asserts also that each composition depicted by Andya's Figures 5–8 contains less than 25% acidic variants, as the figures reveal that the degraded protein amounts to 18–22% of the composition and a person of skill in the art would have understood that acidic variants would be contained in that portion. Pet. 40–42; Ex. 1003 ¶¶ 78–82, 89–91. Further, Petitioner asserts that Andya discloses those acidic variants are predominantly variants that have been deamidated at an asparagine residue of the antibody by stating that rhuMAb HER2 "was observed to degrade by

deamidation (30Asn of light chain)." *Id*. at 42 (citing Ex. 1004, 21 and 28; Ex. 1003 ¶¶ 43–44, 94).

Additionally, Petitioner asserts that Andya inherently discloses that the deamidated variants have Asn30 CDR1 of a V_L region of humMAb4D5-8 converted to aspartate because Andya teaches that Asn30 in the light chain of the antibody is deamidated and asparagine necessarily converts to aspartate when humMAb4D5-8 deamidates at Asn30. Pet. 43–44 (citing Ex. 1003 ¶¶ 96, 98; Ex. 1042 ¶¶ 19–20, 22).

Petitioner asserts that Andya's compositions described in Figures 5–8 comprise a pharmaceutically acceptable carrier because "Andya discloses that an 'object' of the invention is 'to provide a stable reconstituted protein formulation which is suitable for subcutaneous administration.'" Pet. 45 (quoting Ex. 1004, 3). In particular, Petitioner asserts that the compositions are formulated with sodium succinate, trehalose, Tween20, benzyl alcohol, histidine, mannitol, and sucrose, which a person of ordinary skill in the art would have understood to be pharmaceutically acceptable carriers within the meaning of the '218 patent. *Id*. at 45–46 (citing Ex. 1004, 6; Ex. 1001, 19:33–53; Ex. 1003 ¶ 101).

Dependent claim 5 recites "[t]he therapeutic composition of any one of claims 1 to 4, wherein the anti-HER2 antibody comprises the light chain amino acid sequence of SEQ ID NO[:]1 and the heavy chain amino acid sequence of SEQ ID NO:2." Petitioner asserts that the limitations of claim 1 are disclosed by Andya, including a composition comprising humMAb4D5-8, as set forth above. Pet. 46. According to Petitioner, Andya inherently discloses the additional limitations of claim 5 because it is directed to inherent properties of the disclosed antibody, as recognized by the '218

patent Specification. *Id*. at 46–47 (citing Ex. 1001, 4:30–32; 13:65–14:5; 20:39–43) (referring to humMAb4D5-8 comprising the light chain amino acid sequence of (SEQ ID NO:1) and heavy chain (SEQ ID NO:2)).

Dependent claim 6 recites "[t]he therapeutic composition of any one of claims 1 to 4, which is in the form of a lyophilized formulation or an aqueous solution." Dependent claim 7 similarly recites "[t]he therapeutic composition of claim 5, which is in the form of a lyophilized formulation or an aqueous solution." Petitioner asserts that Andya discloses each limitation of claims 1 and 5, as set forth above. Pet. 47. According to Petitioner, Andya further teaches the lyophilized humMAb4D5-8 compositions are reconstituted with water to form aqueous solutions. *Id*. at 47–48 (citing Ex. 1004, Abstract, 6, 21, 26; Ex. 1003 ¶ 107). Thus, Petitioner asserts that Andya's Figures 5–8 depict compositions in aqueous solution. *Id*. at 48.

Based upon our review of the current record, Petitioner's characterization of Andya and Petitioner's declarant testimony as to the knowledge in the art are adequately supported. Further, we discern no deficiency in Petitioner's assertions as to the reasonable inferences an ordinary artisan would make from those references. In particular, as set forth above, Petitioner has shown adequately that Andya discloses a formulation in Example 1 comprising a mixture of anti-HER2 antibody and degraded protein thereof, wherein the degraded protein include deamidated variants understood to be acidic variants of the anti-HER2 antibody, wherein such variants comprise less than 25% of the composition, as depicted by Figures 5–8.

Additionally, as set forth above, Petitioner has demonstrated that Andya discloses inherently that those acidic variants are predominately

deamidated wherein an asparagine residue of the antibody has been deamidated, and wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate.

Further, as set forth above, Petitioner has shown adequately that Andya discloses that its formulations depicted by Figures 5–8 included a pharmaceutically acceptable carrier and that the anti-HER2 antibody is humMAb4D5–8, wherein the antibody inherently comprises the light chain amino acid sequence of SEQ ID NO:1 and the heavy chain amino acid sequence of SEQ ID NO:2, wherein the composition is in the form of an aqueous solution.

Thus, based on the information presented at this stage of the proceeding, Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of claims 1 and 5–7 as anticipated by Andya.

Insofar as Petitioner asserts that certain limitations of the challenged claims would have been "at minimum obvious in light of these disclosures," *see, e.g.* Pet. 40, 42, 43, and 45–48, we determine that the Petitioner has not presented those arguments sufficiently, as it has not explained an obviousness rationale. We decline to speculate as to Petitioner's obviousness rationale regarding claims 1 and 5–7 and determine that Petitioner has not set forth a reasonable likelihood of prevailing in showing the unpatentability of those claims as obvious over Andya.

Our remaining analysis in this section of the Decision focuses on the deficiencies in Patent Owner's arguments in its Preliminary Response as to Petitioner's anticipation challenge of claims 1 and 5–7. Patent Owner asserts that Petitioner "identifies nothing in Andya that indicates that the

Example 1 composition contains any acidic variants." Prelim. Resp. 22. According to Patent Owner, "Andya does not describe the complete contents of the Example 1 composition, but merely indicates that it contains 78–82% 'native (not degraded) protein.'" *Id*. at 23. Patent Owner agrees that such a composition "contains 18–22% non-native (degraded) protein, but there are many types of non-native protein, including acidic variants, neutral variants, and basic variants." *Id*. at 24. Patent Owner asserts that "Andya does not identify the type of non-native protein in the Example 1," and thus, does not disclose expressly or inherently that the composition contains "one or more acidic variants." *Id*. In support of that position, Patent Owner asserts that the European Patent Office and an examiner of a different U.S. Patent Application both determined that Andya's disclosure that Example 1 contains 78-82% native protein does not indicate that the nature of any particular variant in the remainder 18–22%. *Id*. at 24–25 (citing Ex. 1023, 17–18; Ex. 1008, 226).

Patent Owner, however, has not addressed whether the examiner considered all of the disclosures by Andya in Example 1. Nor has Patent Owner addressed whether the examiner or the European Patent Office considered Dr. Scandella's testimony. Here, in addition to drawing our attention to Andya's disclosure in Example 1 that "rhuMAb HER2 was observed to degrade by deamidation (30 Asn of light chain) and isoaspartate formation via a cyclic imide intermediate, succinimide (102 Asp of heavy chain)," Pet. 39 (quoting Ex. 1004, 21), Petitioner also relies upon the testimony of Dr. Scandella. Dr. Scandella explains that a person of skill in the art would have understood that the degraded protein includes deamidated variants because Andya teaches that a major degradation route for rhuMAb

HER2 is deamidation. Ex. 1003 ¶¶ 75–81; Ex. 1004, 28. Further, Petitioner and Dr. Scandella explain that a person of ordinary skill in the art would have considered such deamidated variants to be acidic variants. *Id*. Moreover, Dr. Scandella notes that the Specification of the '218 patent defines "acidic variant" as including deamidated variants. Ex. 1003 ¶ 42 (citing Ex. 1001, 6:14–19). Thus, according to Petitioner and Dr. Scandella, Andya's Figures 5–8 disclose that the reconstituted anti-HER2 antibody formulations described in Example 1 comprise a mixture of both native protein, i.e., anti-HER2 antibody, and one or more acidic variants thereof. Pet. 39–40. Based on the foregoing, in view of the current record, we determine that Petitioner has made a sufficient showing at this stage of the proceeding that Andya disclosed that at least some of the degraded portion of the compositions of Example 1 depicted in Figures 5–8 comprise acidic variants.

Patent Owner asserts that Petitioner improperly relies upon Andya's disclosure that "rhuMAb HER2 was observed to degrade by deamidation (30 Asn of light chain)," Ex. 1004, 21, as that disclosure relates to a screening study and not to the Example 1 composition, Prelim. Resp. 26–27. According to Patent Owner, the relevant issue regarding the Example 1 composition is the amount of native protein and not the form of the non-native protein. *Id*. at 27. Patent Owner asserts that, with regard to the Example 1 composition, Andya merely states that "the major degradation route for rhuMAb HER2 in aqueous solutions is deamidation or succinimide formation," and that the "loss of native protein due to deamidation or succinimide formation was assessed." *Id*. (quoting Ex. 1004, 28). Thus, according to Patent Owner, Andya does not indicate which type of

degradation actually occurred or if the composition contained any acidic variants. *Id*. at 28. However, as Dr. Scandella explains, a person of skill in the art would have understood from Andya's disclosure that a major degradation route for rhuMAb HER2 is deamidation, the degraded protein would comprise at least some deamidated variants. Ex. 1003 ¶¶ 75–81; Ex. 1004, 28.

Further, the plain language of Andya indicates that deamidation occurs under the conditions used for each of the experiments represented in Figures 5–8. According to Andya, "deamidation was minimized at pH 5.0 resulting in degradation primarily at the succinimide. At pH 6.0, slightly greater deamidation was observed in the liquid protein formulation." Ex. 1004 at 19. Because Andya conducted these experiments at either pH 5.0 (Figures 5 and 8) or pH 6.0 (Figures 6 and 7), we infer that deamination is present in the latter, and to a lesser extent (albeit not eliminated) in the former, such that each of the experiments evidence acidic variants.

Patent Owner asserts also that Petitioner has not demonstrated that Andya is enabling. Prelim. Resp. 32–42. Patent Owner "recognizes that the Board has stated that prior art publications should receive a presumption of enablement in IPRs." *Id*. at 32–33 (citing *Samsung Elecs. Co., Ltd. V. Queen's Univ. at Kingston*, IPR2015-00584, Paper 53 at 22–23 and n.4 (PTAB July 27, 2016). However, Patent Owner asserts that demonstrating such enablement is "a proposition of unpatentability for which the petitioner bears the burden of proof, and thus there should be no presumption of enablement." *Id*. at 33. In support of that position, Patent Owner relies, in part, upon 35 U.S.C. § 316(e) and *Aqua Products, Inc. v. Matal*, 872 F.3d 1290, 1306 (Fed. Cir. 2017) (en banc).

Aqua Products explains that, in the absence of anything that might be entitled to deference, the Patent Office may not place the burden of persuasion on a patent owner with respect to the patentability of substitute claims presented in a motion to amend. *See id*. at 1327. Beyond implementing that instruction, generally speaking, practice and procedure before the Board has not changed. *See* Memorandum "Guidance on Motions to Amend in view of *Aqua Products*" (Nov. 21, 2017) (https://www.uspto.gov/sites/default/files/documents/guidance_on_motions_to_amend_11_2017.pdf).

As our reviewing court has explained, the burden of production, i.e., the burden of going forward with evidence, in a patent claim challenge may shift between the parties. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (citing *Tech Licensing Corp. v. Videotek, Inc*. 545 F.3d 1316, 1326–27 (Fed. Cir. 2008)). Patent Owner, has not directed us to any portion of *Aqua Products* changing that law or eliminating the presumption of enablement recognized for prior art printed publications. *See, e.g., In re Antor Media Corp*., 689 F.3d 1282, 1287 (Fed. Cir. 2012).

Here, Petitioner has met its initial burden by relying on Andya and the declaration testimony of Dr. Scandella to support its assertion that Andya discloses each limitation of the challenged claims. *See* Pet. 38–48. Because Petitioner offered Andya into evidence as prior art, and prior art printed publications are presumed to be enabled, the burden of production shifts to Patent Owner to present evidence demonstrating that Andya's disclosure is not enabling.

In that regard, we consider Patent Owner's assertions that Petitioner "identifies nothing in Andya that would teach a person of ordinary skill to make a composition having the amount and identity of acidic variants in the challenged claims, let alone how to do so without undue experimentation." Prelim. Resp. 34–35. Further, Patent Owner asserts that even if Andya disclosed the final output of its formulation was a composition that necessarily falls within the scope of the challenged claims, Andya is still not enabling as it "does not disclose the contents of or specific method of preparing the *starting composition* used in the Andya experiments." *Id*. at 35. Patent Owner supports those contentions by criticizing aspects of Petitioner's enablement discussion without addressing the Wands factors and producing evidence to demonstrate that Andya's disclosure is not enabling. *See* Prelim. Resp. 34–42; *see also In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Thus, based on the current record, we do not find that Patent Owner has rebutted the presumption that Andya is enabling so as to shift the burden of production back to Petitioner at this stage in the proceeding.

Thus, based on the information presented at this stage of the proceeding, Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of claims 1 and 5–7. Accordingly, we institute an *inter partes* review of claims 1 and 5–7 as anticipated by Andya.

E. Obviousness over Harris

Petitioner asserts that claims 1 and 5–7 would have been obvious over Harris. Pet. 61–67.

1. Harris

Harris is a journal review article published on June 23, 1995. Ex. 1005, 1.[6] Harris discusses posttranslational processing involving the removal of lysine or arginine residues from the C-terminus of a protein obtained through mammalian cell culture, along with successful approaches for identifying such variants. *Id*. at 5. Harris discloses that, in theory, the characterization of recombinant proteins is a straightforward matter, however, in practice, a number of variations from the expected structure can be found. *Id*. at 4.

Harris teaches that "[v]ariants may result from either known or novel types of in vivo (posttranslational) modification or from spontaneous (non-enzymatic) protein degradation, such as methionine oxidation, diketopiperazine formation, aspartate isomerization and deamidation of asparagine residues, or succinimide formation." *Id*. at 4–5 (internal citations omitted). Harris explains that cation-exchange chromatography of rhuMAb HER2 shows five charge species. *Id*. at 6 (referring to Fig. 2). Harris states that "[t]he main peak (peak 3) has no Lys^{450} residues, while the more basic peaks 4 and 5 have one or two Lys^{450} residues, respectively." *Id*. Harris explains that "[t]he more acidic peaks 1 and 2 are deamidated at Asn^{30} in one light chain; peak 1 has no Lys^{450} residues, while peak 2 has one Lys^{450} residue." *Id*. Harris Figure 2 is set forth below:

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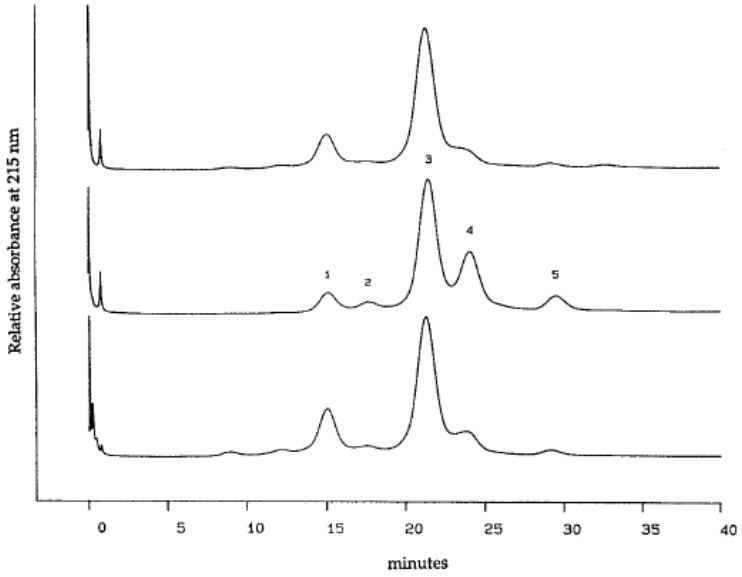
[6] Page numbers refer to those added to the exhibit by Petitioner.



Harris Figure 2 depicts the cation-exchange chromatography of three lots of rhuMAb HER2. *Id*. at 7.

2. Analysis

Petitioner asserts independent claim 1 would have been obvious over the teachings of Harris and the knowledge of a person of ordinary skill in the art. Pet. 6, 61–67. In particular, Petitioner asserts that Harris discloses an anti-HER2 composition by describing the use of rhuMAb HER2, an anti-HER2 antibody. Pet. 61 (citing to Ex. 1005, 5). Petitioner asserts that the composition comprises a mixture of that antibody and one or more acidic variants thereof based upon the results of Harris' cation-exchange chromatography of the antibody. *Id*. at 62–63 (citing Ex. 1005, 6–7, and Figure 2). Specifically, Petitioner asserts that Harris identified five charged species of the composition that are represented by the five numbered peaks in the chromatogram of Figure 2. *Id*. at 62. Petitioner asserts that Harris describes peaks 1 and 2 as "[t]he more acidic peaks" that are "deamidated as

Asn^{30} in one light chain." *Id*. (quoting Ex. 1005, 6–7). According to Petitioner and Dr. Scandella, a person of ordinary skill in the art would have understood that such deamidated Asn^{30} is an acidic variant of rhuMAb HER2. *Id*. (citing Ex. 1003 ¶ 140). Further, based upon the disclosures of Harris, Petitioner asserts that a person of ordinary skill in the art would have understood also that peak 3 represents native rhuMAb HER2, and peaks 4 and 5 represent basic variants. *Id*. at 63 (citing Ex. 1005, 6; Ex. 1003 ¶ 140).

Petitioner asserts also that Harris discloses that its antibody composition contains less than 25% acidic variants. Pet. 63. Specifically, Petitioner asserts that Harris discloses that the acidic variants are contained with peaks 1 and 2 of Figure 2, and a person of ordinary skill in the art "would have recognized upon inspection that the area under the curve for peak 1 combined with peak 2 . . . is less than 25% of the total area under the curve for peaks 1 through 5." *Id*. (citing Ex. 1003 ¶ 141).

Further, Petitioner asserts that Harris inherently discloses acidic variants less than 25%, based upon a mathematical calculation performed by Dr. Scandella. Pet. 63. Petitioner explains that Dr. Scandella calculated the area under the curves for peaks 1–5, using software available at the time of the invention, and confirmed that peaks 1 and 2 represent less than 25% of the total area under the curve for peaks 1–5. *Id*. (citing Ex. 1003 ¶¶ 57–60, 142). Dr. Scandella used the software program Data Thief to convert the chromatograms to digital data, and then used the software program MATLAB to apply baseline corrections, measure peak areas, and calculate peak areas as a percentage of the total area under the curve. Ex. 1003 ¶¶ 57–60, 142. Based on those calculations, Dr. Scandella determined that Harris

necessarily discloses a composition comprising less than 25% acidic variants, i.e., between 13 and 24%. *See id*. at ¶ 60.

Alternatively, Petitioner asserts that such limitation would have been obvious over Harris' disclosures, set forth above. Pet. 55–56. As support, Petitioner notes that the '218 patent explains that about 25% is the amount obtained by "initial Protein A chromatography," a known method. *Id*. at 56 (citing Ex. 1001, 22:60–63). Additionally, Petitioner asserts that there is "nothing critical about the claimed concentration, and compositions falling above the claimed range can easily be brought below merely by collecting and discarding excess acidic variants resolved by chromatography." *Id*. (citing Ex. 1003 ¶121). According to Petitioner, a person of ordinary skill in the art would have been "motivated to do so by the general knowledge that acidic variants and other impurities should be identified and reduced to ensure the antibody has an acceptable level of purity and potency and regulations governing biological products." *Id*. (citing Ex. 1003 ¶¶ 45, 121).

Further, Petitioner asserts that Harris discloses those acidic variants are predominantly variants that have been deamidated at an asparagine residue of the antibody by teaching that peaks 1 and 3 of Figure 2 are deamidated variants and that such deamidation occurs at one or more asparagine residues. Pet. 64 (citing Ex. 1005, 4–6). According to Petitioner and Dr. Scandella, because non-negligible amounts of acidic variants would be expected to be resolved via cation-chromatography, and no other acidic variants were resolved by the cation-exchange chromatography in Harris, a person of skill in the art would have understood that the acidic variants of the rhuMAb HER2 composition are predominantly the deamidated variants,

wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated. *Id*. (citing Ex. 1003 ¶ 144).

Petitioner asserts that, to the extent that Harris does not expressly disclose humMAb4D5-8, it would have been obvious to a person of ordinary skill that rhuMAb HER2 of Harris is humMAb4D5-8. Pet. 64–65 (citing Ex. 1003 ¶¶ 145–146). We understand Petitioner's argument to mean that a skilled artisan would have known the Harris' rhuMAb HER2 is the same as humMAb4D5-8, or that it would have been obvious to select humMAb4D5-8 as the rhuMAb HER2 disclosed by Harris, as humMAb4D5-8 "was the only variant of rhuMAb HER2 in clinical trials" at the time the article was published. *See id.*

Additionally, Petitioner asserts that Harris inherently discloses that the deamidated variants have Asn^{30} in CDR1 of a V_L region of humMAb4D5-8 converted to aspartate because Harris teaches that Asn^{30} in the light chain of the antibody is deamidated and asparagine necessarily converts to aspartate when humMAb4D5-8 deamidates at Asn^{30}. Pet. 65 (citing Ex. 1003 ¶ 147); Ex. 1005, 6.

Petitioner asserts that it would have been obvious to a person of ordinary skill in the art to have included a pharmaceutically acceptable carrier in Harris' rhuMAb HER2 composition. Pet. 66 (quoting Ex. 1003 ¶ 148). Petitioner asserts that numerous such carriers, including those disclosed in the '218 patent, were well known at the time of the invention, as well as methods for employing them. *Id*. According to Petitioner, a person of skill in the art would have had a good reason to include such carriers in Harris' antibody composition to render it suitable for human therapeutic use. *Id*. at 66 (Ex. 1003 ¶ 149).

Dependent claim 5 recites "[t]he therapeutic composition of any one of claims 1 to 4, wherein the anti-HER2 antibody comprises the light chain amino acid sequence of SEQ ID NO:1 and the heavy chain amino acid sequence of SEQ ID NO:2." Petitioner asserts that claim 1 would have been obvious over Harris, including its limitation requiring the composition to comprise humMAb4D5-8, as set forth above. Pet. 66. According to Petitioner, Harris inherently discloses the additional limitations of claim 5 because it is directed to inherent properties of the disclosed antibody, as recognized by the '218 patent Specification. *Id*. at 66–67 (citing Ex. 1001, 4:30–32; 13:65–14:5; 20:39–43) (referring to humMAb4D5-8 comprising the light chain amino acid sequence of (SEQ ID NO[:]1) and heavy chain (SEQ ID NO:2)).

Dependent claim 6 recites "[t]he therapeutic composition of any one of claims 1 to 4, which is in the form of a lyophilized formulation or an aqueous solution." Dependent claim 7 similarly recites "[t]he therapeutic composition of claim 5, which is in the form of a lyophilized formulation or an aqueous solution." Petitioner asserts that claims 1 and 5, would have been obvious over Harris, as set forth above. Pet. 66. According to Petitioner, a person of skill in the art would have mixed Harris' antibody composition with water to form an aqueous solution for injection, or, alternatively, would have lyophilized the composition to preserve biological structures and extend the shelf life. *Id*. at 67 (citing Ex. 1003 ¶¶ 130–131, 153). According to Petitioners and Dr. Scandella, preparing such formulations was within the skill in the art and involved routine methods known in the art. *Id*.

Based upon our review of the current record, we discern no deficiency in Petitioner's characterization of the cited references and the knowledge in the art, or in Petitioner's assertions as to the reasonable inferences an ordinary artisan would make from those references. Thus, based on the information presented at this stage of the proceeding, Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of claims 1 and 5–7 as obvious over Harris.

Our remaining analysis in this section of the Decision focuses on the deficiencies in Patent Owner's arguments in its Preliminary Response as to the challenged claims.

Patent Owner asserts that Petitioner fails to demonstrate that Harris teaches a composition comprising less than about 25% acidic variants. Prelim. Resp. 60. Specifically, Patent Owner asserts that the chromatogram in Harris Figure 2 provide insufficient detail to rely on any calculations derived from it because the drawing "does not provide any quantified points along the x-axis corresponding to different protein components, and it does not provide any quantified points along the y-axis at all (including a reference baseline)." *Id*. at 60–61. However, Patent Owner has not acknowledged or squarely addressed the testimony of Dr. Scandella regarding this matter. Dr. Scandella explained that a person of skill in the art could determine upon visual inspection, and confirm by calculation that acidic variant percentage depicted in Harris' chromatogram. *See, e.g.*, Ex. 1003 ¶¶ 56–57. At this stage in the proceeding, we accord Dr. Scandella's uncontroverted testimony persuasive weight. *See* 37 C.F.R. 42.108(c) ("a genuine issue of material fact created by such testimonial evidence will be

viewed in the light most favorable to the petitioner solely for purposes of deciding whether to institute an *inter partes* review").

Patent Owner asserts also that Petitioner fails to demonstrate that Harris discloses or renders obvious humMAb4D5-8. Prelim. Resp. 61. Based on the current record, we disagree with Patent Owner. Petitioner and Dr. Scandella explain that a person of ordinary skill in the art would have understood that Harris' rhuMAb HER2 antibody is humMAb4D5-8, or, alternatively, that it would have been obvious to select humMAb4D5-8 as Harris' antibody, based upon the characteristics of rhuMAb HER2 disclosed by Harris. Pet. 64–65 (citing Ex. 1003 ¶¶ 145–146).

Further, Patent Owner asserts that Petitioner has not demonstrated that Harris is enabling. Prelim. Resp. 63. Patent Owner relies on the same argument raised regarding the challenge involving Andya that there should be no presumption of enablement for Harris. *Id*. For the same reasons we discussed regarding that argument, we disagree. Harris is presumed to be enabled and the burden of production is on Patent Owner to present evidence demonstrating that Harris' disclosure is not enabling. Patent Owner's argument does not address the Wands factors or produce evidence to demonstrate that Harris' disclosure is not enabling. *See* Prelim. Resp. 63. Thus, based on the current record, we do not find that Patent Owner has rebutted the presumption that Harris is enabling so as to shift the burden of production back to Petitioner at this stage in the proceeding.

Thus, based on the information presented at this stage of the proceeding, Petitioner has shown sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of claims 1

and 5–7. Accordingly, we institute an *inter partes* review of those claims as obvious over Harris.

F. Remaining Ground

The remaining ground is based upon Waterside and challenges the same claims as those involved in the grounds based upon Andya and Harris, discussed above and instituted. Accordingly, we exercise our discretion by declining to proceed on the grounds involving Waterside, which Petitioner asserts to comprise slides depicting the work of Harris and presented at a conference approximately one year after the publication of Harris. Pet. ix, 19. *See* 37 C.F.R. § 42.108(a).

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 1 and 5–7 of the ’218 patent are unpatentable.

At this stage of the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim.

ORDER

Accordingly, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is instituted as to claims 1 and 5–7 of the '218 patent on the following grounds of unpatentability:

Claims 1 and 5–7 under 35 U.S.C. § 102(b) as anticipated by Andya;

Claims 1 and 5–7 under 35 U.S.C. § 103(a) as obvious over Harris;

FURTHER ORDERED that no other proposed ground of unpatentability is authorized; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this Decision.

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