

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOF CORPORATION,
Petitioner,

v.

NEKTAR THERAPEUTICS,
Patent Owner.

IPR2019-01396
Patent 8,809,453 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and
JON B. TORNQUIST, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

INTRODUCTION

NOF Corporation (“Petitioner”) filed a Petition (Paper 1, “Pet.”) requesting an *inter partes* review of claims 1–18 of U.S. Patent No. 8,809,453 B2 (Ex. 1004, “the ’453 patent”). Nektar Therapeutics (“Patent Owner”) filed a Preliminary Response. Paper 7 (“Prelim. Resp.”). With our authorization, Petitioner filed a Reply (Paper 14) and Patent Owner filed a Sur-reply (Paper 16).¹

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a).

For the reasons provided below, we determine that Petitioner has not demonstrated a reasonable likelihood that it would prevail with respect to at least one of the claims challenged in the Petition. Accordingly, we deny institution of an *inter partes* review.

Related Matters

According to Petitioner, the ’453 patent is involved in *Nektar Therapeutics et al. v. Bayer Healthcare, LLC*, 1-18-cv-01355 (D. Del.). Pet. 3. According to Patent Owner, the ’453 patent is asserted in *Baxalta Incorporated v. Bayer Healthcare LLC*, No. 17-1316 (D. Del) (consolidated). Paper 5, 1.

¹ As authorized, the Reply and the Sur-reply are limited to the issue of real party in interest. We do not reach that issue in this Decision, as we decline to institute for other reasons.

Background of Technology and the '453 Patent

The '453 patent discloses “branched, reactive water soluble polymers useful for conjugating to biologically active molecules.” Ex. 1004, 1:22–24.

Before the '453 patent, it was known that “[c]ovalent attachment of the hydrophilic polymer poly(ethylene glycol), abbreviated PEG, is a highly advantageous method of increasing water solubility and bioavailability and extending the circulation time of many biologically active molecules, particularly hydrophobic molecules.” *Id.* at 1:29–33. It was also known that the total molecular weight of the attached polymers should be sufficiently high to provide the advantageous characteristics typically associated with PEG polymer attachment without “adversely impacting the bioactivity of the parent molecule.” *Id.* at 1:36–42.

The '453 patent states that although branched polymers attached to a central core and having a single reactive group for conjugation to a biologically active molecule were known, the methods of forming those prior-art branched PEG molecules were difficult. *Id.* at 1:62–2:9. Thus, according to the '453 patent, “[t]here remain[ed] a need in the art for branched polymer reagents that provide the benefits associated with branched polymers (i.e., high overall molecular weight in a single non-linear polymer molecule), but are easier to synthesize or provide more flexibility in their design than prior art reagents.” *Id.* at 2:10–14.

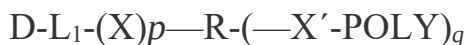
The '453 patent discloses “branched reactive polymers comprising at least two polymer arms, such as PEG arms, attached to a central core through heteroatom linkages such as ether linkages.” *Id.* at 6:40–43. According to the '453 patent, “[s]ince the branched polymers of the invention combine at least two polymer arms in a single molecule, a polymer

with sufficient molecular weight to impart beneficial properties to a biologically active molecule, such as increased water solubility, can be formed using shorter, easier to prepare polymer chains.” *Id.* at 6:46–51.

Illustrative Claim

Among the challenged claims, claim 1 is independent, and is reproduced below:

1. A biologically active conjugate comprising a branched polymer covalently attached to a biologically active molecule, wherein the conjugate has the structure:



wherein:

D is the biologically active molecule;

R is an aliphatic hydrocarbon having a length of at least three carbon atoms;

L₁ is a linkage resulting from the reaction of a functional group on the linker (X), when present, or on the aliphatic hydrocarbon having a length of at least three carbon atoms (R) of the branched polymer and a functional group of the biologically active molecule;

each POLY is a water soluble and non-peptidic polymer that terminates with a hydroxyl or methoxy group;

X' is —O—, —NH—, or —S—;

X is a linker of 1 to 10 atoms in length;

p is 0 or 1; and

q is 2,

and further wherein the branched polymer has a molecular weight of about 12,000 Da to about 100,000 Da.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims Challenged	35 U.S.C. §	Reference(s)
1–18	103	Bentley ²
1–18	103	Bentley, MDD ³
1–18	103	Bentley, Harris ⁴
1–18	103	Bentley, Harris, PSTT ⁵
1–18	103	JP-542 ⁶
1–18	103	JP-542, Katre ⁷

In support of its patentability challenge, Petitioner relies on the Declaration of Yuji Yamamoto, Ph.D. Ex. 1083.

ANALYSIS

Claim Construction

In an *inter partes* review, we construe a claim term “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b).” 37 C.F.R. § 42.100(b). Under that standard, the words of a claim “are generally given their ordinary and customary meaning,” which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Phillips v. AWH*

² Bentley et al., U.S. Patent No. 5,990,237, issued November 23, 1999 (Ex. 1015).

³ Charles et al., *Improving Hepatitis C Therapy*, 5 Modern Drug Discovery 59, 60, 62, 65, 67 (2000) (Ex. 1029) (“MDD”).

⁴ Harris et al., U.S. Patent No. 5,932,462, issued August 3, 1999 (Ex. 1016).

⁵ Bailon et al., *Polyethylen Glycol-Conjugated Pharmaceutical Proteins*, 1 Pharm. Sci. Technol. Today 352–56 (1998) (Ex. 1030) (“PSTT”).

⁶ Sanchika et al., Patent Application Publication No. P2000-1542A, published January 7, 2000 (Ex. 1017) (“JP-542”).

⁷ Katre et al., WO 87/00056, published January 15, 1987 (Ex. 1031) (“Katre”).

Corp., 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to expressly construe any claim terms.

Obviousness over Bentley

Petitioner argues that claims 1–18 would have been obvious over Bentley. Pet. 25–41. Based on this record, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

Bentley

Bentley relates to methods of coupling a PEG polymer to a biomaterial. Ex. 1015, 1:8–10. Bentley explains that covalently attaching the PEG polymer to molecules and surfaces has several advantages, and thus, is important in biotechnology and medicine. *Id.* at 1:14–17, 1:60–2:11.

According to Bentley,

To couple PEG to a molecule such as a protein or a small drug molecule, it is necessary to use an “activated derivative” of the PEG having a functional group at the terminus suitable for reaction with a group on the other molecule. For example, the hydroxyl group of CH₃O—PEG—OH can be converted to an aldehyde group, and this aldehyde group can then be covalently linked to a molecule or surface bearing one or more amine groups using the method of reductive amination.

Id. at 2:12–20.

Bentley’s method “includes in situ preparation of PEG aldehyde hydrates, which can then be used in solution, without isolation, to form

conjugates by reductive amination with a range of biologically active molecules.” *Id.* at 3:4–9. In Bentley, the PEG polymer is either linear or branched, and typically has an average molecular weight of from 200 to 100,000. *Id.* at 6:30–32, 35–36.

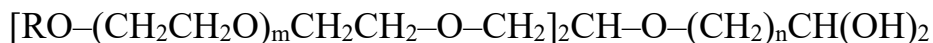
Analysis

Petitioner argues that “Bentley discloses, at col. 7:12-20, a branched PEG aldehyde hydrate polymer for conjugation of biologically active molecules that meets the structure claimed in the ’453 patent. Only the claimed MW range is not expressly disclosed.” Pet. 26 (citing Ex. 1083 ¶¶ 283-311). We are not persuaded.

Bentley teaches that one form of activated PEG aldehyde is “dendritic activated PEG in which multiple arms of PEG are attached to a central core structure.” Ex. 1015, 6:64–66. These dendritic PEGs are commonly known as “star” molecules and can be represented by the formula $Q[\text{poly}]_y$, wherein Q is a branching core moiety and y is from 2 to about 100. *Id.* at 6:66–7:6.

Bentley teaches that

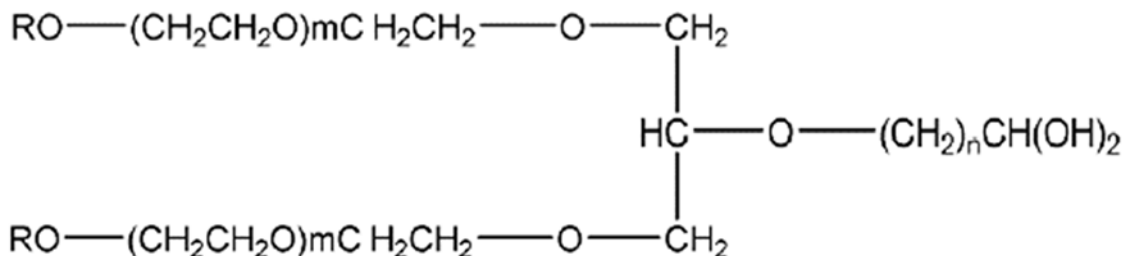
The aldehyde hydrate moiety can be used to provide an active, functional group on the end of the PEG chain extending from the core and as a linker for joining a functional group to the star molecule arms. Additionally, the aldehyde hydrate moiety can also be linked directly to the core molecule having PEG chains extending from the core. One example of such a dendritic activated PEG has a formula of



wherein R is H, alkyl, benzyl, or aryl; m ranges from about 5 to about 3000, [and] n ranges from 1 to 6.

Id. at 7:8–20.

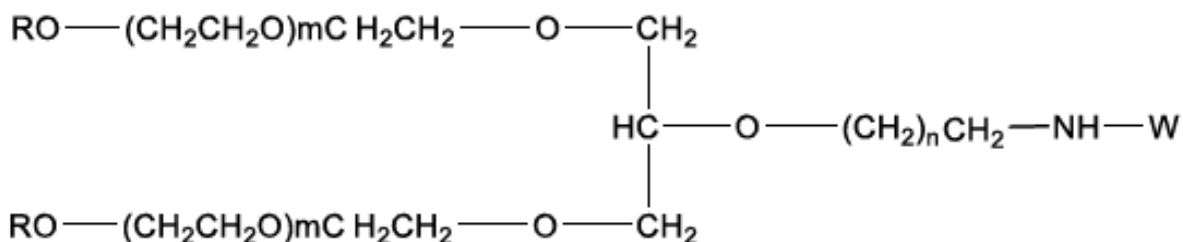
Petitioner argues that an ordinary artisan would recognize this formula as:



The figure above is Petitioner’s depiction of the chemical structure identified at column 7, lines 16–20 of Bentley. Pet. 28 (citing Ex. 1015, 7:12–20).

Petitioner contends that “[a]lthough the branched aldehyde hydrate is not specifically shown conjugated,” Bentley teaches conjugating PEG and related polymers with “proteins, peptides, polysaccharides, oligonucleotides, and small drug molecules.” *Id.* at 27 (quoting Ex. 1015, 3:1–15).

Specifically, Petitioner continues, “one of ordinary skill would understand the ‘–O–(CH₂)_nCH(OH)₂’ of Bentley’s branched polymer would react with a protein, or other amine-containing substance, to form –O–(CH₂)_n–CH₂–NH–PROTEIN.” *Id.* at 30. Thus, according to Petitioner, the following formula represents the product of conjugating Bentley’s branched polymer with a biologically active molecule:



The figure above is Petitioner’s depiction of the chemical structure of the conjugated product. *Id.* at 31 (citing Ex. 1083 ¶ 290).

We disagree with Petitioner's conclusion. First, Bentley states that, because biological properties may vary based on molecular weight and the degree of branching, "not all of these [disclosed] derivatives may be useful for biological or biotechnical applications." Ex. 1015, 6:36–39. Here, Petitioner has not shown the Bentley polymer it relies on (depicted in the formula at lines 16–20 on column 7 of Bentley) is suitable for conjugating with a biologically active molecule.

Second, Bentley notes that "star" molecules are generally described in Merrill (U.S. Patent No. 5,171,264), which is incorporated by reference in Bentley. *Id.* at 7:5–8. Merrill discloses that "star" molecules are useful for creating hydrogels, which are formed by covalently attaching the "star" molecules to a *support surface* and then crosslinking the molecules to render them insoluble. Ex. 2020, Abstract, 1:21–23, 2:5–13, Figure 4. Indeed, using the aldehyde hydrate moiety to anchor the core of Bentley's "star" molecule to the support surface of an affinity column appears consistent with the disclosures of both references. Ex. 1015, 7:44–46 ("PEG aldehyde hydrate and its derivatives can be used for attachment directly to *surfaces* and molecules having an amine moiety.") (emphasis added); Ex. 2020, 4:61–5:10 (noting that Merrill's "star" molecules may be tethered to the support surface by binding one of the polymer arms to an amino group on the support surface).

Third, as Patent Owner points out, Bentley "expressly states that the cited dendritic PEG should be attached to the inert core of the dendrimer—not to a biologically active substance." Prelim. Resp. 25. Indeed, Bentley introduces the formula Petitioner relies on as an example where "the

aldehyde hydrate moiety can also be linked directly to the core molecule having PEG chains extending from the core.” Ex. 1015, 7:12–15.

Petitioner has not directed us to disclosures in Bentley or Merrill of using the dendritic “star” molecules for the biologic applications discussed in the Petition. Nor has Petitioner persuasively explained why one of ordinary skill in the art would have attached the specific dendritic “star” molecule of Bentley to a biologically active *molecule* using the disclosed aldehyde hydrate moiety, as opposed to using active groups on the polymer arms for this purpose. Thus, Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to claim 1 over Bentley.

Because Petitioner’s arguments with respect to dependent claims 2–18 do not cure the deficiencies identified above, Petitioner has also not demonstrated a reasonable likelihood of prevailing with respect to those claims either.

Obviousness over Bentley and Other Prior Art

Petitioner argues that claims 1–18 would have been obvious over the combined disclosures of (1) Bentley and MDD, (2) Bentley and Harris, and (3) Bentley, Harris, and PSTT, respectively. Pet. 41–60.

In these grounds, Petitioner applies Bentley in the same manner as its ground based on Bentley alone. Pet. 41 (“As explained above, claims 1–18 are obvious over Bentley, and the application of Bentley is the same here.”), *see also id.* at 44, 59. Central to this argument is the attachment of a biologically active agent to the aldehyde hydrate moiety of the “star” molecule of Bentley. As noted above, Petitioner has not explained sufficiently why one of ordinary skill in the art would have been motivated to do so. Accordingly, Petitioner has not demonstrated a reasonable

likelihood of prevailing its challenges of claims 1–18 over Bentley and MDD, Bentley and Harris, and Bentley, Harris, and PSTT.

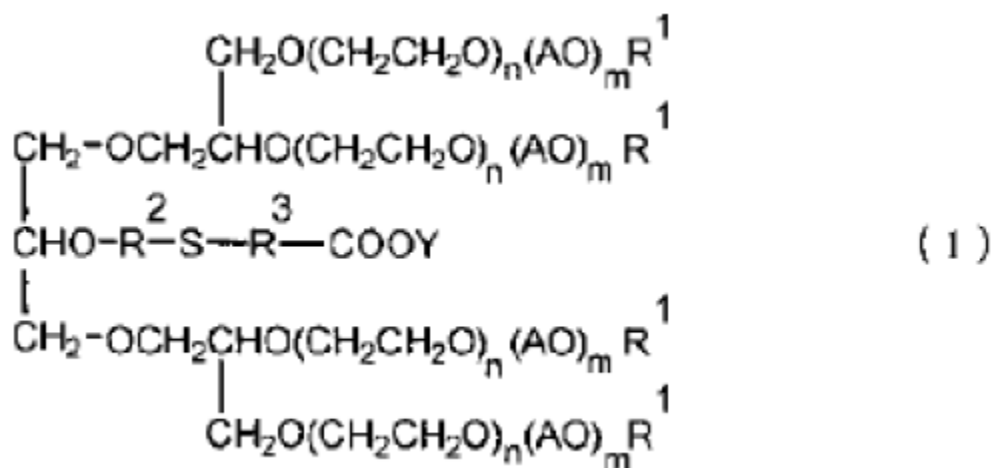
Obviousness over JP-542

Petitioner argues that claims 1–18 would have been obvious over JP-452. Pet. 61–75. Based on this record, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

JP-542

JP-542 discloses “a carboxyl-group-containing polyoxyalkylene compound that is used to modify a compound or a drug” in order to stabilize the drug, decrease its antigenicity, or prolong its residence time in the blood. Ex. 1017, Abstract.

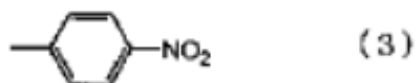
Formula (1) of JP-542 is reproduced below:



Formula (1) illustrates the general structure of the inventive polyoxyalkylene compounds of JP-542. *Id.* ¶ 6. In formula (1), R¹ is a hydrogen atom, a 1- to 24- carbon hydrocarbon, or a 1- to 24- carbon acyl group; R² is a 3- or 4- carbon hydrocarbon; R³ is a 1- to 10- carbon hydrocarbon; AO is a 3- or 4- carbon oxyalkylene; Y is either a hydrogen atom or an active group illustrated by formula (2) or (3); n is 1 to 1000; m is 0 to 250; and n/(n+m) is

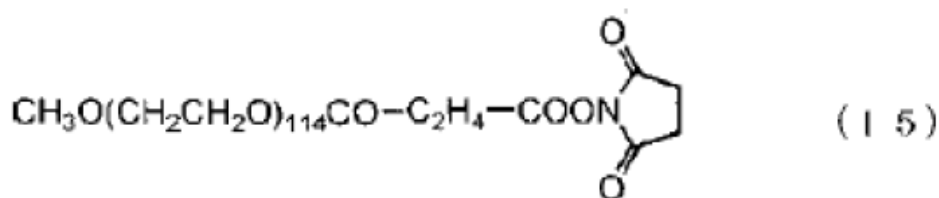
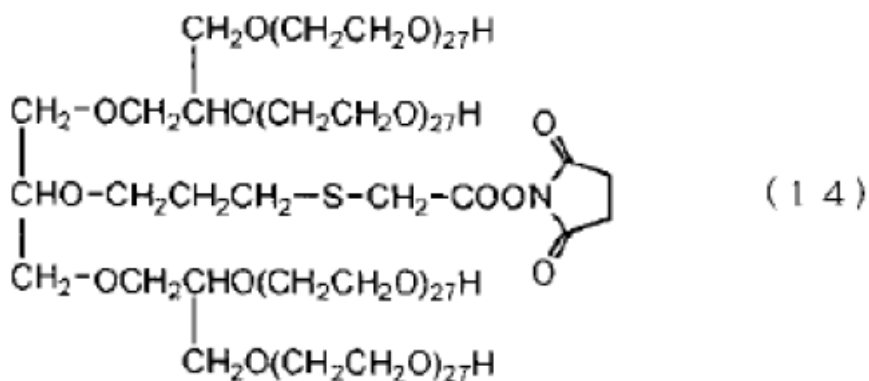
no less than 0.8; and the oxyethylene and the 3- or 4- carbon oxyalkylene
 “may be added in blocks or randomly.” *Id.* ¶ 8.

Formulas (2) and (3) of JP-542 are reproduced below:



Formulas (2) and (3) represent preferred active groups for use in the compound of formula (1). *Id.* ¶ 17.

JP-542 also discloses example species falling within the scope of formula (1) that may be conjugated with a compound or drug. The compounds of formulas (14) and (15) are reproduced below:



Formula (14) depicts a branched polyalkylene compound and formula (15) depicts a linear polyalkylene compound, both of which are conjugated to the active group illustrated in formula (2). *Id.* ¶¶ 9, 52, 56.

In Test Example 1 of JP-542, the branched compound of formula (14) was reacted with L-asparaginase, and in Comparative Test Example 1, the linear compound of Formula (15) was reacted with L-asparaginase. *Id.* ¶¶ 54–57. The resulting PEGlyated compounds were then tested for antigenicity and enzyme activity. *Id.* ¶¶ 57–58, Table 1. The results from these tests are reproduced below:

Table 1

	PEG derivative (Mw)	No. of bound amino groups ^{a)}	Enzyme activity		Antibody binding capacity
			Method A	Method B	
Test example 1	5, 162	50	35	40	0
Comparative test example 1	5, 200	54	15	22	35

a) Number of amino groups bound to the compound among amino groups in asparaginase molecule (ninety-two)

Table 1 provides the test results for Test Example 1 and Comparative Test Example 1. As shown in Table 1, the compound of Test Example 1 had zero antigenicity and retained 35% to 40 % of its enzyme activity. *Id.* ¶¶ 54, 58. In contrast, the compound of Comparative Test Example 1 had an antibody binding capacity of 35% (i.e., some level of antigenicity) and retained only 15 to 22% of its enzyme activity. *Id.* ¶¶ 54–58.

Analysis

Petitioner contends Test Example 1 of JP-542 is a branched polymer covalently attached to a biologically active molecule (Pet. 61–62); has a structure of D-L1-(X)_p-R-(–X'–POLY)_q (*id.* at 63–64); contains a

biologically active molecule in the form of L-asparaginase (*id.* at 64); contains an aliphatic hydrocarbon having at least three carbons (*id.* at 65); contains a linkage L₁ resulted from the reaction of a functional group on the linker X and a functional group of the biologically active molecule (*id.* at 65–66); contains two POLY (O(CH₂CH₂O)₂₇H) arms, each of which is water soluble and terminates in hydroxyl groups (*id.* at 66); contains an ether linkage (–O–) (*id.* at 67); includes a linker that is 6 atoms in length (*id.*); and contains a structure in which p is 1 and q is 2 (*id.* at 68).

Petitioner concedes that Test Example 1 does not have the molecular weight recited in challenged claim 1, but contends formula (1) of JP-542 contemplates much longer polymer arms, and when m=0 in formula (1) and all other variables are maintained as disclosed in formula (14), the potential molecular weight range of the PEG conjugate is about 500 to about 176,000 Da. *Id.* at 69 (citing Ex. 1083 ¶ 406). Because this molecular-weight range overlaps the range recited in claim 1 of the '453 patent, Petition argues there is presumption of obviousness. *Id.* (citing *In re Peterson*, 315 F.3d 1325, 1329–30 (Fed. Cir. 2003)). According to Petitioner, JP-542 teaches modifying molecular weight to prolong residence time of a compound in the body, and thus, an ordinary artisan would have arrived at the claimed molecular weight range through routine experimentation. *Id.* at 69–70 (citing Ex. 1017 ¶¶ 5, 59; Ex. 1083 ¶ 407).

Patent Owner counters that Petitioner is attempting a “bait and switch” by relying on the compound of Test Example 1 (formula (14) conjugated to a biological agent) to provide certain structural limitations of claim 1, but then relying on formula (1) alone to provide the molecular weight limitation of claim 1. Prelim. Resp. 43–44. Patent Owner contends

Petitioner fails to explain why an ordinary artisan would have selected and modified the variables in formula (1) to arrive at the claimed structure, including the variables m , $AO_{(m)}$, Y , R^1 , R^2 , R^3 . *Id.* at 44–46. We agree.

In formula (14) of JP-542, each of the potential variables identified in formula (1) are predetermined. Ex. 1017 ¶ 52. Petitioner does not explain sufficiently why one of ordinary skill in the art, seeking to increase the molecular weight of different conjugated PEG compounds, would have maintained $(AO)_m$, R^1 , R^2 , and R^3 as shown in figure (14) and only modified the variable “ n .” And to the extent these other variables would have been modified, Petitioner does not explain sufficiently why one of ordinary skill in the art would have selected these variables in a manner that would result in a conjugate that satisfies all of the structural limitations of claim 1. Accordingly, Petitioner’s proposed modification appears to be based on a hindsight desire to arrive at the claimed invention, and not on what one of ordinary skill in the art would have been motivated to do based on the prior art and the general knowledge in the art at the time of the invention.

As a result, we determine that Petitioner has not demonstrated a reasonable likelihood that claim 1 would have been obvious over JP-542. Because Petitioner’s arguments with respect to dependent claims 2–18 do not cure the deficiencies identified above, Petitioner has also not demonstrated a reasonable likelihood of prevailing with respect to those claims either.

Obviousness over JP-542 and Katre

Petitioner argues that claims 1–18 would have been obvious over JP-452. Pet. 75–77. Petitioner relies on Katre for its disclosure of adjusting the type and size of a PEG polymer to manipulate the necessary therapeutic

dosages of conjugated drugs. *Id.* at 76. Petitioner does not sufficiently explain, however, why Katre would have taught or suggested to one of ordinary skill in the art manipulating only the variable “n” in figure (1) of JP-542 to achieve the increased molecular weight. Accordingly, for the reasons discussed above, Petitioner has not demonstrated a reasonable likelihood that claims 1–18 would have been obvious over JP-542 and Katre.

CONCLUSION

In view of the foregoing, Petitioner has not demonstrated a reasonable likelihood of prevailing on any grounds set forth in the Petition. Thus, we do not institute an *inter partes* review.

ORDER

In view of the foregoing, it is:

ORDERED that Petitioner’s request for an *inter partes* review of claims 1–18 of the ’453 patent is *denied* and no *inter partes* review is instituted.

IPR2019-01396
Patent 8,809,453 B2

FOR PETITIONER:

Thomas J. Donovan
Mark A. Hagedorn
Vincent P. Liptak
BARNES & THORNBURG LLP
thomas.donovan@btlaw.com
mhagedorn@btlaw.com
vincent.liptak@btlaw.com

FOR PATENT OWNER:

Edgar Haug
Brian Murphy
Angus Chen
Andrew Wasson
Kaitlin Abrams
HAUG PARTNERS LLP
ehaug@haugpartners.com
bmurphy@haugpartners.com
achen@haugpartners.com
awasson@haugpartners.com
kabrams@haugpartners.com