

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEPTUNE GENERICS, LLC,
Petitioner,

v.

NEKTAR THERAPEUTICS,
Patent Owner.

Before LORA M. GREEN, ROBERT A. POLLOCK, and
JACQUELINE T. HARLOW, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

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

I. INTRODUCTION

Neptune Generics, LLC (“Petitioner”) filed a Corrected Petition requesting an *inter partes* review of claims 1–4 of U.S. Patent No. 7,786,133 B2 (Ex. 1001, “the ’133 patent”). Paper 5 (“Pet.”). Nektar Therapeutics (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 11 (“Prelim. Resp.”).

We have jurisdiction 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.” Upon considering the Petition and the Preliminary Response, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–4. Accordingly, we decline to institute an *inter partes* review of those claims.

A. *Related Proceedings*

Petitioner states that it “is unaware of any other matter related to the [’]133 Patent.” Pet. 2; *see also* Paper 9 (listing only related patents and patent applications).

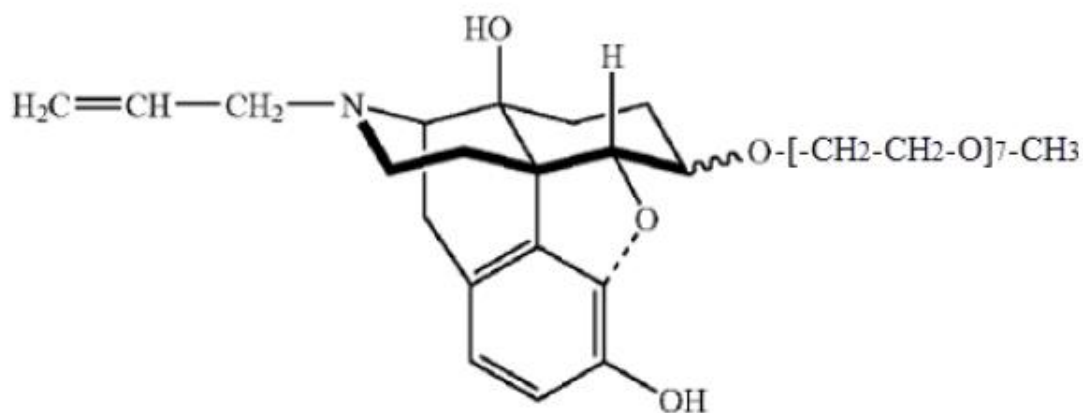
B. *The ’133 Patent (Ex. 1001)*

The ’133 patent issued on August 31, 2010, with Michael D. Bentley, Tacey X. Viegas, Richard R. Goodin, Lin Cheng, and Xuan Zhao as the listed co-inventors. Ex. 1001, (45), (75). The ’133 patent describes conjugates having the formula “O-X-D”, wherein O is a water-soluble oligomer, X is a stable linkage, and D is a moiety derived from a small molecule drug. *Id.* at 3:10–13. The ’133 patent provides examples wherein D is naloxol (*id.* at 36:1–21 (Example 4), 36:22–28 (Example 5); *id.* at

39:12–40:33 (Example 6)), and also looks at the bioavailability (*id.* at 42:22–44:8 (Example 8)), the *in vitro* metabolism (*id.* at 44:10–45:25 (Example 9)), and the antagonist activity on μ -opiate receptors of several PEGylated naloxol derivatives (*id.* at 45:27–46:4 (Example 10)).

C. Challenged Claims

Petitioner challenges claims 1–4 of the '133 patent. The claims are drawn to a conjugate of naloxone or naloxol linked to a polyethylene glycol ("PEG") oligomer, of the following structure:



See Pet. 16 (citing Ex. 1002 ¶ 18).

Claims 1–4 are reproduced below:

1. 6-CH₃—(OCH₂CH₂)₇—O-Naloxol or a pharmaceutically acceptable salt thereof.
2. α -6-CH₃—(OCH₂CH₂)₇—O-Naloxol or a pharmaceutically acceptable salt thereof.
3. β -6-CH₃—(OCH₂CH₂)₇—O-Naloxol or a pharmaceutically acceptable salt thereof.
4. A pharmaceutical composition comprising the compound of any one of claims 1-3, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–4 of the '133 patent on the following grounds (Pet. 19):

References	Basis	Claims Challenged
Bentley ¹	§ 102	1–4
Bentley, Ouchi ² and Erez ³	§ 103(a)	1–4

Petitioner relies also on the Declaration of Peter Wuts, Ph.D. (Ex. 1002).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable constructions in light of the specification of the patent in which they appear. See 37 C.F.R. § 42.100(b); (“Congress implicitly approved the broadest reasonable interpretation standard in enacting the AIA,” and “the standard was properly adopted by PTO regulation.”) *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015), *cert. granted, sub nom., Cuozzo Speed*

¹ Bentley et al., Pub. No. US 2003/0124086 A1; published July 3, 2003 (Ex. 1003) (“Bentley”).

² Ouchi et al., *Synthesis of 5-Fluorouracil-Terminated Monomethoxypoly (Ethylene Glycol)s, Their Hydrolysis Behavior, and Their Antitumor Activities*, 24 J. MACROMOLECULAR SCIENCE: PART A-CHEM: PURE AND APP. CHEM. 1011–32 (1987) (Ex. 1015) (“Ouchi”).

³ Erez et al., *Narcotic Antagonistic Potency of Bivalent Ligands Which Contain β -Naltrexamine. Evidence for Bridging between Proximal Recognition Sites*, 25 J. MED. CHEM. 847–49 (1982) (Ex. 1004) (“Erez”).

Techs. LLC v. Lee, 136 S. Ct. 890 (2016). Under the broadest reasonable construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

We determine that, for purposes of this Decision, none of the terms in the challenged claims require express construction at this time. *See, e.g., Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (noting that only claim terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy).

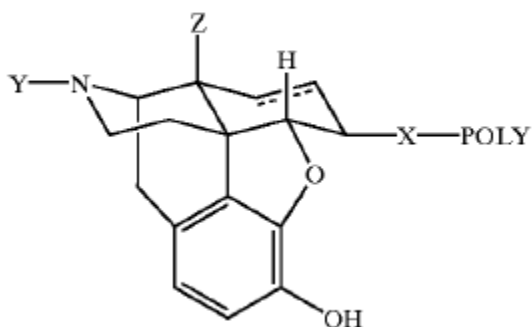
B. Anticipation by Bentley (Ex. 1003)

Petitioner asserts that claims 1–4 are anticipated by Bentley. Pet. 19–33. Patent Owner disagrees. Prelim. Resp. 9–30.

i. Overview of Bentley (Ex. 1003)

Bentley relates to “water-soluble polymer conjugates of biologically active molecules, and in particular, to water-soluble polymer conjugates of opioid antagonists, such as naloxone, and related pharmaceutical compositions and uses thereof.” Ex. 1003 ¶ 2. According to Bentley, the conjugate will generally have the formula POLY-X-A_O, wherein “POLY is a water-soluble and non-peptidic polymer,” such as poly(ethylene glycol); “X is a linkage, preferably a hydrolytically stable linkage covalently attaching the polymer to the opioid antagonist;” and “A_O is the opioid antagonist.” *Id.* ¶¶ 64–68. Bentley provides the two preferred configurations as to where the POLY is linked to the opioid antagonist, Formula Ia and Formula Ib. *Id.* ¶¶ 69–78.

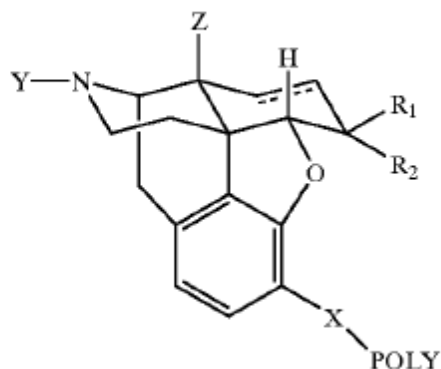
Formula Ia is shown below:



Id. ¶ 69.

In the above formula, “Y is C1-C6 alkyl, substituted C1-C6 alkyl, C3-C6 cycloalkyl, substituted C1-C6 cycloalkyl, C2-C6 alkenyl, substituted C2-C6 alkenyl, C2-C6 alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycle, and substituted heterocycle;” “Z is H or OH;” “the dashed line indicates an optional double bond;” and “X and POLY are as defined above.” *Id.* ¶¶ 70–74.

Formula Ib is shown below:



Id. ¶ 75.

In the above formula, “R₁ and R₂ are each independently hydrogen or OH, or together form =CH₂ or =O,” and XC, Y, Z, the dashed line, and POLY are as defined above for Formula Ia. *Id.* ¶¶ 76–78.

As taught by Bentley:

[T]he particular Y, Z, R₁, and R₂ groups employed will depend on the specific opioid antagonist used to form the polymer conjugate of the invention. Preferred opioid antagonists include naloxone or derivatives thereof (i.e., Y=allyl, Z=OH, R₁ and R₂ together form =O, no optional double bond), nalbuphine or derivatives thereof (i.e., Y=(cyclobutyl)methyl, Z=OH, R₁=H, R₂=OH, no optional double bond), nalmephenone or derivatives thereof (i.e., Y=(cyclopropyl)methyl, Z=OH, R₁ and R₂ together form =CH₂, no optional double bond), naltrexone or derivatives thereof (i.e., Y=(cyclopropyl)methyl, Z=OH, R₁ and R₂ together form =O), no optional double bond), and nalorphine or derivatives thereof (Y=allyl, Z=H, R₁=H, R₂=OH, optional double bond present).

Id. ¶ 80.

As to the polymer, Bentley teaches:

When referring to a polymer conjugate, it is to be understood that the polymer can be any of a number of water soluble and non-peptidic polymers, such as those described herein as suitable for use in the present invention. Preferably, poly(ethylene glycol) (PEG) is the polymer backbone. The term PEG includes poly(ethylene glycol) in any of a number of geometries or forms, including linear forms (e.g., alkoxy PEG or bifunctional PEG), branched or multi-arm forms (e.g., forked PEG or PEG attached to a polyol core), pendant PEG, or less preferably, PEG with degradable linkages therein.

Id. ¶ 83.

Bentley notes that the simplest form of PEG has the formula –CH₂CH₂O–(CH₂CH₂O)_n–CH₂CH₂–, wherein n is from about 2 to 45, typically from 2 to about 20. *Id.* ¶¶ 84–85. The polymer may be end capped with a relatively inert group, such as an alkoxy group. *Id.* at ¶ 86. Bentley

teaches that, for example, methoxy-PEG-OH (“MPEG”) may be used, which has the structure $\text{CH}_3\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-\text{OH}$. *Id.*

As for the linkage “X,” Bentley teaches that it “is intended to encompass any linkage between the polymer and the opioid antagonist molecule having an overall length of from 1 to about 20 atoms, preferably 1 to about 10 atoms.” *Id.* at ¶ 102. Bentley notes:

In Formula Ia above, the X linkage is preferably a secondary amine or amide linkage. In one embodiment of Formula Ia, X has the formula $-\text{NH}-(\text{CHR}_O)_m-\text{O}-$ or $-\text{NH}-\text{C}(\text{O})-(\text{CHR}_O)_n-\text{O}-$, wherein m is 1-12, preferably 1-4 (i.e., 1, 2, 3, or 4) and each R_O is independently H or Cl-C6 alkyl (e.g., methyl or ethyl). In Formula Ib above, the X linkage is preferably a heteroatom, such as an ether or thioether linkage (i.e., X=O or S).

Id. ¶ 103.

Bentley teaches exemplary conjugate structures. *Id.* ¶ 111. In particular, Bentley teaches:

An embodiment of a linear polymer of the invention can be structurally represented as shown below:

R-POLY-X-A_O

Formula V

wherein POLY is a water soluble and non-peptidic polymer backbone, R is a capping group or a functional group, and X and A_O are as defined above. In a preferred embodiment, R is methoxy, POLY is poly(ethylene glycol), X is a hydrolytically stable linkage such as amide, amine, carbamate, sulfide, ether, thioether, or urea, and A_O has the structure shown in Formula Ia or Formula Ib above.

Id. ¶¶ 113–114.

Bentley specifically exemplifies the synthesis of four different compounds, in which 6-amino-6-desoxo-naloxone is the opioid antagonist.

Id. ¶¶ 139–157. As to the four examples, Bentley explains:

Examples 1-4 illustrate methods of forming polymer conjugates using mPEG as the polymer backbone and 6-amino-6-desoxo-naloxone as the opioid antagonist. Examples 1 and 3 illustrate the formation of a hydrolytically stable secondary amine linkage between the polymer backbone and the opioid antagonist. Examples 2 and 4 illustrate the formation of a hydrolytically stable amide linkage between the polymer backbone and the opioid antagonist. Note that 6-amino-6-desoxo-naloxone exists as a mixture of two epimers, alpha and beta. Both epimers are believed to be active and, thus, a mixture of the two epimers can be used.

Id. at ¶ 141.

ii. *Analysis*

“It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus.” *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). Rather, “whether a generic disclosure necessarily anticipates everything within the genus . . . depends on the factual aspects of the specific disclosure and the particular products at issue.” *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1083 (Fed. Cir. 2008). Of “critical importance” in conducting this analysis is “how one of ordinary skill in the art would understand the relative size of a genus or species in a particular technology.” *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706 (Fed. Cir. 2012). On the one hand, “when the class of compounds that falls within the genus is so limited that a person of ordinary skill in the art can ‘*at once envisage* each member of this limited class,’ . . . a reference describing the genus anticipates every species within the genus.” *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (quoting *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006)) (emphasis added). However, where “the number of compounds actually disclosed by [the

asserted prior art] numbers in the millions (including all proposed alternative substituents),” the prior art genus cannot anticipate a later species claim. *Eli Lilly*, 471 F.3d at 1376. A person of ordinary skill in the art would understand to look at any expressed “pattern of preferences” in the prior art, such as preferred embodiments, in assessing the scope of the generic disclosure. *See, e.g., Sanofi-Synthelabo*, 550 F.3d at 1083. Therefore, to anticipate a later-claimed species, a pattern of preferences or other related teaching or suggestion must lead to a genus small enough that a person of ordinary skill in the art would at once envisage the claimed species. *Sanofi-Synthelabo*, 550 F.3d at 1083.

Petitioner contends that Bentley “expressly describes each and every element of the claims of the [’]133 Patent.” Pet. 19. According to Petitioner, “[a]pplying the specific preferences disclosed in [Bentley] leads to a defined and limited class of compounds that would have been at once envisaged by one of ordinary skill in the art.” *Id.* at 20.

Specifically, Petitioner argues that Bentley repeatedly uses naloxone as its preferred embodiment. *Id.* at 21. Petitioner asserts, relying on the Declaration of Dr. Wuts:

It would have been immediately envisioned by one of ordinary skill in the art, instead of reductively aminating the 6-keto group of naloxone, to convert the 6-keto group of naloxone to a PEG ether moiety through a reduction and alkylation sequence after protection of the phenolic hydroxyl. This conversion results in the stable ether linkage required by the compounds of the [’]133 Patent.

Id. (quoting Ex. 1002 ¶ 20).

Dr. Wuts testifies further:

a person of ordinary skill in the art, having studied Bentley, would have at once envisioned the molecules of all of claims 1-

4 of the [']133 Patent and would have been able to synthesize them readily from the disclosures of *Bentley* without undue experimentation or difficulty, especially since the formation of an ether is generally considered to be quite straight forward and the methodology used is called the Williamson ether synthesis which is a very old reaction.

Id. at 22 (quoting Ex. 1002 ¶ 23).

Specifically, in order to get to the compounds of the challenged claims, Petitioner notes that Bentley teaches the formula R-POLY-X-A_O, wherein R is a capping group or functional group, POLY is a water soluble, non-peptide polymer backbone, X is a linkage, and A_O is an opioid antagonist. *Id.* at 24 (citing Ex. 1003 ¶¶ 113–114). Petitioner asserts that Bentley teaches further that “in a preferred embodiment, ‘R is methoxy, POLY is poly(ethylene glycol), X is a hydrolytically stable linkage such as . . . ether, . . . and A_O has the structure shown in Formula Ia,’” wherein the structure of A_O is shown in structure Ia of Bentley. *Id.* at 25 (citing Ex. 1003 ¶¶ 113–114). Citing the testimony of Dr. Wuts, Petitioner contends that as Bentley specifically prefers naloxone as the opioid, the structure becomes 6-CH₃-(OCH₂CH₂)*n*-O-Naloxol. *Id.* at 25–26 (citing Ex. 1002 ¶ 26).

Petitioner contends further, that as explained by Dr. Wuts, Bentley “teaches a polyethylene glycol polymer (PEG) in which the ethylene oxide unit –(CH₂CH₂O)– appears, ‘typically, in the range of 2 to about 20’ times and the polymer is terminated by a methoxy group on one end and by a hydroxyl group, subject to chemical modification on the other end.” *Id.* at 26 (quoting Ex. 1002 ¶ 28). Thus, Petitioner asserts, the genus of naloxone derivatives described by Bentley would be understood by the ordinary artisan as being drawn to the number of ethylene oxide units. *Id.* at 26–27. As Bentley does not provide any preference for the seven monomer units,

the ordinary artisan “would understand and readily envisage the entire genus of about 19 variations.” *Id.* at 27 (quoting Ex. 1002 ¶ 28).

Patent Owner responds that the genus of only about 19 variations is not disclosed by Bentley, but is only arrived at by picking and choosing potential substituents. PO Resp. 12. Specifically, Patent Owner contends that the genus of Bentley is defined by POLY-X-A_O, and Bentley then goes on to define two Formula I compounds, Formula Ia, wherein the polymer is attached at the 6-position, and Formula Ib, wherein the polymer is attached at the 3-position. *Id.* at 13–14 (citing Ex. 1003 ¶¶ 64–68). Patent Owner, therefore, asserts that “the Bentley genus is made up of several variables: the opioid antagonist (which also implicates the substituents thereto), the polymer, the linkage, and the configuration (Ia or Ib).” *Id.* at 14. Patent Owner argues further that “Bentley discloses a substantial range of ‘preferred’ options for these variables.” *Id.*

According to Patent Owner, Bentley lists five preferred opioid antagonists, as well as derivatives thereof. *Id.* (citing Ex. 1003 ¶¶ 79–80). Patent Owner argues further that the term PEG includes poly(ethylene glycol) in a number of geometries, including linear, branched, and forked. *Id.* at 25 (citing Ex. 1003 ¶ 83). Bentley teaches also that the linkage can take many forms, such as “amides, sulfides, amines, and ethers, among others.” *Id.* at 15 (citing Ex. 1003 ¶¶ 100–102). Thus, Patent Owner asserts, “[g]iven the breadth of options presented, there can be no dispute that Neptune’s estimate that Bentley discloses a genus of ‘about 19’ member is off by orders of magnitude.” *Id.*

Moreover, Patent Owner contends that even if one were to rely on Formula V of Bentley as the starting point, Formula V is not a genus of

about 19 compounds. *Id.* at 18. Patent Owner asserts that Petitioner “certainly has not demonstrated that a person of ordinary skill in the art would immediately envisage all of its members.” *Id.*

Patent Owner acknowledges that “Bentley teaches the following preferences for Formula V: ‘In a preferred embodiment, R is methoxy, POLY is poly(ethylene glycol), X is a hydrolytically stable linkage such as amide, amine, carbamate, sulfide, ether, thioether, or urea, and A_O has the structure shown in Formula Ia or Formula Ib above.’” *Id.* at 18–19 (quoting Ex. 1003 ¶ 114). Patent Owner notes that naloxone is only one many preferred opioid antagonists, and argues that Petitioner ignores the derivatives of those compounds. *Id.* at 19–20 (citing Ex. 1003 ¶ 80).

In addition, Patent Owner notes that Formula V encompasses “two possible configurations: one in which the polymer is attached to the opioid antagonist at the 6-position (Formula Ia), and one in which the polymer is attached at the 3-position (Formula Ib),” arguing that Petitioner fails to address the two possible configurations. *Id.* at 21–22.

Petitioner, Patent Owner asserts, also fails to address that Bentley teaches that linkage X “is a hydrolytically stable linkage such as amide, amine, carbamate, sulfide, ether, thioether, or urea.” *Id.* at 22 (quoting Ex. 1003 ¶ 22). And more specifically, Patent Owner argues that Petitioner ignores the teaching of Bentley that amine or amide linkages are preferred for Formula 1a, which has the configuration of the challenged claims, and not an ether linkage. *Id.* at 23–24 (citing Ex. 1003 ¶ 103). Petitioner, Patent Owner argues, rationalizes the use of the ether linkage by asserting that “the formation of an ether is generally considered to be quite straight forward [sic] and the methodology used is called the Williamson ether synthesis

which is a very old reaction.” *Id.* at 24 (quoting Pet. 22). That assertion is irrelevant, Patent Owner asserts, as it has no impact on the size of the genus disclosed by Bentley. *Id.* Further, according to Patent Owner, Bentley teaches also that the linkage can contain additional atoms, which further expands the genus. *Id.* at 24–25 (citing Ex. 1003 ¶ 103).

We agree with Patent Owner. That is, Petitioner has not demonstrated that “the size of [the] Bentley genus ‘depends solely on the number’ of monomer units in the PEG moiety.” Prelim. Resp. 25 (quoting Pet. 26–27). Petitioner fails to demonstrate why the ordinary artisan would immediately envisage Formula V of Bentley in which A_O is the configuration of Formula Ia, the linkage is a simple ether linkage, and having the required number of monomer units in the PEG moiety. *See In re Arkley*, 455 F.2d 586, 587 (CCPA 1972) (noting that an anticipatory reference under 35 U.S.C. § 102 “must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.”).

In particular, as noted by Patent Owner, Bentley teaches that the linkage X “is intended to encompass any linkage between the polymer and the opioid antagonist molecule having an overall length of from 1 to about 20 atoms, preferably 1 to about 10 atoms.” Ex. 1003 ¶ 102; *see also* Prelim. Resp. 15. Bentley notes that for Formula Ia, “the X linkage is preferably a secondary amine or amide linkage,” whereas for Formula Ib, “the X linkage is preferably a heteroatom, such as an ether or thioether linkage.” *Id.* ¶ 103. While Bentley exemplifies naloxone derivatives having the configuration of Formula Ia, they all use a secondary amine or amide linkage between the

polymer backbone and the opioid antagonist. *Id.* ¶ 141. Petitioner does not explain why, given the number of linkages encompassed by “X” in Formula V of Bentley, as well as Bentley’s preference for a secondary amine or amide linkage for compounds with the configuration of Formula Ia, the ordinary artisan would have immediately envisaged the compounds of the challenged claims.

iii. Conclusion

For the reasons set forth above, we conclude that Petitioner has not established a reasonable likelihood that claims 1–4 are anticipated by Bentley.

*C. Obviousness over Bentley (Ex. 1003),
Ouchi (Ex. 1015), and Erez (Ex. 1004)*

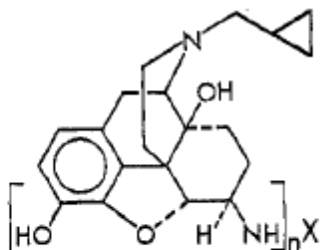
Petitioner contends that claims 1–4 are rendered obvious by the combination of Bentley, Ouchi, and Erez. Pet. 34–50. Patent Owner disagrees. Prelim. Resp. 30–32.

i. Overview of Ouchi (Ex. 1015)

Ouchi teaches the “covalent attachments of 5-fluorouracil (5FU) units to poly(ethylene glycol) monomethoxy ether (MeO-PEG) attached through ester, amide, and ether bonds.” Ex. 1015, Abstract. Ouchi teaches that 5FU has “remarkable antitumor activity.” *Id.* at 1012. According to Ouchi, a “polymeric drug such as 5FU attached to a polymer can be expected to have reduced toxicity, increased duration of antitumor activity, and, additionally, a possible affinity for tumor cells.” *Id.* Ouchi teaches that *n* may be between 1 and 230, or 1 and 110, depending on the conjugate. *Id.* at 1012–1013.

ii. Overview of Erez (Ex. 1004)

Erez teaches “bivalent ligands (P-X-P) containing the β -naltrexamine pharmacophore (P) and a connecting oligoethylene glycol spanner (X),” which were evaluated for narcotic antagonistic activity. Ex. 1004, Abstract. Specifically, Erez teaches the following compounds:



	<u>n</u>	<u>X</u>
1	1	H
2	2	CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂
3	2	(CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂) ₂ O
4	1	CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂ OCH ₃
5	1	CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂ OTs

Id. at 847.

Erez teaches that “bridging of a bivalent ligand between proximal recognition sites . . . leads to enhanced affinity.” *Id.* at 848. According to Erez, the increases in narcotic antagonistic activity of the bivalent ligands are dependent on the length of the spanner. *Id.* Erez notes that different opioid receptors have different selectivity towards the bivalent ligands, suggesting that different receptors have different bridging distances. *Id.* at 849. Erez teaches that “the bivalent ligand approach offers a new avenue for the design of agents which are highly selective for a specific subpopulation of opioid receptors.” *Id.*

iii. *Analysis*

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 18 (1966). An invention “composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. Moreover, a rejection on the ground of obviousness must include “articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The obviousness analysis “should be made explicit” and it “can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR*, 550 U.S. at 418.

Petitioner relies on Bentley as described above in the challenge based on anticipation, asserting that “Bentley discloses the compound of claim 1.” Pet. 35 (emphasis omitted). In particular, Petitioner contends that as “explained by Dr. Wuts, ‘Bentley taught how to prepare drug conjugates, wherein PEG is covalently attached to naloxone derivative through an ether linkage.’” *Id.* at 37 (quoting Ex. 1002 ¶ 34) (emphasis omitted).

Petitioner relies on Ouchi for its teaching that PEG moieties are readily conjugated to the small molecule, 5-fluorouracil, using hydrolysable or non-hydrolysable linkers. *Id.* at 36. Petitioner relies also on Erez for its teaching the conjugation of PEG to β -naltrexamine, which Petitioner argues has a structure similar to that of naloxol, through an amine linkage. *Id.* at 38 (citing Ex. 1002 ¶ 34).

Relying on the Declaration of Dr. Wuts, Petitioner argues that Bentley teaches “a methoxy-PEG conjugated through an ether linkage to a naloxone derivative wherein PEG has repeating subunits in the range of 2-20.” *Id.* at 36 (quoting Ex. 1002 ¶ 34). According to Dr. Wuts, Ouchi, as well as others, taught that “PEG polymers could be conjugated to small molecule drugs through a variety of linker types and a finite number of repeating subunits of PEG (*e.g.*, $n=1, 4, 7, 15$ and 110) that affected various biological and physical aspects of the conjugate.” *Id.* at 36–37 (quoting Ex. 1002 ¶ 34). Dr. Wuts, thus, testifies that the ordinary artisan,

interested in changing the biological and physical aspects of a drug conjugate would have been motivated to prepare the conjugates taught by Bentley and test a variety of sizes of PEG in the conjugate including lengths in the range of $n=2-20$, or $n=1, 4, 7$, and 15 , as taught by Bentley and Ouchi and others.

Id. at 37 (quoting Ex. 1002 ¶ 34) (emphasis omitted).

Petitioner argues further:

[T]he fact that one is an amine and the other is an ether is a moot point given the general interconvertability of these functional groups in a medicinal chemistry sense. Based on the teachings of Ouchi, it would have been obvious to an ordinarily skilled chemist that an ether linkage could be substituted for the amine as demonstrated by Erez, especially given the similarity in the structures of the basic drugs: naltrexamine and naloxol.

Id. at 38–39 (quoting Ex. 1002 ¶ 35).

Therefore, according to Petitioner, the ordinary artisan “would have had a reasonable expectation of success in preparing and testing PEG-naloxol conjugates as described by Bentley with variation in polymer length as described by Ouchi to arrive at claim 1 of the [‘]133 Patent especially since ether synthesis is one of the more commonly used reactions in organic chemistry.” *Id.* at 37–38 (quoting Ex. 1002 ¶ 34) (emphasis omitted); *see also id.* at 42–45 (presenting similar arguments that the ordinary artisan would have had a reason to combine Bentley, Ouchi, and Erez, as well as have a reasonable expectation of success at arriving at the claimed invention).

Patent Owner responds that Petitioner’s obviousness argument fails for similar reasons as the anticipation argument. Prelim. Resp. 30–31. Patent Owner contends further that Petitioner “similarly fails to identify which modifications must be made to arrive at the claimed invention, what reason a person of ordinary skill in the art would have had for making any such modifications, and why such a person would have had a reasonable expectation of success.” *Id.* at 31.

In addition, Patent Owner asserts that the addition of Erez and Ouchi do not make up the deficiencies of Bentley, and are at best, cumulative to that reference. *Id.* at 32. Erez, Patent Owner argues, favors an amine linker, as well as a PEG length where $n=3$. *Id.* Ouchi, according to Patent Owner, supports the use of a variety of linkers, as well as a wide range of PEG chain lengths, and addresses compounds with very different biological properties. *Id.*

We agree with Patent Owner that Petitioner has failed to demonstrate a reasonable likelihood that challenged claims 1–4 are rendered obvious by

the combination of Bentley, Erez, and Ouchi. “The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.” *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994). A very broad genus, without more, may weigh against a determination that a species or relatively narrow subgenus is obvious over the genus; even a relatively small genus does not create an automatic presumption of obviousness—there must still be some reason, stemming from the prior art, to select the claimed species or subgenus, *see, e.g., Baird*, 16 F.3d at 382; *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992).

A related consideration is whether the prior art highlights any “typical,” “preferred,” or “optimum” species within the genus. Highlighted species different from those claimed may weigh against a determination of obviousness. *Baird*, 16 F.3d at 382. On the other hand, typical, preferred, or optimum species structurally similar to those claimed may be evidence supporting a determination of obviousness. *In re Dillon*, 919 F.2d 688, 696 (Fed. Cir. 1990).

We do not disagree with Petitioner that the challenged claims are encompassed by the genus of Bentley, and that all the components of the compounds recited by the challenged claims are also known. To establish the claims are obvious, however, Petitioner must also identify a reason that would have led a person of ordinary skill in the art to combine the elements of Bentley, Ouchi, and Erez in the manner specified by the claims. *See KSR*, 550 U.S. at 418 (“[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.”); *see also id.* (“[A] patent composed of several elements is not proved obvious merely by

demonstrating that each of its elements was, independently, known in the prior art.”).

Specifically, assuming that Formula V of Bentley, i.e., R-POLY-X-A_O, is the proper starting point, Bentley teaches that “[i]n a preferred embodiment, R is methoxy, POLY is poly(ethylene glycol), X is a hydrolytically stable linkage such as amide, amine, carbamate, sulfide, ether, thioether, or urea, and A_O has the structure shown in Formula Ia or Formula Ib above.” Ex. 1003 ¶¶ 113–114. Petitioner has failed provide a reason, with rational underpinning, why the ordinary artisan would have picked the conjugate of Ia, combined with a simple ether linkage, and use the required number of monomer units in the PEG moiety to arrive at the compound of the challenged claims.

In that regard, we note that Bentley teaches that the linkage X “is intended to encompass any linkage between the polymer and the opioid antagonist molecule having an overall length of from 1 to about 20 atoms, preferably 1 to about 10 atoms.” Ex. 1003 ¶ 102. Bentley notes that for Formula Ia, “the X linkage is preferably a secondary amine or amide linkage,” whereas for Formula Ib, “the X linkage is preferably a heteroatom, such as an ether or thioether linkage.” *Id.* ¶ 103. While Bentley exemplifies naloxone derivatives having the configuration of Formula Ia, they all use a secondary amine or amide linkage between the polymer backbone and the opioid antagonist. *Id.* ¶ 141.

Petitioner and its expert, Dr. Wuts, assert that the ordinary artisan would have used an ether linkage “given the general interconvertability of these functional groups.” Pet. 38–39 (quoting Ex. 1002 ¶ 35). Dr. Wuts does not provide a reason with rationale underpinnings, however, why the

ordinary artisan would have chosen a simple ether linkage given Bentley's teaching that the linkage may have a length of preferably 1 to 10 atoms, and given Bentley's preference that X is a secondary amine or amide linkage when the configuration of Formula Ia is used. Moreover, Dr. Wuts simply makes the conclusory statement that the use of amines and ethers are interchangeable in medicinal chemistry, but provides no evidentiary support for that statement. *See* 37 C.F.R. § 42.65(a); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,763 (Aug. 14, 2012) ("Affidavits expressing an opinion of an expert must disclose the underlying facts or data upon which the opinion is based."). Dr. Wuts also provides no reason why the ordinary artisan would have considered amines and ethers to be interchangeable in the context of the conjugates taught by Bentley.

iv. Conclusion

For the reasons set forth above, we conclude that Petitioner has not established a reasonable likelihood that claims 1–4 are rendered obvious by the combination of Bentley, Erez, and Ouchi.

III. CONCLUSION

Upon review of the Petition and Preliminary Response, as well as the evidence relied upon by Petitioner, for the foregoing reasons, we determine that the information presented in the Petition fails to establish a reasonable likelihood that claims 1–4 of the '133 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is DENIED and no trial is instituted.

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