

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOF CORPORATION,
Petitioner,

v.

NEKTAR THERAPEUTICS,
Patent Owner.

IPR2019-01398
Patent 8,273,833 B2

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

TORNQUIST, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

A. Background

NOF Corporation (“Petitioner”) filed a Petition (Paper 1, “Pet.”) requesting an *inter partes* review of claims 1–10 of U.S. Patent No. 8,273,833 B2 (Ex. 1003, “the ’833 patent”). Nektar Therapeutics (“Patent Owner”) filed a Preliminary Response to the Petition. Upon review of the parties’ arguments and supporting evidence, on February 12, 2020, we instituted an *inter partes* review of all claims and grounds asserted in the Petition (Paper 17, “Institution Decision” or “Inst. Dec.”).

Patent Owner subsequently filed a Response (Paper 44, “PO Resp.”), Petitioner filed a Reply (Paper 49, “Pet. Reply”), and Patent Owner filed a Sur-Reply (Paper 53, “Sur-Reply”).

In support of its Petition, Petitioner originally relied upon the declaration testimony of Dr. Yuji Yamamoto. Ex. 1083. In light of scheduling difficulties caused by COVID-19, however, we authorized Petitioner to replace Dr. Yamamoto’s declaration with that of Dr. Todd Emrick (Ex. 1084¹), who also filed a reply declaration (Ex. 1095).

Patent Owner relies on the declaration testimony of Dr. Steven R. Little. Ex. 2036.

With authorization, Petitioner filed a motion requesting a good cause extension of the deadline for issuing a final written decision in this proceeding. Paper 34. Patent Owner opposed this motion. Paper 36. On July 31, 2020, a revised Due Date Appendix was issued and on January 29,

¹ In view of the replacement of Dr. Yamamoto’s declaration (Ex. 1083) with an essentially identical declaration from Dr. Emrick (Ex. 1084), we treat all citations to Exhibit 1083 in the Papers and Exhibits as citations to Exhibit 1084.

2021, the time to administer the present proceeding was extended by up to six months, i.e., from February 12, 2021, up to August 12, 2021. Paper 42 (Revised Due Date Appendix); Paper 59, 2–3 (good cause extension granted by the Chief Administrative Patent Judge); Paper 58, 2–3 (Panel Order extending the current proceeding by up to six months).

An oral hearing was held on July 21, 2020, and a transcript of the hearing is included in the record. Paper 63 (“Tr.”).

B. Real Parties in Interest

Petitioner identifies itself and NOF America Corporation as real parties-in-interest. Pet. 2. Patent Owner identifies itself, Baxalta Incorporation, Baxalta US Inc., and Takeda Pharmaceutical Company Limited as real parties-in-interest. Paper 4, 1.

C. Related Proceedings

Petitioner identifies *Nektar Therapeutics et al. v. Bayer Healthcare, LLC*, 1-18-cv-01355 (D. Del. August, 31, 2018) as a related matter. Pet. 2. Patent Owner identifies *Baxalta Incorporated v. Bayer Healthcare LLC*, No. 17-1316 (D. Del.) (consolidated) as a related matter. Paper 6, 1.

Inter partes review was granted with respect to related patents in IPR2019-01394 and IPR2019-01397. Pet. 2–3; Paper 4, 1–2. Review was denied in IPR2019-01392, IPR2019-01395, and IPR2019-01396. *See* IPR2019-01392, Paper 23; IPR2019-01395, Paper 27; IPR2019-01396, Paper 19.

D. The '833 Patent

The '833 patent discloses “branched, reactive water soluble polymers useful for conjugating to biologically active molecules” and “methods for making and utilizing such polymers.” Ex. 1003, 1:17–19. The '833 patent explains that it was known in the art that covalent attachment of hydrophilic

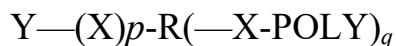
polymer poly(ethylene glycol), or PEG, may increase water solubility and bioavailability of biologically active molecules, particularly hydrophobic molecules. *Id.* at 1:22–30 (citing Greenwald, et al., *J. Org. Chem.*, 60:331–336 (1995)). The total molecular weight of the attached polymers is chosen to provide the advantageous characteristics typically associated with PEG polymer attachment, while at the same time avoiding “adversely impacting the bioactivity of the parent molecule.” *Id.* at 1:30–36.

The '833 patent instructs that the “branched reactive polymer of the invention will typically comprise at least two water-soluble and non-peptidic polymer arms, such as poly(ethylene glycol) arms, covalently attached to an aliphatic hydrocarbon core structure bearing a single functional group.” *Id.* at 7:11–15. “Typically, the total number average molecular weight of the branched reactive polymers of the invention will be about 500 to about 100,000 daltons (Da), preferably about 5,000 to about 60,000 Da, most preferably about 8,000 to about 40,000 Da.” *Id.* at 6:64–7:1.

E. Illustrative Claim

Claim 1 is illustrative of the challenged claims and is reproduced below:

1. A branched reactive polymer having the structure:



wherein:

Y is a functional group reactive with an electrophilic or nucleophilic group;

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

X' is —O—;

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

P is 0 or 1;

q is 2 to about 10; and

each POLY is a water soluble and non-peptidic polyethylene glycol (PEG) polymer that terminates with a hydroxyl or methoxy group,

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

Ex. 1003, 24:10–26.²

F. Prior Art and Instituted Grounds

We instituted review of claims 1–10 of the '833 patent on the following grounds:

Claim(s) Challenged	35 U.S.C. §³	Reference(s)/Basis
1–10	103(a)	Bentley, ⁴
1–10	103(a)	Bentley, MDD ⁵
1–10	103(a)	Bentley, Harris ⁶
1–5, 7–10	103(a)	JP-542 ⁷
6	103(a)	JP-542, Bentley
1–10	103(a)	JP-542, Kohno ⁸

² Although the formula above does not include X', we understand claim 1 to require a branched reactive polymer having the structure: Y—(X)_p-R(—X'-POLY)_q. See Ex. 1003, 7:18; Pet. 20; PO Resp. 14 (Patent Owner asserting that claim 1 requires “the group of branched reactive polymers having the structure Y—(X)_p-R(—X'-POLY)_q”).

³ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the effective filing date of the challenged claims of the '833 patent is before this date, the pre-AIA version of these statutes apply. See 35 U.S.C. § 100(i)(2); Ex. 1003, code (22).

⁴ Bentley, US 5,990,237, issued November 23, 1999 (Ex. 1015) (“Bentley”).

⁵ Steven A. Charles, et al., *Improving Hepatitis C Therapy*, Modern Drug Discovery, September 2000 (Ex. 1029) (“MDD”).

⁶ Harris, US 5,932,462, issued August 3, 1999 (Ex. 1016) (“Harris”).

⁷ Sanchika et al., JP P2000-1542A, published January 7, 2000 (Ex. 1017) (“JP-542”).

⁸ Kohno et al., WO 95/34326, published December 21, 1995 (Ex. 1027) (“Kohno”).

II. ANALYSIS

A. Claim Construction

In this proceeding, the claims of the '833 patent are construed “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) (2019). Under that standard, the words of a claim are generally given their “ordinary and customary meaning,” which is the meaning the term would have had to a person of ordinary skill at the time of the invention, in the context of the entire patent including the specification. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Upon review of the parties’ arguments and supporting evidence, we determine that no claim terms require construction for purposes of this decision. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (“[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.”)).

B. Principles of Law

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter 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. *See 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) if in the record, objective

evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

C. Level of Ordinary Skill in the Art

Petitioner contends a person of ordinary skill in the art would have had a Ph.D. in chemistry, biochemistry, materials science, or a related field and 3–5 years of experience working in the field of synthesis of active PEG polymers for PEGylation of biological molecules. Pet. 17 (citing Ex. 1084 ¶¶ 45–48). Petitioner further contends that one of ordinary skill in the art alternatively could have been a “highly skilled scientist” without a Ph.D., but having “additional years of experience working with PEGylation polymer synthesis and chemistries for modification of biomolecules.” *Id.*

Patent Owner contends a person of ordinary skill in the art would have had “at least a master’s degree in organic chemistry, biochemistry, or a comparable discipline with several years of experience with water-soluble polymers useful for conjugation to biologically active molecules, their synthesis, characterization, and/or application to biologically active molecules.” PO Resp. 6–7 (citing Ex. 2036 ¶¶ 54, 58).

The parties’ definitions of the ordinarily skilled artisan are similar, requiring an advanced degree in a relevant field and several years of experience in synthesizing or applying water-soluble polymers, such as PEG, to biologically active molecules. *Compare* Pet. 17, *with* PO Resp. 6–7. The parties’ definitions differ in that Petitioner requires experience working directly with active PEG polymers used for conjugation to biological molecules, whereas Patent Owner’s definition allows for experience with the broader group of “water-soluble polymers useful for conjugation to biologically active molecules.” Pet. 17; PO Resp. 6–7. Upon review of the ’833 patent and the prior art of record, we adopt Patent

Owner's definition of one of ordinary skill in the art, as it is consistent with the disclosures of the '833 patent and the prior art of record, and more inclusively describes the suitable experience for one of ordinary skill in the art. We note, however, that neither party asserts that selection between the two definitions of the level of ordinary skill in the art would impact any issue presented in this case.⁹

D. Obviousness of Claims 1–10 Over Bentley

Petitioner contends that claims 1–10 would have been obvious over the disclosures of Bentley. Pet. 18–33.

1. Bentley

Bentley discloses a method of coupling a poly(ethylene glycol) polymer (PEG) to a biomaterial. Ex. 1015, 1:8–11. Bentley explains that both linear and branched PEG molecules had been used in the art to improve the solubility of “water insoluble compound[s],” without altering the compound's biological activity. *Id.* at 1:60–2:1. Bentley further explains that conjugation of PEG to a drug molecule may result in enhanced blood circulation lifetime for the conjugated drug due to reduced kidney clearance and reduced immunogenicity. *Id.* at 2:6–11.

Bentley explains that conjugation of PEG to a drug molecule requires the use of an activated derivative “having a functional group at the terminus suitable for reaction with a group on the other molecule.” *Id.* at 2:12–15.

⁹ Petitioner argues in its Reply that Patent Owner fails to account for the general knowledge of one of ordinary skill in the art. Pet. Reply 12–13. Petitioner does not argue, however, that this general knowledge would differ between the two proffered definitions of one of ordinary skill in the art. *Id.* (citing Ex. 1084 ¶¶ 134–139); *see also* Sur-Reply 5 (asserting that Petitioner's resort to general knowledge in the art cannot substitute for record evidence).

For example, a hydroxyl group on the PEG compound can be converted to an aldehyde group (forming PEG acetaldehyde) and then this aldehyde group can be covalently linked to an amine group on a target molecule in a process called reductive amination. *Id.* at 2:15–20.

Bentley indicates that one problem reported in the art with respect to the use of PEG acetaldehyde is its high reactivity, “which leads to condensation side reactions.” *Id.* at 2:42–45. Bentley also reports that PEG acetaldehyde is “difficult to prepare in high purity,” requiring additional purification steps that result in the “loss of valuable bioactive molecules, such as proteins.” *Id.* at 2:46–54. To overcome these difficulties, Bentley discloses the use of activated PEG molecules having an aldehyde hydrate moiety. *Id.* at 3:3–10. According to Bentley, the use of an aldehyde hydrate moiety to conjugate PEG to a target molecule avoids the condensation and oxidation reactions that hindered prior art conjugation methods. *Id.* at 3:9–15.

The activated PEG polymer of Bentley may be linear or branched and typically has an average molecular weight of from 200 to 100,000 Da. *Id.* at 6:35–36. As biological properties may vary based on molecular weight and the degree of branching, Bentley discloses that “not all” activated derivatives “may be useful for biological or biotechnical applications.” *Id.* at 6:35–39.

Bentley reports that “[f]or many biological and biotechnical applications, substantially linear, straight-chain PEG acetaldehyde hydrate is useful.” *Id.* at 6:40–42. This linear PEG may be capped on one end with a relatively nonreactive moiety, such as methyl, benzyl and aryl moieties, and conjugated to either a “surface” or a “substance” “selected from, e.g., proteins, peptides, oligonucleotides, polysaccharides and small drug molecules.” *Id.* at 6:12–15, 6:44–52, 7:44–46. According to Bentley,

“[b]roadly speaking, any material having a reactive amine group accessible to the activated polymer having an aldehyde hydrate group can be used in the present invention.” *Id.* at 6:15–18.

“Another form of activated PEG aldehyde hydrate is dendritic activated PEG in which multiple arms of PEG are attached to a central core structure.” *Id.* at 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 notes that such “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.

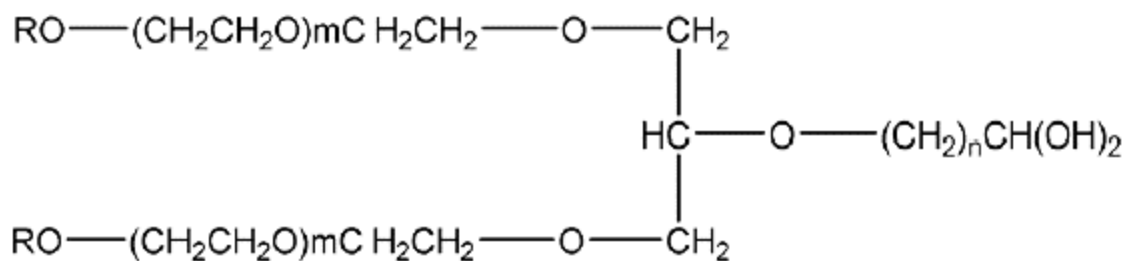
Bentley discloses that the aldehyde hydrate moiety on the “star” molecules can be used to provide an active, functional group on the end of the PEG chain extending from the core, or may act as a linker for joining a functional group to the star molecule arms. *Id.* at 7:8–12.

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
$$[\text{RO}-(\text{CH}_2\text{CH}_2\text{O})_m\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2]_2\text{CH}-\text{O}-(\text{CH}_2)_n\text{CH}(\text{OH})_2$$
wherein R is H, alkyl, benzyl, or aryl; m ranges from about 5 to about 3000, [and] n ranges from 1 to 6.

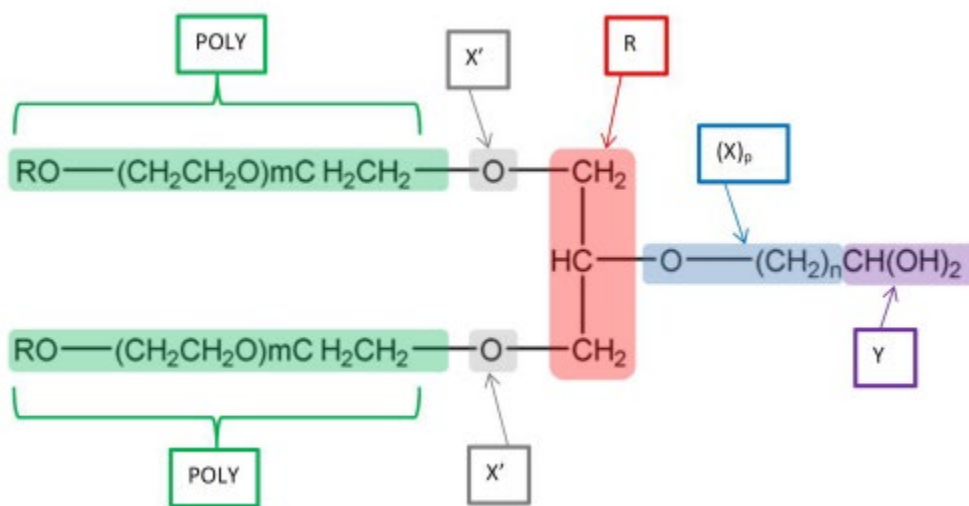
Id. at 7:12–20.

2. Analysis: Claim 1

Petitioner contends the dendritic “star” molecule of Bentley identified above may be drawn as follows:



Pet. 12, 19. The figure above is Petitioner’s depiction of the chemical structure identified at column 7, lines 16–20 of Bentley. *Id.* (citing Ex. 1015, 7:12–20) (referred to herein as “Bentley’s genus” or “the star molecule of Bentley”). Petitioner maps the limitations of claim 1 to this structure in the following annotated figure (*id.* at 19–20):



The figure reproduced above is an annotated and color-coded depiction of the dendritic “star” molecule of Bentley. *Id.* at 18–19. Referring to its annotated figure, Petitioner persuasively demonstrates that Bentley discloses a branched reactive polymer having the formula $\text{Y}-(\text{X})_p\text{-R}-(\text{X}'\text{-POLY})_q$ (*id.* at 19), wherein R is an aliphatic hydrocarbon having three carbon atoms

(red) (*id.* at 21–22), each POLY chain is composed of “polyethylene glycol,” a water soluble and a non-peptide polymer that terminates in a hydroxyl or capping group (green) (*id.* at 23–25), X' is an ether (-O-) heteroatom linkage (grey) (*id.* at 22), X is a linker ($-\text{O}-(\text{CH}_2)_n-$), wherein n is 1 to 6 and p is 1 (blue) (*id.*), q (the number of polymer arms) is 2 (*id.* at 23), and Y is an aldehyde hydrate functional group ($-\text{CH}(\text{OH})_2$) (purple) that is reactive with an electrophilic or nucleophilic group (*id.* at 20–21).

With respect to the requirement that the branched polymer have a “molecular weight of about 12,000 Da to about 100,000 Da,” Petitioner contends that “m” in Bentley’s formula ranges from about 5 to about 3,000, which describes a molecular weight range of about 220 Da to about 132,000 Da for each PEG chain (POLY), and results in a total polymer molecular weight range for the branched reactive polymer of at least 440 to about 264,000 Da. Pet. 25 (citing Ex. 1015, 7:12–20, 14:59–65; Ex. 1084 ¶¶ 313–315). Petitioner further contends that the overlap in the disclosed range of Bentley (at least 440 to about 264,000 Da) with the claimed range (about 12,000 Da to about 100,000 Da) renders the claimed range *prima facie* obvious.¹⁰ *Id.* at 25–27 (citing *In re Peterson*, 315 F.3d 1325, 1329–30 (Fed. Cir. 2003); Ex. 1084 ¶ 315).

¹⁰ Petitioner also asserts that because PEG units are added in whole numbers, one of ordinary skill in the art would at once envisage specific PEG chains providing molecular weights in the claimed range of about 220 to 100,000 Da and this skilled artisan would have been fully capable of implementing these disclosures. Pet. 25–26 (citing *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015)). We need not address this argument because Petitioner does not assert that Bentley anticipates the challenged claims, and the overlapping nature of Bentley’s molecular weight range renders the claimed range *prima facie* obvious.

Patent Owner asserts that Petitioner's arguments with respect to claim 1 fail because (1) a "lead compound" analysis is required in this case, (2) Petitioner has not demonstrated that the reasoning of *Peterson* applies to the facts of this case, (3) Petitioner has not shown that one of ordinary skill in the art would have selected the specific genus of polymers in Bentley for further development, (4) Petitioner has not shown that one of ordinary skill in the art would have selected a subgenus of polymers from Bentley having the claimed molecular weights, (5) Petitioner has not demonstrated a reasonable expectation of success in achieving the claimed invention, and (6) indicia of non-obviousness rebut any prima facie case of obviousness. PO Resp. 13–29, 57–60. We address these arguments below.

a) Law of Obviousness

One overarching dispute between the parties is how the law of obviousness applies in this case. Petitioner argues that we should apply standard principles of obviousness. Pet 18–19; Pet. Reply 2–3. In contrast, Patent Owner argues that we must (or at least should) apply a "lead compound" analysis when assessing whether the claimed genus of chemical compounds would have been obvious over the prior art of record. PO Resp. 9–10, 17–18; Sur-Reply 2–5.

The case law regarding "when a species is patentable over a genus claimed in the prior art is less than clear." *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1364 (Fed. Cir. 2007) (Dyk, J., concurring). We look, therefore, to the general law of obviousness for guidance. In *KSR*, the Supreme Court instructed that we must take "an expansive and flexible approach to the obviousness question," focusing on "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 415, 419. In

conducting this analysis, we must “consider all disclosures of the prior art” (*In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991)), and we do not require that a petitioner “prove that a person of ordinary skill would have been motivated to select one prior art disclosure over another.” *Infineum USA L.P. v. Chevron Oronite Co.*, 2021 WL 210722, at *6 (Fed. Cir. Jan. 21, 2021) (non-precedential). Nor must a petitioner demonstrate that the “prior art suggests that the combination claimed” in the patent “is the preferred, or most desirable, combination.” *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004); *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (noting that in an obviousness inquiry “all disclosures of the prior art, including unpreferred embodiments, must be considered”).

Applying these general principles, a party may take many different paths in establishing that a patent claim would have been obvious over the prior art. One of these paths is based on structural similarity between a claimed chemical compound and a prior art compound. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012); *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008). When a party chooses to argue that a patent claim would have been obvious based on structural similarity to a known compound, this can be proven “by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e., a lead compound) in a particular way to achieve the claimed compound.” *Eisai*, 533 F.3d at 1357.

A lead compound analysis is not the only way to demonstrate obviousness of a claimed compound or genus of compounds (*UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1329 (Fed. Cir. 2018)), and any rigid application of the lead compound test risks running afoul of the broad,

flexible obviousness test set forth by the Supreme Court in *KSR*.
See Otsuka, 678 F.3d at 1291 (noting that new compounds may be made out of theoretical concerns “rather than from attempts to improve on prior art compounds”); *Altana Pharm. AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009) (noting that a “restrictive view of the lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR*”). Here, Petitioner argues that the genus of Bentley, in view of its disclosure of molecular weight ranges that overlap the claimed range, renders claim 1 obvious. This issue is best analyzed using the established case law regarding overlapping ranges. *See Peterson*, 315 F.3d 1329–30; *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (noting that when “the difference between the claimed invention and the prior art is some range or other variable within the claims, . . . the applicant must show that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range”). Thus, we find that a “lead compound” analysis is neither necessary nor the most appropriate analytical framework in this case.

b) Overlapping Ranges

(1) The Parties’ Arguments

As noted above, relying on the reasoning set forth in *Peterson*, Petitioner contends that the 440 to about 264,000 Da molecular weight range taught or suggested in Bentley renders the claimed molecular weight range of “about 12,000 Da to about 100,000 Da” *prima facie* obvious. Pet. 26–27.

Patent Owner argues that, unlike the ranges of a single composition at issue in *Peterson*, claim 1 “does not recite a single composition but rather a set of chemical compounds,” i.e., “the group of branched reactive polymers

having the structure $Y-(X)_p-R-(X'-POLY)_q$,” PO Resp. 13–14. And because Bentley discloses “a genus covering a different set of polymers, which includes between about 5 and 3,000 ethylene glycol subunits,” Patent Owner contends *Peterson* is inapposite. *Id.* at 14.

Patent Owner further argues that even if *Peterson* applied to the facts of this case, *Peterson* is limited to selecting a narrow range from within a somewhat broader range, and Dr. Little determined that the cited genus of Bentley is not narrow, covering at least 300,000 distinct species. *Id.* at 15–16. Patent Owner contends the facts of this case are therefore more similar to those discussed in *In re Baird*, 16 F.3d 380 (Fed. Cir. 1994) and *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992), where it was found that a prior art genus does not, by itself, render obvious specific compounds that fall within that prior art genus. PO Resp. 14.

In response, Petitioner argues that molecular weight is known to be a result-effective variable for PEG polymers and, when “the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” Pet. Reply 13–15 (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955); citing Ex. 1084 ¶¶ 81, 211–247, 315, 323–327; Pet. 1, 26–27, 30–32). Petitioner further argues that Patent Owner presents no argument or evidence to overcome the presumption of obviousness based on overlapping ranges, such as evidence of unexpected properties or results. *Id.* at 14–15. Distinguishing *Baird* and *Jones*, Petitioner notes that these cases were not directed to overlapping ranges, but to the general question of whether a genus disclosure, by itself, renders a species obvious. *Id.* at 15.

In its Sur-Reply, Patent Owner contends that Petitioner’s reasoning with respect to optimizing the molecular weight of Bentley’s PEG arms was

made in the context of biologically active conjugates, yet Petitioner has not demonstrated that considerations for biologically active molecules are relevant to star molecules. Sur-Reply 14. Patent Owner further contends that *Baird* and *Jones* are not distinguishable based on the lack of overlapping ranges in those cases, as Bentley discloses a chemical genus and not overlapping ranges. *Id.* at 15–16. Finally, Patent Owner argues that molecular weight of a branched reactive polymer is not a recognized result-effective variable, as the properties depend on the conjugate as a whole. According to Patent Owner, without knowing the specific biologically active agent, “a branched reactive polymer cannot be generally optimized to achieve a result.” *Id.* at 17.

(2) *Analysis*

In the context of the formula of claim 1, Petitioner persuasively demonstrates—in both the Petition and the Reply—that the variables Y, (X)_p, R, X', POLY, p, and q in Bentley are fixed and result in a polymer that falls within the structural formula of claim 1 of the '833 patent. Pet. 19–25; Pet. Reply 6. In particular, R is a three carbon aliphatic hydrocarbon (Pet. 21–22), POLY is poly(ethylene glycol) (*id.* at 23–25), X' is –O– (*id.* at 22), X is –O–(CH₂)_n– (wherein n is 1–6)¹¹ (*id.*), p is 1 (*id.*), q is 2 (*id.* at 23), and Y is an aldehyde hydrate functional group (*id.* at 20–21).

The only variable set forth in Bentley that could potentially result in a species outside the scope of claim 1 is molecular weight. The claimed molecular weight range (“about 12,000 Da to about 100,000 Da”) is, however, obvious over the range disclosed in Bentley (between about 440

¹¹ Although “n” can vary from 1–6 in Bentley’s genus, Petitioner persuasively demonstrates that no matter the value selected for n, Bentley’s genus satisfies the (X)_p limitation of claim 1. Pet. 22.

and 264,000 Da) for at least two interrelated reasons. First, “even a slight overlap in range establishes a *prima facie* case of obviousness.” *Peterson*, 315 F.3d at 1329. The burden of production then shifts to Patent Owner to demonstrate that the invention would not in fact have been obvious, “generally by showing that the claimed range achieves unexpected results relative to the prior art.” *Id.* at 1330 (quoting *In re Geisler*, 116 F.3d 1465, 1469–70 (Fed. Cir. 1997)). Patent Owner does not attempt to demonstrate that the claimed molecular weight range achieves unexpected results relative to Bentley, or any other piece of prior art.¹²

Second, when a variable is “result-effective” and “the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Applied Materials*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting *Aller*, 220 F.2d at 456). It is undisputed that the molecular weight range recited for Bentley’s polymers overlaps the claimed range of “about 12,000 Da to about 100,000 Da,” thereby disclosing the “‘general conditions’ of the claim.” *Applied Materials*, 692 F.3d at 1295 (quoting *Aller*, 220 F.2d at 456 (noting that any overlap between the claimed and disclosed ranges serves to disclose the “general conditions” of the claim)). The evidence of record also persuasively demonstrates that molecular weight is a result-effective variable for PEG polymers, whether they are attached to a biologically active molecule or to surfaces, such as in a hydrogel. Ex. 1015, 6:35–37; Ex. 1016, 32:52–33:7, 35:54–57; Ex. 2020, Table 1; Ex. 1029, 4; Ex. 1095

¹² Patent Owner asserts that the prior art would have discouraged selection of molecular weights within the claimed range. PO Resp. 25. We address and reject this argument in Section II.D.2.(c).(3) below.

¶ 227¹³; see *E.I. DuPont de Nemours & Co. v. Synvina CV*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (noting that a variable is “result-effective” if it was recognized in the prior art that a “property is affected by the variable”). For example, Bentley discloses that the biological properties of a PEG conjugated compound “can vary with molecular weight” (Ex. 1015, 6:35–37), MDD found that the size and branching of PEG polymers “directly influenced the pharmacokinetic properties and biological activity” of a protein drug (Ex. 1029, 4), and Merrill discloses that the properties of a hydrogel depend on the molecular weight of each individual polymer arm and the total molecular weight of the PEG molecule (Ex. 2020, Table 1; PO Resp. 25–26 (Patent Owner asserting that optimal properties were achieved with lower molecular weights for each polymer arm)). Thus, it would not have been inventive to optimize molecular weight within the range disclosed in Bentley.

We disagree with Patent Owner that the reasoning of *Peterson* is inapplicable in this case. PO Resp. 14–15. *Peterson* applies the decades-old legal principle that in cases involving overlapping ranges “even a slight overlap in range establishes a *prima facie* case of obviousness.” *Peterson*, 315 F.3d at 1329. This legal principle is not restricted to certain types of technologies or claims, e.g., claims reciting a single composition versus a chemical genus. See *E.I. DuPont*, 904 F.3d at 1006 (recognizing that this principle applies in IPRs); *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392

¹³ As discussed below, the parties vigorously dispute whether Bentley’s genus of polymers is intended for attachment to biologically active molecules or to surfaces, such as the hydrogels of Merrill. Pet. 19; PO Resp. 22–26; Pet. Reply 8–15. In either case, though, molecular weight is a result-effective variable.

F.3d 1317, 1322 (Fed. Cir. 2004) (applying the doctrine of overlapping ranges to elongated grips for exercise weights).

Patent Owner further asserts that even if the reasoning of *Peterson* is applicable, it is limited to situations where a narrow range is selected from within a somewhat broader range, and Dr. Little determined that the cited genus of Bentley is not narrow, covering at least 300,000 distinct species. PO Resp. 15–16. Patent Owner contends the facts of this case are similar to those in *Genetics Institute v. Novartis Vaccines and Diagnostics*, 655 F.3d 1291, 1306 (Fed. Cir. 2011), where the prior art disclosed a “large breadth of possible protein variants” and provided “no motivation to optimize for some value within” the disclosed range. *Id.* at 17.

Patent Owner’s argument is unavailing. *Peterson* focuses on whether the disclosed *range* is “somewhat broader” than the claimed range, and Dr. Little does not assert that the 440 to about 264,000 Da molecular weight range of Bentley is significantly broader than the “about 12,000 Da to about 100,000 Da” molecular weight range recited in claim 1 of the ’833 patent. *See Peterson*, 315 F.3d at 1329–30.¹⁴ Moreover, Dr. Little’s calculation of

¹⁴ As generally alluded to by Patent Owner, a prior art range may be so large that it effectively does “not teach any specific amounts or combinations.” *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015). In that case, the burden of producing evidence of teaching away, unexpected results, and other pertinent secondary considerations does not shift to Patent Owner. *Id.* Patent Owner does not argue that the molecular weight range of Bentley is so large as to effectively not teach any specific amounts or combinations, and the evidence of record demonstrates that the 5 to 3,000 range of ethylene glycol subunits in Bentley, resulting in a total molecular weight for the polymer of between 440 and 264,000 Da, is consistent with the molecular weight ranges recited in the prior art. For example, Merrill discloses molecular weight ranges of 100,000 to 300,000 Da for star molecules, as well as specific examples having molecular weights from

over 300,000 potential species within Bentley's formula takes into account the possibility of varying R, m, and n in Bentley's formula. Ex. 2036

¶¶ 235–239. Petitioner persuasively demonstrates, however, that the calculations based on varying R and n utilize a false reference point, as all of these polymers fall within the scope of the genus of claim 1.

Genetics Institute does not suggest a different conclusion because the disclosed polymers of Bentley differ (in relevant part) only in the molecular weight of the polymer arms, and the evidence of record demonstrates that there was ample reason to optimize within the molecular weight range set forth in Bentley. *See Genetics Institute*, 655 F.3d at 1306 (noting that the prior art reference provided a motivation to make smaller, truncated proteins, not the larger truncated proteins recited in the claim at issue); Ex. 1015, 6:35–36 (Bentley disclosing that “PEG typically has average molecular weights of from 200 to 100,000.”); Pet. Reply 8.

With respect to *Baird* and *Jones*, both of these cases stand for the proposition that a disclosed genus does not, by itself, render obvious every species within the genus. *Baird*, 16 F.3d at 382; *Jones*, 958 F.2d at 350. But the genus may still render the species obvious if the reference teaches or fairly suggests selecting particular values for variables that will result in species that fall within the claimed genus. *Baird*, 16 F.3d at 382. In this case, all variables of the recited genus of claim 1 in Bentley are fixed and fall within the claimed structural formula except molecular weight, and the

79,000 to 229,000 Da for Type I stars and 190,000 to 371,000 Da for Type II stars. Ex. 2020, 3:61–64, Table I. Likewise, Harris discloses multi-armed PEG polymers with molecular weights from about 100 to 100,000 Da, and specifically claims two-armed PEG polymers having a molecular weight from about 40,000 to 100,000 Da. Ex. 1016, Abstract, Claims 1, 8, 19.

overlapping molecular weight ranges provide the motivation to select variables that would result in species that fall within the genus of claim 1 of the '833 patent. *Peterson*, 315 F.3d at 1130 (“The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”); *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980) (“[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.”). Moreover, the prior art of record persuasively demonstrates that two-armed PEG polymers with molecular weights within the range recited in claim 1 of the '833 patent were known and commercially available. Ex. 1038, 14 (Shearwater Polymers Catalog describing commercially available, two-armed mPEG polymers for attachment to proteins having molecular weights of 10,000, 20,000, and 40,000 Da); Ex. 1016, claims 7, 8. As such, *Jones* and *Baird* do not support the non-obviousness of the challenged claims.

In view of the foregoing, we find that the case law regarding overlapping ranges, as set forth in *Peterson* and *Applied Materials*, applies in this case and that the molecular weight range of claim 1 is prima facie obvious over the overlapping molecular weight range disclosed in Bentley.

c) Selecting the Genus and Sub-Genus of Bentley

Petitioner contends that one of ordinary skill in the art would have selected the star molecule of Bentley and optimized the molecular weight of the polymers through routine experimentation, “depending on the biologically active molecule and desired properties.” Pet. 26 (citing Ex. 1084 ¶ 315). Patent Owner contends that Bentley does not disclose a particular use for the star molecules relied upon by Petitioner or its

properties, and without knowledge of the pertinent properties of the PEG polymer, Petitioner cannot establish that one of ordinary skill in the art would have selected the genus for further development or selected a sub-genus of compounds from within this genus that fall within the scope of claim 1. PO Resp. 17–30.

(1) Uses for the Genus of Bentley

Bentley discloses that PEG polymers are useful for conjugation to biomolecules and biologically active materials and that the disclosed aldehyde hydrate moiety may be used to conjugate the PEG polymers to a range of biologically active molecules, including proteins, peptides, polysaccharides, oligonucleotides, and small drug molecules. Ex. 1015, 3:3–9, 4:52–55. Bentley further discloses that branched star molecules are generally described in Merrill, which discloses that star molecules may be used to form a cross-linked gel for use in affinity columns. *Id.* at 7:5–8; Ex. 2020, 2:5–23, Abstr.

At the institution stage, and absent a specific discussion in Bentley of the intended uses for the star molecule relied upon by Petitioner, we were not persuaded by Petitioner’s argument that these polymers would be used for conjugation to biologically active materials, as opposed to being cross-linked for use in an affinity column, as disclosed in Merrill. *See* Inst. Dec. 20–21; *see also* IPR2019-01396, Paper 19 at 9 (PTAB Feb. 10, 2020) (denying institution of review) (“Petitioner has not shown the Bentley polymer it relies on . . . is suitable for conjugating with a biologically active molecule.”).

Upon review of the evidence and arguments set forth during this proceeding, it is evident that the intended uses for Bentley’s star molecules must be broader than Merrill’s cross-linked gels for use in an affinity

column. As noted by Patent Owner, Merrill discloses that it is desirable to have a high value of [OH] and a low swelling ratio, and that the star molecules should have “about 6 to about 50 arms.” PO Resp. 23–25; *see* Ex. 1095 ¶¶ 159–161 (citing Ex. 2020, 2:58–59, 7:37–41). This is inconsistent with Bentley’s use of only two polymer arms, as opposed to “about 6 to about 50 arms,” and its use of alkyl, benzyl, or aryl capping groups, in place of [OH] groups. Ex. 1015, 7:19; PO Resp. 33. Indeed, Patent Owner asserts that use of methoxy end caps would render the polymers “ineffective for their intended purpose” in a cross-linked gel. PO Resp. 33.

The use of only two polymer arms and capping groups is, however, consistent with conjugating the disclosed polymers to biologically active materials, the other primary purpose expressly disclosed in Bentley. Ex. 1015, 3:2–4 (“This invention provides a method for conjugating PEG and related polymers with substances including biomaterials and biologically active materials.”), 6:44–50 (explaining that capped PEG “can be useful, for example, if it is desirable simply to attach the polymer chains at various amine sites along a protein chain”); Ex. 1095 ¶¶ 161–162, 208–209. Thus, we credit Dr. Emrick’s testimony that one of ordinary skill in the art reading Bentley would have understood that Bentley’s genus is intended for broader uses beyond affinity columns, including conjugation to biologically active molecules.

Patent Owner argues that there is no inconsistency between Bentley and Merrill because hydroxyl is the first listed option for the R group of Bentley’s polymer. Sur-Reply 11 (citing Ex. 1015, 7:19). While the inclusion of the hydroxyl group is consistent with Merrill, the use of only two PEG arms and the inclusion of capping groups are not (as both parties

have argued), and Dr. Emrick persuasively testifies that end capped, two-armed branched polymers were understood in the art to be useful for conjugation to biologically active molecules. Ex. 1095 ¶¶ 159–161, 167; Ex. 1016, claims 7–8 (Harris disclosing polymers with two mPEG arms and overlapping molecular weight ranges conjugated to a biologically active molecule); Ex. 1063, claims 1–21; Ex. 1038, 14 (Shearwater Polymers Catalog describing commercially available, two-armed mPEG polymers intended for attachment to proteins).

For the reasons stated above, and upon review of the trial record as a whole, we credit Dr. Emrick’s testimony—first set forth in the Petition—that one of ordinary skill in the art would have understood that Bentley’s polymers are intended for conjugation to biologically active materials. Ex. 1095 ¶¶ 155–162; Ex. 1084 ¶¶ 106, 315.

(2) Selection of Bentley’s Genus

In the Institution Decision, we found sufficient reason for selecting the genus of Bentley based on the uses expressly disclosed in Merrill. Inst. Dec. 20. Patent Owner contends the general utility of the star molecules described in Merrill does not explain why one of ordinary skill in the art would have selected the specific star molecule of Bentley as a “lead compound” for further development. PO Resp. 19–20.

Patent Owner’s argument is not persuasive because (1) we do not apply a “lead compound” analysis in this case, and (2) for the reasons discussed above, on the complete trial record, we credit Dr. Emrick’s testimony that one of ordinary skill in the art would have understood that the genus of Bentley is useful for conjugation to biologically active materials, which is a specific and persuasive reason to select this genus of compounds for further development. Ex. 1095 ¶¶ 159–165; Ex. 1084 ¶¶ 103–106.

(3) Selection of Species Within Bentley's Genus

Patent Owner asserts that even if one of ordinary skill in the art would have selected Bentley's genus for further development or refinement, Petitioner still has not demonstrated that one of ordinary skill in the art would have selected from within this disclosure the sub-genus of compounds having molecular weights of "about 12,000 Da to about 100,000 Da."

PO Resp. 23. Patent Owner reasons that Merrill generally seeks shorter PEG arms and "contains experimental data that would have discouraged" a person of ordinary skill in the art from selecting "polymers corresponding to the claimed molecular weight." PO Resp. 24–28. In particular, Patent Owner contends Merrill teaches that it "is desirable to have a high value of [OH] and a low swelling ratio q in order that the biomaterial remain approximately in the shape in which it was cast" *Id.* at 27 (quoting Ex. 2020, 7:37–40). And, according to Patent Owner, Merrill's experimental data indicates that the greatest value of [OH] was exhibited by star molecules with individual arms having a molecular weight (^MPEO) of 3,460 Da. *Id.* at 28 (citing Ex. 2020, Table 1).

As asserted by Patent Owner, the prior art must be considered for all that it teaches, including teachings that may lead towards or away from the claimed invention. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). On this point, we are not persuaded that Merrill teaches away from total molecular weights of "about 12,000 Da to about 100,000 Da," because Merrill's teachings are directed to cross-linked polymer gels for affinity columns, and Dr. Emrick persuasively explains why Bentley's genus is not limited to such uses.

Patent Owner also argues that the genus of polymers disclosed in Bentley is merely an intermediate that would have to be coupled to the core

of an undisclosed star molecule. PO Resp. 20–21. Absent some motivation for doing so, Patent Owner contends “it cannot be said that it would have been obvious to stop the process for synthesizing the disclosed end product and isolate the claimed intermediate.” *Id.* at 21 (quoting *In re Gyurik*, 569 F.2d 1012, 1018 (CCPA 1979)).

Petitioner responds that Bentley’s molecules are not intermediates, but instead fully-activated derivatives in which the aldehyde hydrate moiety is “linked directly to the core molecule having PEG chains extending from the core.” Pet. Reply 9–11.

Bentley describes its genus as having PEG chains extending from the core, which requires that the core be part of the recited, activated compounds. Ex. 1015, 7:12–14; Pet. Reply 10–11. Thus, we agree with Petitioner that Bentley’s polymers are fully-activated derivatives ready for use. Pet. Reply 11. We note, however, that even if the recited genus was an intermediate requiring attachment to a core molecule or some other structure, this is reason enough for one of ordinary skill in the art to form such compounds, i.e., for their subsequent attachment to a biologically active molecule or surface. *See Gyurik*, 596 F.2d at 1019 (Baldwin, J., concurring) (noting that it is irrelevant that a chemical compound is an intermediate or precursor if “some additional practical reasons were provided for recovering the claimed precursor”).

In view of the foregoing, we find that one of ordinary skill in the art following the express disclosures of Bentley would have had a reason to produce species that fall within the scope of claim 1 of the ’833 patent.

d) Reasonable Expectation of Success

To demonstrate obviousness, Petitioner has the burden to demonstrate both that a skilled artisan would have been motivated to combine the

teachings of the prior art and that the skilled artisan would have had a reasonable expectation of success in so doing. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

Patent Owner contends Petitioner's lack of explanation as to why one of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention is fatal to Petitioner's unpatentability arguments. PO Resp. 30. Patent Owner further contends that it was understood in the art that as you get to higher molecular weights, issues can arise, such as increased polydispersity. *Id.* at 32. Without accounting for these potential negative effects, Patent Owner contends Petitioner cannot demonstrate that one of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. *Id.*

Patent Owner's arguments are unavailing for at least two reasons. First, the law requires a reasonable expectation of success in meeting the limitations of the *claimed invention*, and the claims do not require any level of purity, polydispersity, or activity for the genus of polymers recited in claim 1. Ex. 1003, 24:10–26; *Intelligent Bio-Systems*, 821 F.3d at 1367 (“The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the *claimed invention*.”) (emphasis added). There is also no persuasive argument or evidence presented in this proceeding that one of ordinary skill would have had any problem in achieving a molecular weight above 12,000 Da and below 100,000 Da. Indeed, as noted by Dr. Emrick, PEG polymers within this molecular weight range were ubiquitous in the prior art and commercially available. Ex. 1084 ¶¶ 190–193, 324–327, 365; Ex. 1095 ¶ 220; Ex. 1015, 6:35–36 (“PEG typically has average molecular weights of

from 200 to 100,000”); Ex. 1016, Abstract (disclosing a method of producing pure PEG polymers with molecular weights from 100 to 100,000 Da); Ex. 1027, 14:6–11 (explaining that one of ordinary skill in the art can vary the length of the polymer arms to optimize or confer the desired biological activity); Ex. 1029, 4 (providing examples of 5,000 Da linear and 20,000 and 40,000 Da branched polymers conjugated to interferon- α -2a).

Second, in this ground, Petitioner does not seek to combine the teachings of two or more references, or two disparate disclosures from the same reference, to arrive at the claimed invention. Rather, Petitioner merely applies Bentley’s single, express disclosure of polymer structure and overlapping molecular weight ranges. Bentley is Patent Owner’s own patent and Patent Owner should not be heard to argue that one of ordinary skill in the art would have had any difficulty in achieving the same molecular weight that is both described *and claimed* in its own patent. *See* Ex. 1015, 6:35–36 (“PEG typically has average molecular weights of from 200 to 100,000”), 14:59–65 (claiming the same number of repeating units ($m=5$ to 3,000) as is recited for the genus of Bentley relied upon by Petitioner). In any event, Bentley is presumptively enabled and this presumption may be applied against Patent Owner in this case to demonstrate a reasonable expectation of success in achieving the disclosed and claimed molecular weight ranges. *See Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1341–42 (Fed. Cir. 2006).

In view of the foregoing, we credit the testimony of Dr. Emrick and find that there is ample record evidence demonstrating that one of ordinary skill would have had a reasonable expectation of success in simply following Bentley’s express disclosures to arrive at the subject matter recited in claim 1 of the ’833 patent.

e) Conclusion With Respect to Claim 1

Upon review of Petitioner's and Patent Owner's arguments and supporting evidence, we determine that Petitioner demonstrates by a preponderance of the evidence that Bentley teaches or suggests all of the limitations of claim 1 and that a person of ordinary skill in the art would have been motivated with a reasonable expectation of success to implement these teachings to arrive at the subject matter of claim 1 of the '833 patent.

3. Dependent Claims 2–10

Petitioner asserts that Bentley also discloses the limitations of claims 2–10. Pet. 27–33.

a) Dependent Claims 2 and 3

Claim 2 depends from claim 1 and further requires that each PEG terminates with a hydroxyl group. Ex. 1003, 24:27–29. Claim 3 depends from claim 1 and further requires that each PEG terminates with a methoxy group. *Id.* at 24:30–32.

Bentley allows R to be H, alkyl, benzyl, or aryl. Ex. 1015, 7:19. As Bentley expressly contemplates R being H, we agree with Petitioner that the subject matter of claim 2 would have been obvious in view of the disclosures of Bentley. Pet. 27.

With respect to claim 3, Bentley discloses that “PEG can be capped on one end with a relatively nonreactive moiety such as a moiety selected from the group consisting of alkyl moieties, typically methyl, benzyl moieties and aryl moieties.” Ex. 1015, 6:44–47. Bentley also discloses that “PEG is commonly used as methoxy-poly(ethylene glycol), or mPEG in brief, in which one terminus is the relatively inert methoxy group.” *Id.* at 1:29–31. Given these disclosures, Petitioner contends one of ordinary skill

in the art would have immediately understood that the “alkyl” of R could be a methoxy group. Pet. 27–28.

Patent Owner argues that the intended purpose of Merrill is to purify or separate therapeutic proteins from an affinity column and Merrill itself emphasizes the importance of having a high concentration of terminal hydroxyl groups that are available for attachment to biospecific affinity ligands and a support surface. PO Resp. 33 (citing Ex. 2020, 2:10–13). According to Patent Owner, the use of a methoxy end-cap on such PEG polymers “would not only render the star molecules ineffective for their intended purpose . . . but also interfere with cross-linking, which is essential to the formation of a hydrogel.” *Id.* (citing Ex. 2020, 3:24–26; Ex. 2040, 27:15–28:1, 28:2–29:11).

Petitioner argues in response that the fact that Merrill desires a high [OH] value simply confirms that Bentley’s star molecules are not limited to the applications of Merrill, but instead are meant for applications where methoxy end-capping is common, such as protein modification. Pet. Reply 11–12.

Patent Owner argues in its Sur-Reply that “[a]t most, Petitioner’s argument implies that end-capping all of the PEG arms would not be useful for Merrill—it implies nothing as to the uses of the cited Bentley polymers.” Sur-Reply 11. Thus, Patent Owner contends the use of methoxy end-caps in Bentley does not establish that Bentley’s polymers would be used for protein attachment. *Id.*

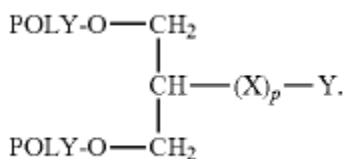
For the reasons set forth in Section II.D.2.c.(1), we credit the testimony of Dr. Emrick that one of ordinary skill in the art would have understood that Bentley’s genus of polymers was intended for conjugation to biologically active molecules (where methoxy end caps are routinely used),

and are not limited to use in affinity columns (where methoxy end caps would render the star molecules ineffective for their intended purpose). And because Bentley discloses that R may be alkyl and that the alkyl group is typically a methyl group, we find that Bentley teaches or suggests using a methyl group on its star molecules. Ex. 1015, 6:44–47, 7:19. Thus, we agree with Petitioner that Bentley teaches or suggests the subject matter of claim 3.

In view of the foregoing, Petitioner demonstrates by a preponderance of the evidence that Bentley teaches or suggests the subject matter of claims 2 and 3.

b) Claims 4, 5, and 10

Claim 4 depends from claim 1 and further requires that Y is selected from the group including, among other things, “aldehyde hydrate.” Ex. 1003, 24:33–40. Claim 5 depends from claim 1 and further requires that p is 1 and X is selected from the group consisting of, among other things, “(–O–alkylene–)_m”. *Id.* at 24:41–45. Claim 10 depends from claim 1 and requires that the branched reactive polymer has the following structure (*id.* at 24:54–60):



The figure above is the structure recited in claim 10 of the '833 patent.

Petitioner persuasively demonstrates that Y in Bentley is an aldehyde hydrate (claim 4), p is 1 and X is (–O–(CH₂)_n), i.e., “(–O–alkylene–)_m” (claim 5), and the structure of the branched polymer of Bentley matches the structure recited in claim 10. Pet. 28, 32–33.

Patent Owner does not dispute that Bentley teaches or suggests the limitations of claims 4, 5, and 10, apart from its arguments directed to independent claim 1, discussed above. PO Resp. 32.

Upon review of Petitioner's arguments and supporting evidence, we determine that Petitioner demonstrates by a preponderance of the evidence that Bentley teaches the subject matter of claims 4, 5, and 10.

c) Claim 6

Claim 6 depends from claim 1 and further requires that p is 0 and Y is hydroxyl. Ex. 1003, 24:46–47. Petitioner contends the subject matter of claim 6 would have been obvious to a person of ordinary skill in the art preparing the branched reactive polymers of Bentley. Pet. 29.

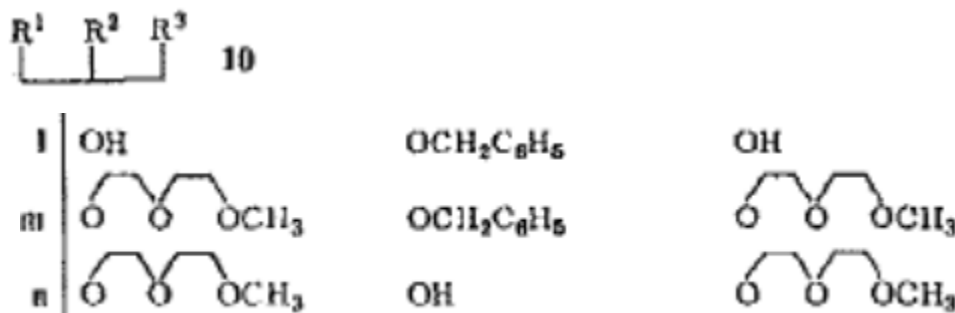
As Petitioner relies on the disclosures of Liebigs¹⁵ in its challenge to claim 6, we provide a brief overview of that reference.

(1) Liebigs

Liebigs is an article titled “Neutral ligands with surfactant structure – Synthesis, Complexation, Ion Transfer.” Ex. 1019, 770.¹⁶ Liebigs discloses several starting materials and associated ligands for forming the disclosed compounds, including “biologically interesting” polymers based on glycerol. *Id.* at 770–774. Liebigs contains a table showing glycerol ether compounds based on disclosed formula 10 and having constituents R¹, R², and R³. *Id.* at 773. Liebigs also discloses a synthesis pathway (10l, 10m, and 10n) for adding or removing ligands at positions R¹, R², and R³ (depicted, respectively, from left to right in the table reproduced below). *Id.*

¹⁵ Edwin Weber, *Neutral ligands with surfactant structure – Synthesis, Complexation, Ion Transfer*, Liebigs Ann. Chem. 770–801, 1983. Ex. 1019.

¹⁶ Our citations are to the original page numbers of Liebigs.



The table above, which is a portion of a larger table provided in Liebigs, shows three possible combinations of R¹, R², and R³ for formula 10. *Id.* In the pathway depicted in 10l, 10m, and 10n, the hydroxyl groups of 10l (2-benzyl-1,3-glycerol) are used to couple mPEG arms at positions R¹ and R³ (as depicted in 10m). *Id.* at 775. The –O–benzyl group at R² (10m) is then deprotected to provide a hydroxyl at R² (10n), while the PEG arms remain at R¹ and R³. Ex. 1084 ¶¶ 194–195, 322.

(2) Analysis

Petitioner asserts that Bentley teaches that the first step in making the claimed polymers is reacting “a PEG polymer having at least one hydroxyl group with a halide substituted compound” and that Liebigs discloses such a compound: 2-benzyloxy-1,3-propanediol. Pet. 29 (citing Ex. 1019, 5:29–44). Petitioner further asserts that Liebigs discloses the chemistry necessary to introduce higher molecular weight mPEG chains on the terminal carbon atoms of the core molecule and then deprotect the central hydroxyl to allow for reaction with a halide-substituted compound. *Id.* at 29–30. According to Petitioner, the deprotected precursor (10n), when modified to have the full length PEG arms of Bentley, discloses every limitation of claim 6. Pet. 29; Ex. 1084 ¶ 322; Ex. 1095 ¶ 213.

Patent Owner contends Petitioner’s hypothetical synthesis is neither disclosed nor suggested anywhere in Bentley, and amounts to nothing more

than a retrospective “picking and choosing” of prior art elements to purportedly yield the claimed compound. PO Resp. 33–34.

Bentley does not disclose how to make its disclosed star molecules, but does provide guidance on the general steps necessary to form its activated polymers, as well as signposts that would lead one of ordinary skill in the art to appropriate starting materials. First, Bentley discloses that PEG molecules may be built from a core molecule based on glycerol, a three-carbon compound. Ex. 1015, 1:38–52, 7:1–2, 7:24–28. Second, Bentley discloses that to form the recited polymers, a PEG polymer having at least one hydroxyl group is reacted with a halide substituted compound and that the resulting polymer precursor is then converted to an activated polymer having an active aldehyde hydrate moiety. *Id.* at 5:3–40, 5:45–47. Given that Bentley’s core has three carbon atoms with PEG arms extending from its terminal carbon atoms, and given Bentley’s instruction that the PEG polymer should have at least one hydroxyl group for subsequent reactions, we find persuasive Dr. Emrick’s testimony that one of ordinary skill in the art looking for appropriate starting compounds for synthesizing the star molecule of Bentley would have looked to the 2-benzyloxy-1,3-propanediol of Liebigs. Ex. 1084 ¶¶ 321–322; Ex. 1095 ¶ 213. We further credit Dr. Emrick’s testimony that once this starting material is selected, one of ordinary skill would have understood how to attach PEG arms to the first and third carbon atoms of the glycerol core and then deprotect and react the hydroxyl functional group on the central carbon atom to form the disclosed aldehyde hydrate precursor moiety of Bentley. Ex. 1084 ¶ 322; Ex. 1095 ¶¶ 213–214. Finally, we credit Dr. Emrick’s testimony that the deprotected precursor of Liebigs/Bentley reads upon the limitations of claim 6 of the ’833 patent. Ex. 1084 ¶¶ 321–322; Ex. 1095 ¶ 214.

Although this pathway for forming Bentley's genus of polymer molecules is hypothetical in the sense that it is not expressly disclosed in Bentley or Liebigs, we are persuaded that one of ordinary skill in the art following Bentley's express disclosures and guided by the structure of the star molecule set forth in Bentley, would have found it obvious to form the intermediate recited in claim 6 of the '833 patent using Liebigs' starting materials and synthesis pathway.

d) Claims 7–9

Claim 7, 8, and 9 depend from claim 1 and further require that the branched polymer has a molecular weight of “about 20,000 Da” (claim 7), “about 40,000 Da” (claim 8), and “about 60,000 Da” (claim 9). Ex. 1003, 24:48–53. Petitioner contends that the 440 to 264,000 Da molecular weight range of Bentley encompasses the claimed molecular weight ranges recited in claims 7–9, rendering these claims *prima facie* obvious. Pet. 30–31. Petitioner further argues that linear PEG polymers of 10, 20, and 30 kDa were “well-known and commercially available, thus allowing [one of ordinary skill in the art to produce] branched dimers of 20, 40 and 60 kDa.” *Id.* at 32 (citing Ex. 1038, 4, 7, 11, 12, 20, 22 (Shearwater catalog 2000); Ex. 1084 ¶ 327).

Patent Owner asserts that Petitioner “offers no reason why a [person of ordinary skill in the art] would have selected polymers having a molecular weight of 20,000, 40,000, or 60,000 Daltons,” and its expert was unable to identify an example of any prior art application utilizing PEGs of 60,000 Da. PO Resp. 34. Patent Owner further asserts that Merrill does not teach, suggest, or contemplate any star molecule with an individual arm of 20,000, 40,000, or 60,000 Da, and expresses a preference for at most 10,000 Da arms. *Id.* at 35.

Bentley discloses a range of repeating polymer units that directly translates to a molecular weight range of 440 to 264,000 Da. This range fully encompasses the molecular weight ranges recited in claims 7–9, thereby rendering those ranges *prima facie* obvious. *Peterson*, 315 F.3d at 1329. Patent Owner does not assert that the molecular weights recited in claims 7–9 provide unexpected results and, for the reasons discussed above, we find that the prior art does not teach away from applying Bentley’s expressly recited range of molecular weights. Accordingly, the overlap in ranges renders the molecular weight ranges of claims 7–9 *prima facie* obvious.

As Patent Owner notes, and Dr. Emrick concedes, the optimum molecular weight for the PEG arms of a PEG/biologically active molecule conjugate will vary based on the target molecule and the desired properties of the conjugate. Sur-Reply 9–10; Ex. 1084 ¶ 247; Ex. 1095 ¶ 216. This is unremarkable and does not change the analysis because Petitioner demonstrates: (1) that one of ordinary skill in the art would have selected Bentley’s genus of star molecules for conjugation to biologically active materials, (2) that molecular weight was known to be a result-effective variable for PEG conjugates, and (3) that discovery of the optimum value for molecular weight for any PEG molecule conjugated to a biologically active material is within the ordinary skill in the art using routine experimentation. *See* Ex. 1084 ¶¶ 212–247, 293; Ex. 1095 ¶¶ 215–220, 224; *see Boesch*, 617 F.2d at 276 (“This accords with the rule that discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.”). If that optimum value falls within the range expressly disclosed in Bentley for its genus of PEG polymers, its selection is obvious, absent evidence of unexpected results (which is not argued here). *See Boesch*, 617

F.2d at 276; *Aller*, 220 F.2d at 827 (“More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”).

Accordingly, Petitioner demonstrates by a preponderance of the evidence that Bentley teaches the subject matter of claims 7–9.

4. *Secondary Considerations*

Objective indicia of non-obviousness, or “secondary considerations,” guard against hindsight reasoning in an obviousness analysis, and are often “the most probative and cogent evidence in the record.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) (citations omitted). As such, objective indicia of non-obviousness must be considered in every case in which they are presented. *Id.* (citing *Transocean Offshore Deepwater Drilling Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012)).

Objective indicia of non-obviousness include evidence of, among other things, a long-felt but unsolved need in the art and teaching away. *See Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1376–1381 (Fed. Cir. 2000). Patent Owner contends there was a long-felt but unmet need in the art for the polymers of the ’833 patent and that the prior art teaches away from polymer arms with molecular weights of “about 12,000 to about 100,000 Da,” “about 20,000 Da,” “about 40,000 Da,” and “about 60,000 Da.” PO Resp. 50, 52.

a) *Long-Felt but Unmet Need*

Patent Owner contends the ’833 patent expressly sets out the “long-felt but unmet need for the claimed branched reactive polymer and biologically active conjugates thereof in the ’833 patent” (PO Resp. 50):

There remains a need in the art for new 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. (quoting Ex. 1003, 2:4–8). Pointing to several other portions of the '833 patent, Patent Owner argues that the '833 patent satisfied this long-felt need by providing “a branched reactive polymer and biologically active conjugates thereof that are more easily synthesized and purified.” *Id.* at 52.

In its Sur-Reply, Patent Owner notes that Dr. Emrick testifies that difficulties associated with producing high molecular weight polymers have been known for 80 years and that examples “where very high molecular weights are made with a low polydispersity are impressive.” Sur-Reply 24 (citing Ex. 2040, 41:23–42:2). Patent Owner further notes that Dr. Little testifies that overcoming polydispersity issues with high molecular weight polymers is precisely what the inventor’s claimed structure is designed to do. *Id.* (citing Ex. 1093, 120:5–13, 118:18–123:7; Ex. 2040, 41:23–42:2).

Patent Owner’s evidence of long-felt need is not persuasive for at least two reasons. First, Patent Owner’s evidence of long-felt need stems primarily from self-serving statements in the '833 patent, and not from independent sources. PO Resp. 58–60. Second, as Petitioner notes, to be relevant, the evidence of secondary considerations must result from something that is “both claimed and novel.” Pet. Reply 22 (citing *In re Kao*, 639 F.3d 1057, 1058 (Fed. Cir. 2011)). Polydispersity levels, as well as methods of producing the claimed polymers, are not recited in the challenged claims, and Patent Owner presents no evidence that generally producing high molecular weight polymers was novel. Indeed, Bentley discloses every limitation of claim 1, either expressly or via overlapping

ranges, and claims polymers with a molecular weight of over 200,000 Da. Pet. Reply 24–25. Likewise, Harris specifically discloses and claims high molecular weight PEG polymers (100,000 Da) and indicates that these compounds can be formed using a “simple” method. Ex. 1016, 7:33–37, 9:35–42, 18:33–45.

Accordingly, we find that Patent Owner’s evidence of long-felt need is entitled to little, if any, weight.

b) Teaching Away

“A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). The mere disclosure of alternative designs, however, does not teach away, and “just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.” *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (citing *In re Fulton*, 391 F.3d at 1201; *Gurley*, 27 F.3d at 553).

Patent Owner contends Merrill teaches away from polymer arms longer than 10,000 Da and expresses a preference for polymer arms of 3,460 Da. PO Resp. 53. Patent Owner’s arguments related to Merrill are not persuasive because, for the reasons detailed above in Section II.D.2.c.(1), we find that Bentley’s polymers are not limited to the uses set forth in Merrill, and Patent Owner does not contend that Merrill teaches away from longer polymer arms for conjugation to biologically active materials.

5. Conclusion with Respect to Obviousness of Claims 1–10 over Bentley

Upon review of the record as a whole, including Petitioner’s obviousness arguments and Patent Owner’s evidence of secondary considerations, and for the reasons discussed above, we determine that Petitioner demonstrates by a preponderance of the evidence that the subject matter of claims 1–10 is unpatentable as having been obvious over the disclosures of Bentley.

E. Obviousness of Claims 1–10 Over Bentley and MDD and Bentley and Harris

Petitioner contends that claims 1–10 of the ’833 patent would also have been obvious over the disclosures of Bentley in view of MDD or Harris. Pet. 33–51. In view of our determination that claims 1–10 would have been obvious over Bentley’s disclosures alone, we do not address these additional grounds of unpatentability. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding a petitioner “is entitled to a final written decision addressing all of the claims it has challenged”); *Boston Sci. Scimed, Inc. v. Cook Grp. Inc.*, Nos. 2019-1594, -1604, -1605, 2020 WL 2071962, at *4 (Fed. Cir. Apr. 30, 2020) (non-precedential) (recognizing that the “Board need not address issues that are not necessary to the resolution of the proceeding” and, thus, agreeing that the Board has “discretion to decline to decide additional instituted grounds once the petitioner has prevailed on all its challenged claims”).

F. JP-542 Based Grounds

Petitioner also contends that claims 1–5 and 7–10 would have been obvious over JP-542, claim 6 would have been obvious over JP-542 and Bentley, and claims 1–10 would have been obvious over JP-542 and Kohno.

Pet. 51–71. As we determine that claims 1–10 would have been obvious over Bentley alone, we do not address Petitioner’s JP-542-based grounds.

III. CONSTITUTIONAL CHALLENGE

Patent Owner contends subjecting the ’833 patent to *inter partes* review violates its constitutional rights. In particular, Patent Owner contends (1) that subjecting a patent effectively filed before September 16, 2012 to *inter partes* review “is an impermissibly retroactive, unconstitutional taking”; (2) subjecting a pre-AIA patent to *inter partes* review “violates the Due Process Clause of the Fifth Amendment by eviscerating the Patent Owner’s substantive vested rights”; and (3) *inter partes* review violates the “Appointments Clause, rendering it constitutionally impermissible for the PTAB to order the cancellation of any patent claims.” PO Resp. 53–58.

Patent Owner’s arguments are foreclosed by the decisions in *Celgene Corp. v. Peter*, 931 F.3d 1342, 1360–63 (Fed. Cir. 2019) and *United States v. Arthrex, Inc.*, 141 S. Ct. 1970, 1986–87, 1997 (2021). As such, we do not further consider or address Patent Owner’s arguments.

IV. CONCLUSION¹⁷

For the reasons set forth above, we determine that Petitioner demonstrates by a preponderance of the evidence that claims 1–10 of the '833 patent would have been obvious over Bentley.

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–10	103(a)	Bentley	1–10	
1–10	103(a)	Bentley, MDD ¹⁸		
1–10	103(a)	Bentley, Harris ¹⁹		
1–5, 7–10	103(a)	JP-542 ²⁰		
6	103(a)	JP-542, Bentley ²¹		
1–10	103(a)	JP-542, Kohno ²²		
Overall Outcome			1–10	

¹⁷ Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. See 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. See 37 C.F.R. § 42.8(a)(3), (b)(2).

¹⁸ We do not address Petitioner's grounds based on Bentley and MDD.

¹⁹ We do not address Petitioner's ground based on Bentley and Harris.

²⁰ We do not address Petitioner's ground based on JP-542.

²¹ We do not address Petitioner's ground based on JP-542 and Bentley.

²² We do not address Petitioner's ground based on JP-542, Kohno.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–10 are unpatentable as obvious over the disclosures of Bentley; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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