

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GRÜNENTHAL GMBH,
Petitioner,

v.

ANTECIP BIOVENTURES II LLC,
Patent Owner.

Case PGR2017-00022
Patent 9,408,862 B2

Before TONI R. SCHEINER, FRANCISCO C. PRATS, and
GRACE KARAFFA OBERMANN, *Administrative Patent Judges*.

Opinion for the Board filed by *Administrative Patent Judge* PRATS.

Opinion Concurring by *Administrative Patent Judge* OBERMANN.

FINAL WRITTEN DECISION
35 U.S.C. § 328(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

A. Statement of the Case

Grünenthal GMBH (“Petitioner”) filed a Petition (Paper 2, “Pet.”) requesting a post-grant review of claims 1–30 of U.S. Patent No. 9,408,862 B2 (Ex. 1001, “the ’862 patent”). Antecip Bioventures II LLC (“Patent Owner”) filed a Patent Owner Preliminary Response. Paper 10 (“Prelim. Resp.”).

Patent Owner also filed a disclaimer of claim 1 of the ’862 patent. Prelim. Resp. 1, 4; *see also* Disclaimer of Patent Claim Under 37 CFR § 1.321(a) (entered August 23, 2017). Claims 2–30, therefore, are the only claims of the ’862 patent at issue in this decision.

After considering the Petition and the Preliminary Response, we instituted trial as to claims 2–30, but not as to all grounds of unpatentability presented by Petitioner. *See* Decision to Institute 3, 44–45 (Paper 16, “Dec.”).

Thereafter, Patent Owner filed a Response (Paper 27, “PO Resp.”), and Petitioner filed a Reply (Paper 37, “Reply”).

After Petitioner filed its Reply, we modified our Decision to Institute, pursuant to the Supreme Court’s decision in *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348 (2018), and instituted trial as to all challenged claims and all grounds of unpatentability presented by Petitioner. Paper 40, 2. We also instructed the parties to confer to determine whether they desired changes to the original schedule and/or additional briefing. *Id.* The parties did not request changes to the original schedule or additional briefing.

Patent Owner also filed a Corrected Contingent Motion to Amend.

Paper 33. Petitioner filed an Opposition to Patent Owner's Motion to Amend (Paper 38), and Patent Owner filed a Reply to Petitioner's Opposition to the Motion to Amend (Paper 42).

Patent Owner also filed a Motion to Exclude Evidence (Paper 46), and Petitioner filed an Opposition to Patent Owner's Motion to Exclude (Paper 48).

An oral hearing was held on July 24, 2018, and the hearing transcript has been entered in the record. Paper 49 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6(b). This Final Written Decision is entered pursuant to 35 U.S.C. § 328(a).

"In a post-grant review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence." 35 U.S.C. § 326(e).

We conclude that Petitioner has proved by a preponderance of the evidence that claims 1–30 of the '862 patent are unpatentable.

We also conclude that the preponderance of the evidence supports Petitioner's unpatentability challenge to the proposed new claims presented in Patent Owner's Motion to Amend, and therefore *deny* Patent Owner's Motion to Amend.

Patent Owner's Motion to Exclude Evidence is *denied-in-part* and *dismissed-in-part* as moot.

B. Related Proceedings

The parties state that the '862 patent is not involved in any related administrative or judicial proceedings. Pet. 4; Paper 5, 1. The parties inform us that a patent in a different family involving similar technology is

under challenge in PGR2017-00008, which involves the same parties as this proceeding. Pet. 4; Paper 5, 1.

C. Asserted Grounds of Unpatentability

Petitioner advances the following grounds of unpatentability (Pet. 6–7):

Claims	Statutory Basis	References
2–30	§ 112(a), lack of enablement	
3 and 4	§ 112(a) and (b), lack of enablement and indefiniteness	
17–30	§ 102	Leonard ¹
17–30	§ 103	Leonard
17–30	§ 103	Leonard, Merrion Poster ²
2–16	§ 103	Fox, ³ Laslett, ⁴ Leonard, Merrion Poster

¹ US 7,704,977 B2 (issued April 27, 2010) (Ex. 1009).

² T.W. Leonard et al., *Studies of bioavailability and food effects of MER-101 zoledronic acid tablets in postmenopausal women*, Poster Presentation, 2009 Breast Cancer Symposium, AMER. SOC. CLIN. ONCOLOGY (Oct. 2009) (Ex. 1040).

³ US 2004/0063670 A1 (published April 1, 2004) (Ex. 1007).

⁴ Laura Louise Laslett et al., *Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial*, 71 ANN. RHEUM. DIS. 1322–1328 (2012) (Ex. 1008).

Petitioner supports its asserted grounds with a declaration by Stephen Bruehl, Ph.D. (“Bruehl Decl.” (Ex. 1003)), and a declaration by Dr. Clive G. Wilson (“Wilson Decl.” (Ex. 1005)).

Patent Owner supports its Response with two declarations by Dr. William Wargin (“Wargin Decl.” (Ex. 2002); “Supp. Wargin Decl.” (Ex. 2024)). Patent Owner also submits a declaration by Brent A. Johnson (Ex. 2034) in support of its Reply to Petitioner’s Opposition to Patent Owner’s Motion to Amend.

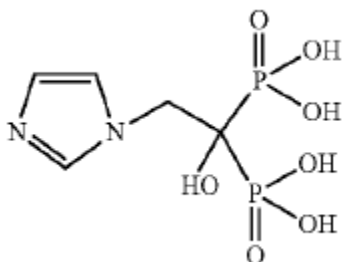
Petitioner supports its Reply with another declaration by Dr. Clive G. Wilson (“Wilson Reply Decl.” (Ex. 1076)), an affidavit by Christopher Butler (Ex. 1081 (“Butler Affidavit”)), a declaration by David Brayden, Ph.D. (“Brayden Decl.” (Ex. 1084)), and another declaration by Stephen Bruehl, Ph.D. (“Bruehl Reply Decl.” (Ex. 1098)).

D. The ’862 Patent (Ex. 1001)

The earliest possible priority date for the ’862 patent is May 27, 2014. See Ex. 1001, cover page.

The ’862 patent discloses that pharmaceutical compositions containing “zoledronic acid, Compound 1, and/or Compound 2 (subject compositions), may be used for a number of medical purposes, such as treatment of undesirable conditions or diseases, including disease or conditions related to bone, cancer, and/or pain.” *Id.* at 1:48–52.

The ’862 patent discloses that zoledronic acid “is also referred to as zoledronate” and has the following structure:



Id. at 5:42–54.

The '862 patent discloses that zoledronic acid's oral bioavailability can be increased by administering the drug in the form of a disodium salt:

The oral bioavailability of zoledronic acid in a subject composition may be enhanced by orally administering the zoledronic acid in the disodium salt form. For example, the bioavailability of zoledronic acid may be improved by at least about 10%, at least about 20%, at least about 30%, at least about 50%, and/or up to about 100%, or up to about 200%, as compared to administration of zoledronic acid in the diacid form.

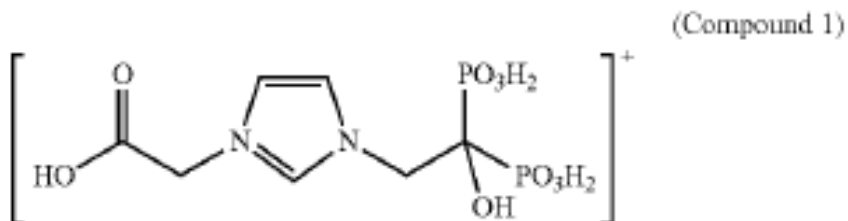
Id. at 7:35–42.

The sole working example provided in the '862 patent describes syntheses for Compounds 1 and 2. *Id.* at 17:1–18:12 (Example 1).

Claims 2 and 17 are the challenged independent claims of the '862 patent and read as follows:

2. A method of treating knee pain comprising orally administering a dosage form to a human being suffering from knee pain, wherein the dosage form comprises:

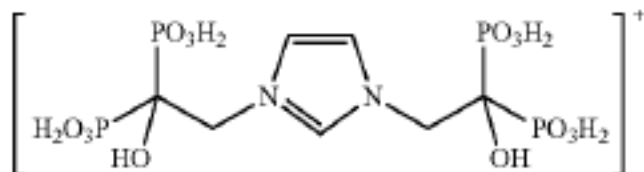
- a) zoledronic acid; or
- b) one of the following:
 - 1) zoledronic acid and



in an amount that is less than 0.1% w/w and greater than 0% w/w;

2) zoledronic acid and

(Compound 2)



in an amount that is less than 0.1% w/w and greater than 0% w/w;

or

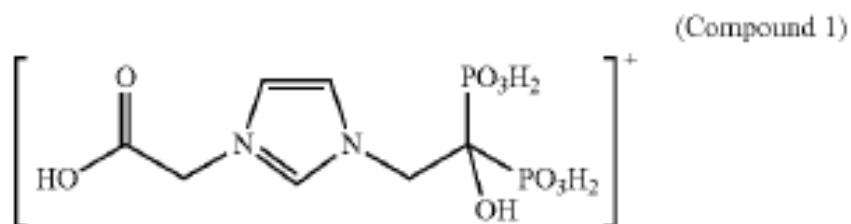
3) zoledronic acid and a combination of Compound 1 in an amount that is less than 0.1% w/w and greater than 0% w/w, and Compound 2 in an amount that is less than 0.1% w/w and greater than 0% w/w;

wherein the dosage form is free of therapeutically active agents that are not zoledronic acid, Compound 1, or Compound 2;

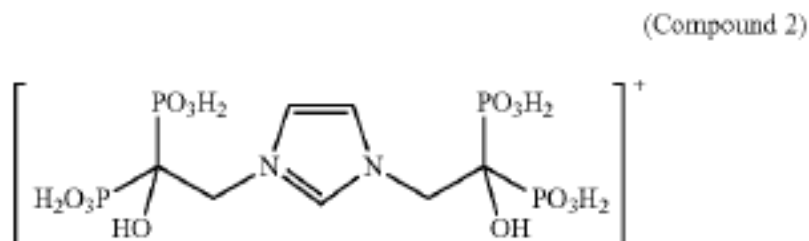
wherein any amount in % w/w is based upon the total weight of zoledronic acid, Compound 1, and Compound 2; and

wherein the bioavailability of zoledronic acid in the dosage form is from about 1.1% to about 4%.

17. A pharmaceutical dosage form comprising:
- a) zoledronic acid; or
 - b) one of the following:
 - 1) zoledronic acid and



in an amount that is less than 0.1% w/w and greater than 0% w/w;
2) zoledronic acid and



in an amount that is less than 0.1% w/w and greater than 0% w/w;
or

3) zoledronic acid and a combination of Compound 1 in an amount that is less than 0.1% w/w and greater than 0% w/w, and Compound 2 in an amount that is less than 0.1% w/w and greater than 0% w/w;

wherein the dosage form is free of therapeutically active agents that are not zoledronic acid, Compound 1, or Compound 2;

wherein any amount in % w/w is based upon the total weight of zoledronic acid, Compound 1, and Compound 2; and

wherein the bioavailability of zoledronic acid in the dosage form is from about 1.1% to about 4% in a human being.

Ex. 1001, 25:65–26:40, 27:14–28:13 (emphasis added to show limitations primarily at issue).

II. ANALYSIS

A. Claim Construction

The Board interprets the claims of an unexpired patent using the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.200(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, claim terms are given 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).

Only those claim terms in controversy need be construed, and then only to the extent necessary to resolve the dispute. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

We determine that construction of certain terms in claims 3 and 4 is necessary to resolve the issue of indefiniteness as to those claims; accordingly, we provide an express claim construction only as to claims 3 and 4.

Claim 3 depends from independent claim 2, reproduced above, and recites that the zoledronate-containing dosage form “is administered in an amount and frequency that results in an AUC [area under the curve] of zoledronic acid, over a four week period, that is about 100 ng·h/mL to about 2000 ng·h/mL.” Ex. 1001, 26:41–44.

Claim 4 depends from claim 2, and recites that the zoledronate-containing dosage form “is administered in an amount that results in an AUC of zoledronic acid, over a twenty-four hour period, that is about 20 ng·h/mL to about 500 ng·h/mL.” *Id.* at 26:45–48.

Petitioner contends that a skilled artisan would have most reasonably understood the AUC dosage requirement in claim 3 to mean the “sum of the AUCs/time period of dose clearance for all doses during a four week period.” Pet. 18–19 (citing Ex. 1005 ¶ 49 (Wilson Decl.)).

Petitioner contends that a skilled artisan would have understood the AUC dosage requirement in claim 4 to mean that “the AUC/time=24 is calculated by taking the cumulative AUC observed over twenty-four hours and dividing by the number of hours (twenty-four) to arrive at AUC/time as claimed.” Pet. 17–18 (citing Ex. 1005 ¶¶ 43–46).

Petitioner contends that these constructions of claims 3 and 4 are reasonable because, based on prior art zoledronate treatment regimens described in Leonard and the Merrion Poster, “only this interpretation would result in a formulation that meets the AUC limitation of claim[s 3 and] 4 and also have the bioavailability required by dependency from claim 2.” Pet. 18 (citing Ex. 1005 ¶ 48); *see also* Pet. 19 (same assertion).

In response, Patent Owner contends that Petitioner’s proposed constructions are not reasonable because claims 3 and 4 use “terminology [that] is known in the art,” and because modifying the units in the manner posited by Petitioner would be inconsistent with the units actually recited in the claims. Prelim. Resp. 3 (citing Ex. 2002 ¶ 16 (Wargin Decl.)).

In our Decision to Institute, we concluded that Patent Owner has the better position, and the full trial record continues to support Patent Owner’s position. As explained in Chapter 3 of *Modern Pharmaceutics*,⁵ cited by

⁵ David W.A. Bourne & Lewis W. Dittert, *Pharmacokinetics (Chapter 3)*, in *MODERN PHARMACEUTICS* (Gilbert S. Banker & Christopher T. Rhodes eds., 2d. ed. 1990) (Ex. 1063).

Petitioner's witness Dr. Wilson (see Ex. 1005 ¶¶ 53–61), the area under the curve, or AUC, is the area beneath the plot of the plasma concentration of the drug (in grams per milliliter) versus time, and may be calculated using the “trapezoidal rule” explained therein. Ex 1063, 125–126 (Modern Pharmaceuticals). Thus, in an example discussed on pages 125–126 of Modern Pharmaceuticals, the AUC is “86.7 hr · $\mu\text{g/ml}$.” *Id.* at 126. The AUC units described in Modern Pharmaceuticals, hr · g/ml, are, therefore, consistent with the units recited in claims 3 and 4 of the '862 patent.

Accordingly, Petitioner does not persuade us that the AUC values recited in claims 3 and 4 should be adjusted in the manner posited. Rather, because the units recited in claims 3 and 4 are consistent with a textbook definition of the term at issue (AUC), we agree with Patent Owner that claims 3 and 4 should be construed according to the actual language in the claims, without adjustment to the AUC values.

In sum, for the reasons discussed, we construe claim 3 as encompassing a method of treating knee pain in a human by administering a zoledronate-containing dosage form having a bioavailability of about 1.1% to about 4% as recited in claim 2 (Ex. 1001, 26:39–40), and wherein the zoledronate-containing dosage form “is administered in an amount and frequency that results in an AUC [area under the curve] of zoledronic acid, over a four week period, that is about 100 ng·h/mL to about 2000 ng·h/mL.” *Id.* at 26:41–44.

We construe claim 4 as encompassing a method of treating knee pain in a human by administering a zoledronate-containing dosage form having a bioavailability of about 1.1% to about 4% as recited in claim 2, and wherein the zoledronate-containing “is administered in an amount that results in an

AUC of zoledronic acid, over a twenty-four hour period, that is about 20 ng·h/mL to about 500 ng·h/mL.” *Id.* at 26:45–48.

B. A Person of Ordinary Skill in the Art

Petitioner advances distinct characterizations for a person of ordinary skill in the art, depending on whether claims 2–16 of the ’862 patent (directed to methods of treating knee pain), or claims 17–30 (direct to pharmaceutical dosage forms), are at issue. Pet. 9–10.

Although Patent Owner disagrees with certain aspects of Petitioner’s characterizations, the parties are in general agreement that, as to claims 2–16, an ordinary artisan possessed at least a medical degree and several years’ experience treating patients with bisphosphonates, the category of drug to which the claimed drug, zoledronate, belongs. See Prelim. Resp. 2; Pet. 9.

As to claims 17–30, although the parties’ proposed characterizations differ somewhat, the parties are in general agreement that an ordinarily skilled artisan possessed at least a Ph.D. in biochemistry, medicinal chemistry, pharmacology, pharmacokinetics, pharmacodynamics, pharmaceuticals, or a related discipline, and experience in formulating pharmaceutical dosage forms and studying their pharmacokinetics. Pet. 9–10; Prelim. Resp. 3.

When evaluating the parties’ contentions regarding the asserted grounds, we take into consideration both parties’ assertions regarding the level of ordinary skill. We discern no material differences between the parties’ respective definitions that would alter the outcome of this decision based on our acceptance of one over the other. We note also that the cited references may evidence the level of ordinary skill in the art. See *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

C. Whether the Merrion Poster (Ex. 1040) Qualifies as Prior Art

1. The Parties' Contentions

Petitioner contends that the Merrion Poster “is prior art because it was publicly presented and available to the public well before May 27, 2014.”

Pet. 53. In particular, Petitioner asserts that the Merrion Poster “is a poster presentation given in San Francisco, CA in October 2009 at the ASCO Breast Cancer Symposium entitled, ‘Studies of Bioavailability and Food Effects of MER-101 Zoledronic Acid Tablets in Postmenopausal Women.’” *Id.*

Petitioner also asserts that the Merrion Poster “was cited as a reference in the ’862 patent, but was not applied by the Examiner in any claim rejections.” *Id.* at 54. Petitioner further asserts that “a related Merrion poster presentation concerning the same pharmaceutical dosage forms was the subject of a rejection during prosecution of the related ’244 application” and that “Patent Owner ultimately abandoned the application without overcoming the rejection.” *Id.*

Patent Owner contends, for a number of reasons, that Petitioner has not advanced evidence sufficient to show that the Merrion Poster qualifies as prior art. PO Resp. 42–48.⁶

Petitioner responds that the asserted October 2009 date appearing on the face of the Merrion Poster “is corroborated by Exhibit 1064 which is an abstract with the same title, authors, and poster number, which states that the poster was presented at General Poster Session B.” Reply 16.

⁶ Patent Owner did not challenge the prior art status of the Merrion Poster in the Preliminary Response. See Prelim. Resp. *generally*.

Moreover, Petitioner contends the Merrion Poster was publicly available online no later than March 2011 because it was archived on March 2, 2011 by the Wayback Machine, “which uses programs known as crawlers to compile copies of web files, ‘preserving these files as they exist at the point of time of capture’ and thereby provides access to archived records for a given URL.” *Id.* at 16–17 (citing Ex. 1081 ¶¶ 2–4 (Butler Affidavit)).

2. Analysis

Petitioner bears the burden of establishing unpatentability of the challenged claims by a preponderance of the evidence. 35 U.S.C. § 326(e). That burden includes establishing that references relied upon qualify as prior art. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378–81 (Fed. Cir. 2015).

The governing statute here, 35 U.S.C. § 102(a),⁷ states: “A person shall be entitled to a patent unless—(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention”

As seen above, Petitioner’s contention that the Merrion Poster qualifies as prior art relies on the poster’s public availability, based on its

⁷ The first inventor to file provisions of the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”) apply to any application for patent, and to any patent issuing thereon, that contains or contained at any time a claim to a claimed invention that has an effective filing date on or after March 16, 2013. AIA § 3(n)(1). As noted above, the earliest possible priority date for the ’862 patent is May 27, 2014. *See* Ex. 1001, cover page.

alleged presentation at a symposium in San Francisco in 2009. *See* Pet. 53.

Our reviewing court’s decisions regarding similar disclosures at communal events, in contrast, generally involve whether the document at issue constitutes a printed publication. *See, e.g., In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004) (setting out a list of “factors [to] aid in resolving whether or not a temporarily displayed reference that was neither distributed nor indexed was nonetheless made sufficiently publicly accessible to count as a ‘printed publication’ under § 102(b)”). Nonetheless, because the Merrion Poster’s qualification as prior art is based ultimately on its presentation at an allegedly public symposium, we find that our analysis is guided by our reviewing court’s decisions involving the public accessibility of documents disclosed at meetings or other similar events.

“A given reference is ‘publicly accessible’ upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.” *SRI Int’l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

As explained in *Klopfenstein*, factors useful for determining public accessibility based on displays at communal events include the following: “[1] the length of time the display was exhibited, [2] the expertise of the target audience, [3] the existence (or lack thereof) of reasonable expectations that the material displayed would not be copied, and [4] the simplicity or ease with which the material displayed could have been copied.” *In re Klopfenstein*, 380 F.3d at 1350; *see also Medtronic, Inc. v. Barry*, 891 F.3d

1368, 1382 (Fed. Cir. 2018) (“[T]he size and nature of the meetings and whether they are open to people interested in the subject matter of the material disclosed are important considerations. Another factor is whether there is an expectation of confidentiality between the distributor and the recipients of the materials.”).

In the present case, as Patent Owner contends (*see* PO Resp. 45–47), Petitioner’s unpatentability grounds that cite to the Merrion Poster present no specific discussion or evidence regarding the circumstances of the poster’s display at the 2009 symposium, other than the poster itself (*see* Pet. 53–54). Accordingly, because Petitioner presents no meaningful evidence or related discussion suggesting that the Merrion Poster was displayed in a manner that would have allowed interested and ordinarily skilled artisans exercising reasonable diligence to locate the poster, we agree with Patent Owner that Petitioner has not met its burden of establishing that the Merrion Poster qualifies as prior art to the claims of the ’862 patent.

As noted above, in its Reply, Petitioner cites to Exhibit 1064 as evidence corroborating the Merrion Poster’s display at the 2009 symposium, and also cites to Exhibit 1081 as evidence that the Merrion Poster was available online at least as early as March 2, 2011. Reply 16–17.

However, as explained by our reviewing court in relation to the similar *inter partes* review (IPR) proceedings under the AIA, “[i]t is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement **that the initial petition** identify ‘with particularity’ the ‘evidence that supports the grounds for the challenge to each claim.’” *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3); *emphasis added*).

Section 322(a), which governs the contents of petitions in the post-grant proceeding presently before us, is essentially identical to § 312(a) in relevant part. *See* 35 U.S.C. § 322(a)(3).

Thus, it was Petitioner's burden in the first instance to establish in its Petition that the Merrion Poster qualifies as prior art, by identifying with particularity the evidence supporting its challenges based on that reference. We find, therefore, that Petitioner's newly submitted evidence regarding the circumstances of the Merrion Poster's display, presented for the first time in the Reply, is not timely. Similarly, we find that Petitioner's new theory of public availability of the Merrion Poster, online accessibility, is also not timely presented for the first time in the Reply.

Further, even if Petitioner's new evidence were timely, we are not persuaded that it is sufficient to establish that the Merrion Poster qualifies as prior art. Exhibit 1064 is a single, undated page that includes an abstract authored by T.W. Leonard, C. McHugh, K. Madigan, A. Walsh, and J. Fox, who appear to be the same authors listed on the Merrion Poster. *See* Ex. 1064; Ex. 1040. Exhibit 1064 includes bioavailability disclosures that are consistent with those presented in the Merrion Poster. *See id.* Exhibit 1064 includes a heading that identifies the abstract as poster number 317, and the heading reads "General Poster Session B (Board #A69), Fri, 12:00 PM - 1:30 PM and 5:30 PM - 7:00 PM." Ex. 1064. Like the abstract in Exhibit 1064, the Merrion Poster is marked as poster number 317. *See* Ex. 1040.

The information shared by Exhibit 1064 and the Merrion Poster is, at best, circumstantial evidence that the Merrion Poster might have been displayed for three hours on a Friday in October 2009 at the symposium indicated on the poster. Although the duration of the alleged display is

relevant, Exhibit 1064 does not provide any meaningful information suggesting that the circumstances of the poster's alleged display were such that interested and ordinarily skilled artisans exercising reasonable diligence could locate the poster. Petitioner does not persuade us, therefore, that Exhibit 1064 establishes that the Merrion Poster qualifies as prior art.

Petitioner also does not persuade us that Exhibit 1081 establishes that the Merrion Poster qualifies as prior art. In particular, we find that Mr. Butler's affidavit, discussing the ability of the Wayback Machine's crawler programs to locate and provide online dates for archived web files (*see* Ex. 1081 ¶¶ 2–5), is insufficient by itself to establish that the Merrion Poster was publicly accessible as of March 2, 2011.

As our reviewing court has explained, the online presence of a document, by itself, is insufficient to establish that the document qualifies as prior art. *See Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349–50 (Fed. Cir. 2016). To the contrary, as in the case of other documents, the proponent of the document in question must “establish[] that an interested party exercising reasonable diligence would have located” the document in question on the web. *Id.* at 1349. Probative evidence of the public accessibility of online documents includes evidence that interested persons were aware of the document's online presence and were able to access it, *id.*, as well as “evidence that a query of a search engine before the critical date, using any combination of search words, would have led to the [document] appearing in the search results.” *Id.* at 1350.

Petitioner advances no persuasive evidence along those lines in support of the online version of the Merrion Poster reproduced in Exhibit 1081. Rather, Petitioner conclusorily asserts that an artisan of ordinary skill

“could have located and accessed the Merrion Poster at least as of March 2, 2011, because ‘web pages locatable by crawlers of the Wayback Machine would have been locatable to interested persons using typical search engines.’” Reply 17 (citing *Creston Elecs., Inc. v. Intuitive Building Controls, Inc.*, IPR2015-01460, Paper 14 at 14 (PTAB January 14, 2016)).

Other than the *Creston* decision, however, Petitioner cites to no support, evidentiary or otherwise, suggesting that the version of the Merrion Poster appearing at the specific URL shown in Exhibit 1081 (Ex. 1081 at 6) would have been located online by interested persons of ordinary skill exercising reasonable diligence. The *Creston* decision is not precedential, moreover, and Petitioner does not explain persuasively how the factual circumstances in that case mandate a finding in this case that the Merrion Poster would have been publicly accessible as of the critical date.

In sum, for the reasons discussed, we find that Petitioner has not met its burden of establishing that the Merrion Poster qualifies as prior art to the claims of the ’862 patent.

D. Enablement—Claims 2–30

1. The Parties’ Contentions

As seen above, independent claims 2 and 17 both recite a dosage form “wherein the bioavailability of zoledronic acid in the dosage form is from about 1.1% to about 4%.” Ex. 1001, 26:39–40 (claim 2), 28:12–14 (claim 17). Petitioner contends that the specification of the ’862 patent does not provide a disclosure sufficient to allow a skilled artisan to make or use dosage forms that meet the bioavailability requirement in claims 2 and 17. Pet. 19–25.

In particular, Petitioner contends that it was known in the art that the oral bioavailability of zoledronate in humans was 1% or lower. Pet. 20. In contrast, Petitioner contends, the '862 patent specification does not provide any examples of zoledronate-containing dosage forms, nor does the '862 patent present any “pharmacokinetic data demonstrating that, contrary to the prevailing understanding in the art, orally administered zoledronic acid could have an oral bioavailability of from about 1.1% to about 4% without enhancement.” *Id.* at 21 (citing Ex. 1005 ¶ 66 (Wilson Decl.)).

Although Petitioner acknowledges the '862 patent's disclosure that bioavailability enhancement may be obtained by formulating zoledronate in the form of the disodium salt, Petitioner contends that the '862 patent “does not provide any examples of formulations containing disodium salts, or any experimental data showing a bioavailability of from about 1.1% to about 4% using a disodium salt form.” *Id.* at 22. Therefore, Petitioner contends, “[b]ecause the patent contains no pharmacokinetic data and no exemplary formulations, a POSA would not know how to formulate a disodium salt of zoledronic acid to achieve the claimed bioavailability.” *Id.* at 23.

In response, Patent Owner contends that Petitioner's enablement challenge is inadequate because Petitioner ignores the disclosures in the '862 patent explaining how to prepare zoledronic acid-containing compositions, including the identification of useful excipients and bioavailability enhancers, and because Petitioner did not submit evidence explaining the amount of experimentation that would have been required to produce compositions having the claimed bioavailability based on those disclosures. PO Resp. 6–10, 16–19, 21–23.

Patent Owner contends, moreover, that the '862 patent specification provides a number of disclosures explaining that the oral bioavailability of zoledronic acid can be enhanced by preparing the drug in the form of a disodium salt, which was known in the art. *Id.* at 10–15.

2. Analysis

We find that Petitioner has shown by a preponderance of the evidence that claims 2 and 17, and their dependent claims, fail to comply with the enablement requirement of 35 U.S.C. § 112(a).

Section 112(a) states:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same

“[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.” *Trustees of Boston University v. Everlight Electronics Co., Ltd.*, 896 F.3d 1357, 1362 (Fed. Cir. 2018) (bracketing in original; internal quotations omitted).

That is, “there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill [in the art] how to make and how to use the invention as broadly as it is claimed.” *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).

As noted above, independent claims 2 and 17 both recite a dosage form “wherein the bioavailability of zoledronic acid in the dosage form is from about 1.1% to about 4%.” Ex. 1001, 26:39–40 (claim 2), 28:12–14 (claim 17).

More broadly than the bioavailability range recited in claims 2 and 17, the '862 specification discloses that, “[i]n some embodiments, an oral dosage form may have an oral bioavailability of zoledronic acid of about 0.01% to about 10%, about 0.1% to about 7%, about 0.1% to about 5%, etc.” *Id.* at 13:11–14.

As Petitioner contends, however, the '862 specification includes no working examples of preparing any dosage form. We acknowledge that working examples are not required to enable claims. *See, e.g., Vaeck*, 947 F.2d at 497. Nonetheless, in addition to the absence of working examples, the '862 patent does not include any detailed descriptions of specific dosage forms, including the particular ingredients included therein, that illustrate how to prepare a dosage form that meets the bioavailability requirements of claims 2 and 17.

Petitioner identifies the absence of specific guidance in the '862 patent directing a skilled practitioner to a particular set of ingredients that provides dosage forms having the zoledronic acid bioavailability values recited in claims 2 and 17. In addition, Petitioner advances evidence that skilled artisans would have understood that zoledronic acid has an oral bioavailability of 1% or less, which is significantly lower than the upper limit of 4% recited in claims 2 and 17. *See* Pet. 20 (citing Exs. 1027–

1030)^{8,9,10,11}; *see also* Ex. 1027 ¶ 6 (“The low oral bioavailability of zoledronic acid, which is <1% of the oral dose, can be attributed to poor permeability in the gastrointestinal (GI) tract.”); Ex. 1028 at 184 (“Owing to their poor lipophilicity, less than 1% of orally taken BPs [bisphosphonates] are absorbed in the gut”); Ex. 1029 at 124 (“Orally administered BPs have shown approximately 1% bioavailability”); Ex. 1030 at 395 (“Oral bisphosphonates are poorly absorbed (usually less than 1% for nitrogen-containing bisphosphonates) and when taken with food or beverages create complexes that cannot be absorbed.”).

Patent Owner contends that the disclosures in Exhibits 1027–1030 regarding the oral bioavailability of zoledronate are unsupported by clinical data (PO Resp. 24–25), and moves to exclude those publications (Paper 46). As discussed below, we decline to exclude those exhibits.

We acknowledge the testimony of Petitioner’s expert, Dr. Wilson, that it would not have been unusual to see a zoledronic acid bioavailability greater than 1% in some individuals. Ex. 2022, 72:14–15 (Wilson Deposition). Patent Owner, however, advances no persuasive evidence

⁸ WO 2011/014781 A1 (published Feb. 3, 2011) (Ex. 1027).

⁹ Ieva Ruza et al., *Clinical experience with intravenous zoledronic acid in the treatment of male osteoporosis: evidence and opinions*, 5 THER. ADV. MUSCULOSKEL. DIS. 182–198 (2013) (Ex. 1028).

¹⁰ Luca Dalle Carbonare et al., *Safety and tolerability of zoledronic acid and other bisphosphonates in osteoporosis management*, 2 DRUG, HEALTHCARE AND PATIENT SAFETY 121–137 (2010) (Ex. 1029).

¹¹ Michael Pazianas et al., *Eliminating the need for fasting with oral administration of bisphosphonates*, 9 THERAPEUTICS AND CLINICAL RISK MANAGEMENT 395–402 (2013) (Ex. 1030).

showing that the absence of clinical data in Exhibits 1027–1030 would have caused an ordinary artisan to disregard the disclosures regarding bioavailability in those exhibits, or would have considered the general bioavailability values disclosed in Exhibits 1027–1030 to be inaccurate. To the contrary, Patent Owner concedes that the '862 patent describes 1% oral bioavailability of zoledronic acid “[a]s a baseline” that can be improved upon. PO Resp. 13 (citing Ex. 1001 at 8:3).

Given the unrebutted evidence that skilled artisans would have understood zoledronic acid generally to have an oral bioavailability of 1% or less, and given the absence of specific guidance in the '862 patent specification directing skilled artisans to a particular set of ingredients that provides dosage forms having the 1.1% to 4% zoledronic acid bioavailability values recited in claims 2 and 17, Petitioner persuades us that the '862 patent specification does not provide a disclosure that would have enabled a skilled artisan, without undue experimentation, to make a dosage form having the full bioavailability range required by claims 2 and 17, and their dependent claims.

Patent Owner’s arguments do not persuade us to the contrary. We acknowledge, as Patent Owner contends, that in certain instances our reviewing court has required the proponent of non-enablement to explain the quantity of experimentation required to arrive at the subject matter of the challenged claims. See PO Resp. 6 (citing *Cephalon, Inc. v. Watson Pharmaceuticals, Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013); *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1321 (Fed. Cir. 2003)). Here, however, because of the absence of specific guidance in the '862 patent leading skilled artisans to zoledronic acid dosage forms having the

bioavailability values recited in claims 2 and 17, we agree with Petitioner that the '862 patent does not provide a sufficiently specific discrete starting point for quantifying further experimentation.

We acknowledge, as Patent Owner contends, that the '862 patent specification discloses that its dosage forms can include specific concentrations of microcrystalline cellulose, crosslinked polyvinylpyrrolidone, fumed silica, and magnesium stearate as dosage form excipients. PO Resp. 7–8, 15–19 (citing Ex. 1001 at 14:25–15:67 ('862 patent)).

We agree with Patent Owner that columns 14 and 15 of the '862 patent specification explain the types of excipients that may be included in zoledronic acid-containing dosage forms. Nonetheless, none of the disclosures in columns 14 and 15 mentions anything about the bioavailability of dosage forms containing those excipients, nor is there any disclosure that any of the named excipients allows preparation of a dosage form having a bioavailability in the range recited in claims 2 and 17.

We acknowledge, as Patent Owner contends (PO Resp. 10–15), that the '862 patent discloses that the disodium salt can be used to enhance the oral bioavailability of zoledronate as much as 200% as compared to the diacid form. See Ex. 1001, 7:35–42. The '862 patent, however, does not disclose with any specificity the bioavailability of any disodium salt form of zoledronate. Nor does the '862 patent disclose that a disodium salt form of zoledronate provides a bioavailability that meets the requirements of claims 2 and 17. Nor does the '862 patent describe specifically the preparation of any dosage form containing a zoledronate disodium salt.

We acknowledge, as Patent Owner contends, that multiple disodium salt forms of zoledronate were known in the art. *See, e.g.*, Ex. 1035, at 3–4 (WO 2005/005447 A2 (published January 20, 2005) (“Aronhime”)). We acknowledge also the disclosure in the non-prior-art ’669 publication identified by Patent Owner, in which disodium salts were used to increase the oral bioavailability of zoledronate in dogs by 46% with a weight adjustment for the control animals, and 84% without any weight adjustment, which would result in oral bioavailability values of almost 1.46% to almost 1.84%. *See* Ex. 2005 ¶ 146 (the ’669 publication).

Claims 2 and 17, however, recite a bioavailability range of about 1.1% to 4%, which encompasses bioavailability values significantly higher than shown in the ’669 publication. Thus, even assuming that the disclosures in the ’669 publication remedy the absence of an express description of dosage forms in the ’862 patent, the disclosures in the ’669 publication do not persuade us that the ’862 patent enables the full scope of the dosage forms recited in claims 2 and 17.

We acknowledge Patent Owner’s assertion that it “believes [it] is possible” to use different disodium salt forms of zoledronic acid to prepare dosage forms having the full scope of bioavailabilities recited in claims 2 and 17. PO Resp. 13. We also acknowledge Patent Owner’s assertion that a skilled artisan needed only perform routine bioavailability tests to determine *if* known disodium salt forms of zoledronic could achieve the full scope of bioavailabilities recited in claims 2 and 17. *Id.* at 13–15.

It might thus be plausible, based on the disclosures in the ’669 publication, that known disodium salt forms of zoledronic, if tested, could achieve the full scope of bioavailabilities recited in claims 2 and 17. Such

plausibility, however, is insufficient to provide an enabling disclosure for claims 2 and 17:

“If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to ‘inventions’ consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the ‘inventor’ would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis.”

In re ‘318 Patent Infringement Litigation, 583 F.3d 1317, 1327 (Fed. Cir. 2009) (quoting *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005)).

We acknowledge, as Patent Owner contends, that the ’862 patent discloses that, in addition to disodium salts, bioavailability enhancers may be used to increase the bioavailability of zoledronic acid. PO Resp. 21–23; *see also* Ex. 1001, 9:51–55 (“In some embodiments, the disodium salt form of zoledronic acid provides an enhancement to bioavailability, as compared to the diacid form of zoledronic acid, which adds to any enhancement to bioavailability provided by any bioavailability-enhancing agents in the dosage form.”).

As Patent Owner contends, and as discussed below, Leonard discloses the use of specific fatty acid compounds to increase the bioavailability of zoledronic acid. Ex. 1009, 35:12–21 (claim 2 of Leonard). As Patent Owner also contends, the Fosamax® Label states that “[i]ntravenous ranitidine was shown to double the bioavailability of oral alendronate,” which, like zoledronate, is a bisphosphonate. Ex. 1013, 14.

The '862 patent, however, does not mention or disclose *any* specific bioavailability enhancing agents that may be used, alone or along with a disodium salt form of zoledronate, to provide a dosage form having a bioavailability that meets the requirements of claims 2 and 17. To the contrary, as discussed above, the '862 patent specification does not describe any particular dosage form, and lacks any specific guidance in directing skilled artisans to a particular set of ingredients, or amounts thereof, that provides dosage forms having the 1.1% to 4% zoledronic acid bioavailability values recited in claims 2 and 17.

We note, moreover, that the '862 specification discloses, as a baseline for enhancement, a bioavailability as low as 0.01%. Ex. 1001, 13:11–14. We also note that the zoledronic acid bioavailability range taught in Leonard, 2.5% to 13%, only partially covers the about 1.1% to about 4% recited in claims 2 and 17 of the '862 patent. See Ex. 1009, 35:12–21 (claim 2 of Leonard).

We are not persuaded that the prior art disclosure of enhancers capable of increasing zoledronic acid bioavailability remedies the absence, *in the '862 patent specification*, of specific disclosures that enable claims 2 and 17. As Petitioner contends, although the '862 patent specification need not disclose what is well known in the art, “that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement.” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366, (Fed. Cir. 1997) (citation omitted).

Thus, while we acknowledge our concurring colleague's concerns expressed below, similar to the current record,

when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Id.

In sum, for the reasons discussed, we determine that Petitioner has shown by a preponderance of the evidence that the '862 patent specification does not provide a disclosure that would have enabled a skilled artisan, without undue experimentation, to make a dosage form having the full 1.1% to 4% bioavailability range required by claims 2 and 17.

Claims 3–12, 15, and 16, which depend from claim 2, and claims 18–26, 29, and 30, which depend from claim 17, all require the dosage form recited in those claims to have the same zoledronic acid bioavailability as claims 2 and 17. See Ex. 1001, 26:41–27:2, 27:9–13, 28:14–30, 28:37–40. Accordingly, for the reasons discussed, we determine that Petitioner has also shown by a preponderance of the evidence that claims 3–12, 15, 16, 18–26, 29, and 30 are not enabled by the '862 patent specification.

Claims 13 and 27 depend from claims 2 and 17, respectively, and limit the dosage form to one in which the bioavailability of zoledronic acid in the dosage form is from about 1.3% to about 4% in a human being. See Ex. 1001, 27:3–5, 28:31–33. Claims 14 and 28 depend from claims 2 and

17, respectively, and limit the dosage form to one in which the bioavailability of zoledronic acid in the dosage form is from about 1.5% to about 4% in a human being. *See id.* at 27:6–8, 28:34–36.

As discussed above, Petitioner persuades us that the '862 patent specification does not provide a disclosure enabling the preparation of dosage forms having zoledronate bioavailabilities as high as 4%. Thus, although claims 13, 14, 27, and 28 recite narrower bioavailability ranges than claims 2 and 17, claims 13, 14, 27, and 28 nonetheless encompass dosage forms that are not enabled, based on essentially the same reasoning advanced by Petitioner as to claims 2 and 17. Accordingly, we determine that Petitioner has also shown by a preponderance of the evidence that claims 13, 14, 27, and 28 are not enabled by the '862 patent specification.

E. Indefiniteness/Enablement—Claims 3 and 4

1. The Parties' Contentions

As noted above, claim 3 depends from independent claim 2 and recites that the zoledronate-containing dosage form “is administered in an amount and frequency that results in an AUC [area under the curve] of zoledronic acid, over a four week period, that is about 100 ng·h/mL to about 2000 ng·h/mL.” Ex. 1001, 26:41–44.

As also noted above, claim 4 depends from claim 2, and recites that the zoledronate-containing dosage form “is administered in an amount that results in an AUC of zoledronic acid, over a twenty-four hour period, that is about 20 ng·h/mL to about 500 ng·h/mL.” *Id.* at 26:45–48.

Petitioner advances its indefiniteness and enablement challenges to claims 3 and 4 as component portions of a single ground of unpatentability. Pet. 28–31.

Petitioner contends that claims 3 and 4 are indefinite because the '862 patent “does not provide any guidance as to how these AUC values were calculated or what they represent,” and a skilled artisan, therefore, “simply would not have known whether the claimed AUC values represent, for example, the total AUC over a particular time period, an average AUC over that time period, or an AUC that must be maintained over the entirety of the time period.” Pet. 29–30 (citing Ex. 1005 ¶¶ 84, 85 (Wilson Decl.)).

As to enablement, Petitioner contends that the '862 patent specification “simply lacks any instruction to a POSA [person of ordinary skill in the art] of how to make and use a dosage form satisfying the AUC limitations of claims 3-4 using forms other than a disodium salt, such as the diacid form.” *Id.* at 30 (citing Ex. 1005 ¶ 87). Petitioner contends further that an ordinary artisan “would have to perform extensive trial and error experimentation to figure out how to achieve the claimed AUC values,” and in particular “would have to perform various pre-clinical and clinical studies wherein different amounts of zoledronic acid were administered, their plasma concentration vs. time curves determined, and the area under those curves measured.” *Id.* at 31 (citing Ex. 1005 ¶ 89).

As to indefiniteness, Patent Owner responds that an ordinary artisan would have understood the metes and bounds of claims 3 and 4, again contending, among other things, that the AUC recitations in those claims use “terminology [that] is known in the art.” Prelim. Resp. 12.

As to enablement, Patent Owner contends that the data from the dog experiments in the '669 publication show that the disodium salt and diacid forms of zoledronate would provide AUCs in humans with routine experimentation. *Id.* at 13–14.

2. Analysis

a. Indefiniteness

In our Decision to Institute this proceeding, we determined that Petitioner had not shown that it was more likely than not that claims 3 and 4 are unpatentable under 35 U.S.C. § 112(b) for indefiniteness. Dec. 18–20. We, therefore, did not include Petitioner’s indefiniteness challenge to claims 3 and 4 among the grounds for which we instituted trial. *See id.* at 44–45.

As noted above, after instituting this proceeding, we modified our Decision to Institute, pursuant to the Supreme Court’s decision in *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, and instituted trial as to all challenged claims and all grounds of unpatentability presented by Petitioner. Paper 40, 2. As noted above, we also instructed the parties to confer to determine whether they desired changes to the original schedule and/or additional briefing, *see id.*, and the parties did not request changes to the original schedule or additional briefing.

Accordingly, we consider Petitioner’s indefiniteness challenge to claims 3 and 4 based on the record as of the time of the Institution Decision. As we explained in our Institution Decision, Petitioner does not persuade us that an ordinary artisan would not have known what the AUC values in claims 3 and 4 represent. *See* Pet. 29–30 (citing Ex. 1005 ¶¶ 84, 85 (Wilson Decl.)); Dec. 18–20.

We acknowledge Dr. Wilson’s significant credentials, education, and experience. *See* Ex. 1006 (Dr. Wilson’s CV). Dr. Wilson’s testimony as to indefiniteness, however, simply restates the indefiniteness contentions advanced in the Petition, without providing a specific factual basis that

explains his opinion, other than the lack of AUC data in the '862 patent specification. Ex. 1005 ¶¶ 84, 85.

As discussed above in relation to the construction of claims 3 and 4, however, the AUC calculation was a well-known measurement in the pharmaceutical arts. Specifically, Chapter 3 of *Modern Pharmaceutics*, a textbook cited by Dr. Wilson (*see id.* ¶¶ 53–61), explains that the area under the curve, or AUC, is the area beneath the plot of the plasma concentration of the drug (in grams per milliliter) versus time, and may be calculated using the “trapezoidal rule” explained therein. Ex 1063, 125–126 (*Modern Pharmaceutics*). Thus, in an example discussed on pages 125–126 of *Modern Pharmaceutics*, the AUC is “86.7 hr · µg/ml.” *Id.* at 126. The AUC units described in *Modern Pharmaceutics*, hr · g/ml, are therefore consistent with the units recited in claims 3 and 4 of the '862 patent.

Accordingly, because the AUC parameter recited in claims 3 and 4 is consistent with a textbook definition of the term, Petitioner does not persuade us that an ordinary artisan would not have understood what the AUC values in claims 3 and 4 of the '862 patent represent. Petitioner does not persuade us, therefore, that it has shown by a preponderance of the evidence that claims 3 and 4 are unpatentable for indefiniteness.

b. Enablement

As noted above, as part of its indefiniteness challenge to claims 3 and 4, Petitioner also presents an enablement challenge to claims 3 and 4. *See* Pet. 30–31. As discussed above, we find that Petitioner has not shown sufficiently that claims 3 and 4 are indefinite.

Nonetheless, as also discussed above, Petitioner persuades us that it has shown sufficiently that the specification of the '862 patent does not

provide a disclosure that would have enabled a skilled artisan, without undue experimentation, to make a dosage form having the zoledronate bioavailability required by claim 2, from which both claims 3 and 4 depend.

Thus, even assuming, as Patent Owner contends, that an ordinary artisan would have been able to routinely determine a dosage regimen for the claimed dosage form that provides AUCs encompassed by claims 3 and 4, that would not remedy the absence of disclosure in the '862 patent of an enabling disclosure, on the current record, of a dosage form meeting the bioavailability requirements of claim 2. Accordingly, because Petitioner has sufficiently shown non-enablement as to claim 2, and because Patent Owner's arguments as to the enablement of claims 3 and 4 rely solely on its arguments presented as to claim 2, we find that Petitioner has shown by a preponderance of the evidence that claims 3 and 4 of the '862 patent are unpatentable for lack of enablement under 35 U.S.C. § 112(a).

F. Anticipation—Leonard (Claims 17–30)

1. Leonard (Ex. 1009)

Leonard discloses “a pharmaceutical composition and oral dosage forms comprising a bisphosphonate in combination with an enhancer to enhance intestinal delivery of the bisphosphonate to the underlying circulation.” Ex. 1009, Abstract. Leonard discloses that zoledronate is among suitable bisphosphonates for use in its dosage forms. *Id.* at 4:8–13.

Leonard explains that, although bisphosphonates were known for treating bone resorption disorders such as osteoporosis, oral administration of bisphosphonates had a number of limitations, including upper gastrointestinal tract (GIT) irritation, and low oral bioavailability, as low

0.76% in women and 0.59% in men, or significantly lower if the drug was taken with food. *Id.* at 1:64–2:37.

To address those issues Leonard discloses that its bisphosphonate-containing dosage forms include “an enhancer to promote absorption of the bisphosphonate at the GIT cell lining wherein the enhancer is a medium chain fatty acid or a medium chain fatty acid derivative having a carbon chain length of from 6 to 20 carbon atoms” *Id.* at 3:56–60. Leonard discloses that “[m]ost preferably, the enhancer is sodium caprate.” *Id.* at 7:9–10.

Leonard explains its focus on oral bisphosphonate dosage forms as follows:

Provision of a solid oral dosage form which would facilitate the administration of a drug together with an enhancer is desirable. The advantages of solid oral dosage forms over other dosage forms include ease of manufacture, the ability to formulate different controlled release and extended release formulations and ease of administration. Administration of drugs in solution form does not readily facilitate control of the profile of drug concentration in the bloodstream. Solid oral dosage forms, on the other hand, are versatile and may be modified, for example, to maximize the extent and duration of drug release and to release a drug according to a therapeutically desirable release profile. There may also be advantages relating to convenience of administration increasing patient compliance and to cost of manufacture associated with solid oral dosage forms.

Id. at 3:36–50.

Example 17 of Leonard describes a study of the absorption in human subjects of a 1 mg intravenous dose of zoledronate, as compared to orally administered tablets composed of sodium caprate and either 10 mg or 20 mg

of zoledronate. *Id.* at 27:40–30:21. Table 17 of Leonard, reproduced below, provides some results of the comparison:

TABLE 17

Excretion Interval	Least-Squares Means (mg) ¹		Ratio ²	CV % ³	90% Confidence Interval ⁴	
	20 mg	Zometa			Lower	Upper
(hrs)						
0-12	0.378	0.465	0.813	—	0.495	1.132
0-24	0.411	0.499	0.824	—	0.501	1.146
0-36	0.431	0.521	0.827	—	0.504	1.151
0-48	0.446	0.538	0.830	—	0.507	1.153
Ln-Transformed Results:						
0-12	0.349	0.408	0.856	50.8	0.604	1.212
0-24	0.378	0.439	0.861	50.9	0.608	1.220
0-36	0.395	0.458	0.863	51.2	0.608	1.225
0-48	0.408	0.473	0.865	51.6	0.608	1.230

¹Least-squares geometric means for ln-transformed data.

²Ratio calculated as the 20 mg least-squares mean divided by the Zometa least-squares mean. None of the comparisons was detected as statistically significant by ANOVA ($\alpha = 0.05$).

³Estimated intra-subject coefficient of variation, $CV \% = 400 * \text{SQRT}(e^{\text{MSE}} - 1)$, where MSE is the mean square error term from the ANOVA.

⁴Confidence interval on the ratio.

Id. at 29:40–60.

In particular, Table 17 provides a “summary of the statistical comparisons of zoledronic acid urinary excretion following administration of a single 20 mg tablet dose and a 1 mg injection to 12 fasted, postmenopausal females.” *Id.* at 29:36–39.

Regarding the results of Example 17, Leonard states that “[n]o statistically significant differences were detected with regard to mean cumulative urinary excretion. The 10 mg and 20 mg tablets had a mean 48-hour urinary excretion approximately equal to 0.5 mg. The 1 mg Zometa® [zoledronate intravenous] injection treatment has a similar mean amount excreted over this time.” *Id.* at 28:62–67.

Claim 2 of Leonard reads as follows:

2. A solid oral dosage form which is effective in delivering therapeutically effective amounts of zoledronic acid

and an enhancer to an intestine, said composition comprising zoledronic acid and an enhancer, wherein the enhancer is a medium chain fatty acid or a salt of a medium chain fatty acid having a carbon chain length of from 6 to 20 carbon atoms, is solid at room temperature, and is the only enhancer present in the composition, *and wherein upon oral delivery of the composition to a human subject, the zoledronic acid has a bioavailability of 2.5% to 13.0%.*

Id. at 35:12–21 (emphasis added).

2. *The Parties' Contentions*

To show that Leonard describes a dosage form having all of the features required by claim 17 of the '862 patent, the independent claim challenged in this ground, Petitioner directs us to claim 2 of Leonard, and also Table 17, reproduced above. Pet. 33–41.

In particular, Petitioner contends that the bioavailability range in claim 2 of Leonard's zoledronate-containing dosage form sufficiently overlaps the bioavailability range of claim 17 so as to anticipate claim 17. *Id.* at 40–41. Moreover, Petitioner contends, when the lower end value (0.507) of the 90% confidence ratio of oral (20 mg zoledronate tablet) versus intravenous (1 mg injection) absorption in Table 17 is adjusted for the differences in dosage amounts, the bioavailability of the 20 mg tablet is 2.5%, which falls within claim 17's range of about 1.1% to about 4%. *Id.* at 40 (citing Ex. 1005 ¶¶ 100, 102 (Wilson Decl.)).

As to claims 18–30 of the '862 patent, which all depend from claim 17, Petitioner identifies teachings in Leonard which are purported to describe features of Leonard's dosage form that correspond to the features recited in the dependent claims. *Id.* at 41–46.

Patent Owner contends that, because Petitioner did not file an affidavit under 37 C.F.R. § 42.61(c) asserting first-hand knowledge of how

the data in Leonard was generated, the Leonard reference is not enabled, and Petitioner therefore cannot rely on the data in Leonard in support of its anticipation challenge. PO Resp. 26–30. Patent Owner contends, moreover, that Leonard fails to describe dosage forms having all of the features in the challenged claims, because Leonard does not describe the ingredients in its dosage forms with sufficient precision. *Id.* at 30–31, 35–39.

Patent Owner contends, in addition, that the bioavailability range in Leonard’s claim 2 cannot be considered anticipatory because Leonard’s invention operates differently than the claimed invention. *Id.* at 32–34. Patent Owner contends also that Leonard’s data regarding the 90% confidence bioavailability ratio in Example 17 of the reference does not equate to a disclosure of a dosage form having a bioavailability within the range recited in the ’862 patent claims. *Id.* at 34–35.

3. Analysis—Anticipation of Claim 17 by Leonard

We determine that Petitioner has shown by a preponderance of the evidence that claim 17 of the ’862 patent is unpatentable under 35 U.S.C. § 102(a)(1) as anticipated by Leonard.

Claim 17 recites a pharmaceutical dosage form in which zoledronate is the only required therapeutically active agent, and which contains no therapeutically active agents other than zoledronate, Compound 1, or Compound 2. *See* Ex. 1001, 27:14–28:13. Claim 17 recites that “the bioavailability of zoledronic acid in the dosage form is from about 1.1% to about 4%.” *Id.* at 28:11–13.

As seen above, claim 2 of Leonard recites a pharmaceutical dosage form, which contains zoledronate as the sole active agent, and which has a bioavailability of 2.5% to 13.0%. Ex. 1009, 35:12–21. The dosage form of

claim 2 of Leonard therefore includes all of the features required by claim 17 of the '862 patent.

We acknowledge that, despite the significant overlap, the claimed and prior art bioavailability ranges are not identical. As Petitioner points out, however, in evaluating whether a claimed range is anticipated, “when the prior art discloses a range, rather than a point, the court must evaluate whether the patentee has established that the claimed range is critical to the operability of the claimed invention.” *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 871 (Fed. Cir. 2015); *see also id.* at 870 (explaining “the importance of establishing the criticality of a claimed range to the claimed invention in order to avoid anticipation by a prior art reference disclosing a broader, overlapping range”) (citing *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1342–1346 (Fed. Cir. 2012)).

In the present case, given the wide variation of suitable bioavailability ranges in the '862 patent (as broad as from about 0.01% to about 10% (Ex. 1001, 13:34–37)), Petitioner persuades us that the bioavailability range recited in claim 17 of the '862 patent lacks sufficient criticality to distinguish it from the range of Leonard's claim 2, for the purposes of anticipation.

In addition, as Petitioner contends, and as seen above, Table 17 of Leonard describes a distribution of bioavailability values resulting from administration of a 20 mg tablet containing zoledronic acid as the sole active ingredient, and the data includes a value that falls within the range recited in claim 17. *See* Ex. 1009, 29:40–60 (Table 17 disclosing ratio of 0.507 at lower end of 90% confidence interval of ratio of oral versus intravenous absorption); *see also* Ex. 1005 ¶¶ 100–102 (Wilson Decl.) (.0507 ratio of

oral versus intravenous absorption adjusted for dosage difference yields 2.54% bioavailability for tablet containing 20 mg zoledronate). We discern no error in Dr. Wilson's calculations based on Table 17, and given his education and experience (*see* Ex. 1006), we credit his testimony on this issue.

Because Table 17 of Leonard discloses that administration of a 20 mg tablet containing zoledronic acid as the sole active ingredient results in a bioavailability value that falls within the range recited in claim 17, Petitioner persuades us that Leonard's 20 mg zoledronate tablet anticipates claim 17. *See Ineos v. Berry Plastics*, 783 F.3d at 869 ("When a patent claims a range, . . . that range is anticipated by a prior art reference if the reference discloses a point within the range.").

In sum, for the reasons discussed, Petitioner persuades us that claim 2 of Leonard recites a dosage form having all of the features of the dosage form recited in claim 17 of the '862 patent. Petitioner also persuades us, for the reasons discussed, that Example 17 of Leonard discloses a dosage form having all of the features of the dosage form recited in claim 17 of the '862 patent. Accordingly, Petitioner persuades us that it has shown by a preponderance of the evidence that Leonard anticipates claim 17 of the '862 patent.

Patent Owner's arguments do not persuade us to the contrary. We acknowledge Patent Owner's contentions that Petitioner and Dr. Wilson improperly rely on the truth of the data presented in Leonard. *See* PO Resp. 25–30 (citing 37 C.F.R. § 42.61(c); also citing Ex. 2022, 86:20–88:20 (Wilson Deposition)).

The full text of the rule relied upon by Patent Owner states as follows:

A specification or drawing of a United States patent application or patent is admissible as evidence only to prove what the specification or drawing describes. If there is data in the specification or a drawing upon which a party intends to rely to prove the truth of the data, an affidavit by an individual having first-hand knowledge of how the data was generated must be filed.

37 C.F.R. § 42.61(c).

We first note that § 42.61(c) is a procedural rule regarding the admissibility of evidence. We are not persuaded, therefore, that § 42.61(c) provides a legal basis for concluding that a patent or patent application is non-enabling as prior art, as Patent Owner contends. See PO Resp. 25–30. In that regard, other than the challenge based on § 42.61(c), Patent Owner advances no specific legal or evidentiary basis for concluding that the disclosures discussed above in Leonard, relied upon by Petitioner, would have failed to enable a skilled artisan to prepare the dosage form recited in claim 17 of the '862 patent. We note, in particular, that a “reference may be read for all that it teaches, including uses beyond its primary purpose.” *In re Mouttet*, 686 F.3d 1322, 1331 (Fed. Cir. 2012).

Section 42.61(c), moreover, expressly provides that the specification of the patent or application at issue is admissible to prove what that specification describes. In the present case, notwithstanding Patent Owner’s contentions and Dr. Wilson’s testimony to the contrary, it is abundantly clear that Petitioner relies on the disclosures in Leonard’s Example 17, and in Leonard’s claim 2, for what they describe—a dosage form having all of the features required by the challenged claims.

The text of the governing statute, in particular, underscores the fact that Petitioner necessarily, and properly, relies on Leonard for what it describes. As noted above, 35 U.S.C. § 102(a)(1) states that a person may not obtain a patent if “the claimed invention was patented” or “described in a printed publication.” As discussed above, Petitioner cites claim 2 of Leonard as evidence that the invention of claim 17 of the ’862 patent had already been patented by Leonard. And as also discussed above, Petitioner cites Example 17 as evidence that Leonard had described a dosage form having all of the features of the challenged claims, before Patent Owner filed the application that matured into the ’862 patent.

In sum, for the reasons discussed, Patent Owner does not persuade us that 37 C.F.R. § 42.61(c) precludes Petitioner from relying on the disclosures in Leonard, discussed above, in challenging the claims of the ’862 patent. Patent Owner also does not persuade us that (*see* PO Resp. 30–31) the relevant disclosures in Leonard are insufficiently specific to describe the dosage form in claim 17 of the ’862 patent.

In particular, Patent Owner does not persuade us (*see id.*) that Leonard fails to describe a dosage form that contains zoledronic acid and no other active ingredients, as recited in claim 17. As noted above, claim 2 of Leonard recites a pharmaceutical dosage form which contains zoledronate as the only named active agent, and which has a bioavailability range substantially overlapping the range recited in claim 17 of the ’862 patent. *See* Ex. 1009, 35:12–21. Patent Owner does not explain specifically why the disclosure in claim 2 of Leonard is insufficient to describe a dosage form having zoledronic acid as the sole active ingredient.

Patent Owner does not persuade us, moreover, that Petitioner failed to show that Example 17 of Leonard, from which Leonard obtained the data in Table 17, describes a dosage form having zoledronic acid as the sole active ingredient. Patent Owner relies on the deposition testimony of Petitioner's expert, Dr. Wilson, as evidence that Leonard fails to describe a dosage form containing zoledronic acid as the sole active ingredient, because the ingredients in the dosage forms of Example 17 are allegedly not described with sufficiently clarity. PO Resp. 30–31 (citing Ex. 2022, 89:11–94:2 (Wilson Deposition)).

Example 17 of Leonard states that the “oral dosage form under consideration was an enterically coated tablet containing sodium caprate and either 10 mg or 20 mg of zoledronic acid formed in accordance with the methods of Examples 6, 8 and 13.” Ex. 1009, 27:49–52. In his initial declaration, Dr. Wilson analyzed Examples 6, 8, and 13 of Leonard in light of Example 17, and testified that a skilled artisan “preparing the zoledronic acid formulation of Leonard Example 17 according to the methods of Examples 6, 8 and 13 would have made a formulation containing the listed excipients, and would use zoledronic acid as the only active ingredient in place of leuprolide or parnaparin sodium.” Ex. 1005 ¶ 97.

Even assuming for the sake of argument that Dr. Wilson was confused during his deposition about which *excipients* were included in the oral dosage forms of Leonard's Example 17 (see Ex. 2022, 89:11–94:2 (Wilson Deposition)), Patent Owner directs us to no testimony by Dr. Wilson, or other evidence of record, suggesting that any active ingredients other than zoledronic acid were present in the dosage forms of Leonard's Example 17. Nor does Patent Owner direct us to any persuasive evidence suggesting that

the disclosure in relation to Leonard's Example 17 was so vague as to make it impossible to determine whether zoledronic acid would have been the sole active ingredient in the dosage form.

To the contrary, in reviewing Leonard's Example 6, 8, and 13, we note that the sole active ingredient identified in Examples 6 and 8 is parnaparin sodium,¹² and the sole active ingredient in Example 13 is leuprolide. See Ex. 1009, 20:17–21:8, 21:43–22:14, 24:4–22. We are not persuaded, therefore, that in referencing Examples 6, 8, and 13 for preparation procedures, Leonard's Example 17 would have been understood as including more than a single active ingredient.

In sum, for the reasons discussed, Patent Owner does not persuade us that Petitioner fails to show by a preponderance of the evidence that Leonard describes a dosage form in which zoledronic acid is the sole active ingredient. Moreover, that Leonard uses an enhancer to prepare dosage forms having bioavailabilities encompassed by claim 17 of the '862 patent does not persuade us that Leonard fails to anticipate claim 17. See PO Resp. 31–34.

In particular, Patent Owner does not persuade us that, because the dosage forms described in Leonard use an enhancer to achieve bioavailabilities encompassed by claim 17 of the '862 patent, Leonard's dosage forms “operate[] differently” than the dosage forms recited in claim 17. *Id.* at 32.

Claim 17 of the '862 patent uses the transitional term “comprising” to describe ingredients in the claimed dosage form. See Ex. 1001, 27:14.

¹² Parnaparin is a low molecular weight heparin (“LMWH”) product. See Ex. 1009, 18:50–51.

Thus, except for the clause excluding active ingredients other than zoledronic acid, Compound 1, and/or Compound 2, claim 17 encompasses any unnamed additional ingredients, including the enhancer in Leonard's dosage forms. *See Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) (“‘Comprising’ is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.”).

Moreover, contrary to Patent Owner's contention that the presence of a bioavailability enhancer demonstrates that Leonard's dosage forms operate differently than the claimed dosage form, the '862 patent expressly discloses that bioavailability enhancers may be included in the disclosed dosage forms. *See Ex. 1001, 13:7–8* (“Some dosage forms may have ingredients added to enhance the bioavailability.”).

We acknowledge Patent Owner's contention that, to the extent Leonard's Example 17 can be reproduced, “the entire 90% confidence interval, not just part of it, is more or less a property of the particular dosage form itself.” PO Resp. 34. Patent Owner does not explain specifically, however, how that fact demonstrates that Petitioner failed to show that the 20 mg dosage form in Leonard's Example 17 had a bioavailability encompassed by claim 17 of the '862 patent.

In sum, having considered the evidence and arguments advanced by both Petitioner and Patent Owner, Petitioner persuades us, for the reasons discussed, that it has shown by a preponderance of the evidence that Leonard anticipates claim 17 of the '862 patent.

4. *Analysis—Anticipation of Claims 18–20, 23, 24, and 26–30 by Leonard*

As to claims 18–20, 23, 24, and 26–30, which all depend from claim 17, Petitioner identifies disclosures in Leonard purporting to describe each of the features of the dosage forms required by those claims. Pet. 41–46. Patent Owner does not assert error in Petitioner’s contentions regarding claims 18–20, 23, 24, and 26–30. See PO Resp. 25–39.

Having reviewed the cited portions of Leonard in light of the contentions by Petitioner, and in light of the absence of specific controverting argument or evidence from Patent Owner, we find that Petitioner has shown by a preponderance of the evidence that claims 18–20, 23, 24, and 26–30 are unpatentable under 35 U.S.C. § 102(a)(1) as anticipated by Leonard.

5. Analysis—Anticipation of Claims 21 and 22 by Leonard

We determine that Petitioner has not shown by a preponderance of the evidence that claims 21 and 22 of the ’862 patent are unpatentable under 35 U.S.C. § 102(a)(1) as anticipated by Leonard.

Claim 21 of the ’862 patent recites “[t]he dosage form of claim 17, comprising about 50 mg to about 100 mg of zoledronic acid.” Ex. 1001, 28:20–21.

Claim 22 of the ’862 patent recites “[t]he dosage form of claim 17, comprising about 100 mg to about 200 mg of zoledronic acid.” *Id.* at 28:20–21.

Petitioner cites column 9, lines 49–51, of Leonard as disclosing compositions “containing anywhere from 0.5 micrograms to about 1,000 mg zoledronic acid.” Pet. 41. Petitioner contends that, although that range is “broader than and completely encompasses” the ranges recited in challenged claims 21 and 22, “a prior art reference that discloses a broader, overlapping

range anticipates a claimed range unless the claimed range is ‘critical’ to the claimed invention.” *Id.* (citing *Ineos*, 783 F.3d at 870); *see also* Reply 15 (citing the ’862 patent as disclosing a suitable range of 0.005 mg to 2,000 mg in dosage forms).

Patent Owner contends that the disclosure at column 9, lines 49–51, of Leonard relates only to drugs in general, and not zoledronic acid specifically. PO Resp. 35–37. Patent Owner contends that the range of 1 mg to 25 mg recited in claims 1 and 34 of Leonard is the only range of dosage amounts specific to zoledronic acid. *Id.* at 36. Patent Owner contends that if applied to zoledronic acid, higher values encompassed by the broader range taught in Leonard encompass toxic dosages. *Id.*

We find that the preponderance of the evidence supports Patent Owner’s position.

To find anticipation, “it is not enough that the prior art reference . . . includes multiple, distinct teachings that [an ordinary] artisan might somehow combine to achieve the claimed invention.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). Instead, the reference “must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.” *Id.* (quoting *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972)).

Petitioner identified two anticipatory dosage form embodiments in Leonard—the dosage form recited in claim 2 of Leonard, and the 20 mg dosage form described in Example 17 of Leonard. *See* Pet. 31–41.

We acknowledge Leonard’s general disclosure that its dosage forms

can contain 0.5 µg to about 1000 mg of a drug (Ex. 1009, 9:49–51), and that zoledronic acid is one of the drugs that can be included in its dosage forms (*id.* at 6:13–37). Those disclosures, however, cannot change the fact that the dosage form of Example 17 has 20 mg of zoledronic acid, which is outside the ranges recited in claims 21 and 22.

In addition, Petitioner does not persuade us that Leonard’s broader disclosure regarding the amount of drug in its compositions relates directly to the particular dosage form recited in claim 2 of Leonard. We find, therefore, that arriving at the dosage form of claims 21 and 22 of the ’862 patent requires excessive picking and choosing, such that Leonard does not anticipate claims 21 and 22.

In sum, for the reasons discussed, we determine that Petitioner has not shown by a preponderance of the evidence that claims 21 and 22 of the ’862 patent are unpatentable under 35 U.S.C. § 102(a)(1) as anticipated by Leonard.

6. Analysis—Anticipation of Claim 25 by Leonard

We determine that Petitioner has not shown by a preponderance of the evidence that claim 25 of the ’862 patent is unpatentable under 35 U.S.C. § 102(a)(1) as anticipated by Leonard.

Claim 25 of the ’862 patent recites “[t]he dosage form of claim 17, wherein at least 10% of the weight of the dosage form is zoledronic acid.” Ex. 1001, 28:27–28.

As Petitioner notes, the tablet containing 20 mg zoledronate in Leonard’s Example 17 was “formed in accordance with the methods of Examples 6, 8, and 13.” Ex. 1009, 27:51–52.

Petitioner contends, based on calculations by its expert, Dr. Wilson,

that the tablet in Leonard's Example 8 has 37% active agent, thereby meeting the requirements of claim 25. Pet. 44.

Patent Owner contends that, while Leonard's Example 17 states that its dosage form was formed in accordance with Examples 6, 8, and 13, each of those examples uses different percentages of active ingredient, and the dosage form of Example 17 therefore does not inherently contain at least 10% zoledronic acid. PO Resp. 38.

We agree with Patent Owner that Petitioner has not established that the dosage form of Leonard's Example 17 inherently contains at least 10% zoledronic acid, as claim 25 of the '862 patent requires. Although we acknowledge the calculations by Dr. Wilson, we note that the anticipatory dosage form of Leonard's Example 17 contains 20 mg zoledronic acid. Ex. 1009, 27:49–52.

The tablets of Example 8, on which Dr. Wilson bases his calculations, had a mean tablet weight of 772 mg. *Id.* at 21:66. Because 20 mg is significantly less than 10% of 772 mg, we are not persuaded that Dr. Wilson's calculations establish that the dosage form of Leonard's Example 17 inherently contains at least 10% zoledronic acid, as claim 25 of the '862 patent requires. We, therefore, determine that Petitioner has not shown by a preponderance of the evidence that Leonard anticipates claim 25.

G. Obviousness—Leonard (Claims 17–30)

1. The Parties' Contentions

Petitioner contends that, in addition to anticipating claims 17–30 of the '862 patent, Leonard also renders obvious the dosage forms recited in those claims. Pet. 46–53. In particular, Petitioner contends, because Leonard describes zoledronate-containing oral dosage forms with

bioavailability and dosage ranges that overlap the ranges recited in claims 17–30, in the forms recited in those claims, Leonard renders the dosage form recited in those claims obvious. *See id.*

Patent Owner reiterates its argument that Leonard’s bioavailability range operates differently than the claimed range, because Leonard uses an enhancer. PO Resp. 39–40. Patent Owner contends that Leonard does not suggest the dosage forms of claims 17–30 because modifying Leonard’s dosage forms to have the bioavailabilities in those claims would render Leonard’s dosage forms unsuitable for their intended purpose. *Id.* at 40–41. Patent Owner also reiterates its contentions, discussed above, as to claims 21, 22, and 25. *Id.* at 41.

2. Analysis—Obviousness of Claim 17 over Leonard

We determine that Petitioner has shown by a preponderance of the evidence that claim 17 is unpatentable for obviousness in view of Leonard.

“Where a claimed range overlaps with a range disclosed in the prior art, there is a presumption of obviousness. . . . The presumption can be rebutted if it can be shown that the prior art teaches away from the claimed range, or the claimed range produces new and unexpected results.” *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006) (citation omitted).

In the present case, the bioavailability range of 2.5% to 13.0% disclosed in claim 2 of Leonard, noted above, significantly overlaps the bioavailability range of about 1.1% to about 4% recited in claim 17 of the ’862 patent. Petitioner persuades us, therefore, that it is proper to presume that the dosage form recited in claim 17 of the ’862 patent would have been obvious to an ordinary artisan.

It might be true, as Patent Owner contends (*see* PO Resp. 40–41), that Leonard prefers dosage forms having higher bioavailability levels than recited in claim 17 of the '862 patent. That fact, however, does not negate Leonard's express disclosure, noted above, of an oral zoledronate-containing dosage form with a bioavailability range that overlaps the bioavailability range recited in claim 17.

Moreover, given Leonard's express disclosure of an oral zoledronate-containing dosage form with a bioavailability range that overlaps the bioavailability range recited in claim 17, Patent Owner does not persuade us that an ordinary artisan would need to modify Leonard's dosage forms in a manner that would render Leonard's dosage forms unsuitable for their intended purpose.

In sum, because Leonard discloses a dosage form with a bioavailability range overlapping the range in claim 17 of the '862 patent, and because the resulting presumption of obviousness of claim 17 has not been sufficiently rebutted, Petitioner persuades us that it has shown by a preponderance of the evidence that the dosage form of claim 17 would have been obvious to an ordinary artisan in view of Leonard.

3. Analysis—Obviousness of Claims 18–20, 23, 24, and 26–30 in view of Leonard

As to claims 18–20, 23, 24, and 26–30, which all depend from claim 17, Petitioner identifies disclosures in Leonard purporting to teach or suggest each of the features of the dosage forms required by those claims. Pet. 49–53. Patent Owner does not assert error in Petitioner's contentions regarding claims 18–20, 23, 24, and 26–30. *See* PO Resp. 39–41.

Having reviewed the cited portions of Leonard in light of the contentions by Petitioner and in light of the absence of specific controverting

argument or evidence from Patent Owner, we find that Petitioner has shown by a preponderance of the evidence that claims 18–20, 23, 24, and 26–30 are unpatentable for obviousness in view of Leonard.

4. *Analysis—Obviousness of Claims 21 and 22 in view of Leonard*

We determine that Petitioner has shown by a preponderance of the evidence that claims 21 and 22 are unpatentable for obviousness in view of Leonard.

Claim 21 of the '862 patent recites “[t]he dosage form of claim 17, comprising about 50 mg to about 100 mg of zoledronic acid.” Ex. 1001, 28:20–21.

Claim 22 of the '862 patent recites “[t]he dosage form of claim 17, comprising about 100 mg to about 200 mg of zoledronic acid.” *Id.* at 28:20–21.

Petitioner contends that, even if Leonard does not expressly disclose compositions containing the amounts of zoledronic acid recited in claims 21 and 22, the dosage forms recited in claims 21 and 22 would have been obvious in view of Leonard’s disclosure of a range of suitable zoledronic acid amounts that overlaps the ranges recited in claims 21 and 22. *See* Pet. 49–50. Petitioner contends in particular that the '862 patent “is devoid of any suggestion that administration of the particular amounts claimed is critical, or associated with any advantageous or unexpected results.” *Id.*

In addition, Petitioner contends, because an ordinary artisan would have considered it a routine matter to optimize the amount of zoledronic acid for use in Leonard’s dosage forms, dosage forms having zoledronic acid amounts recited in claims 21 and 22 would have been obvious. *Id.* at 50–51 (citing Ex. 1005 ¶ 128 (Wilson Decl.)).

In response, Patent Owner cites to its previous contentions in relation to the anticipation ground, discussed above, that Leonard's general disclosure about drug amounts in its dosage forms does not refer to zoledronic acid specifically. PO Resp. 41 ("For the same reasons asserted above in Sections II(C)(1) and II(C)(2) respectively, claims 21, 22, and 25 are not obvious over Leonard.").

In this instance, we find that the preponderance of the evidence supports Petitioner's position. As discussed above, excessive picking and choosing is prohibited when evaluating a reference for anticipation. See *Net MoneyIN*, 545 F.3d at 1371 (citing *Arkley*, 455 F.2d at 587). In the context of obviousness, however, picking and choosing "may be entirely proper." *Arkley*, 455 F.2d at 587. Thus, Patent Owner's reliance on its arguments in relation to anticipation is insufficient to show that Petitioner failed to establish the obviousness of claims 21 and 22.

In addition, as noted above, claim 2 of Leonard recites a pharmaceutical dosage form, which contains zoledronate as the sole active agent, and which has a bioavailability of 2.5% to 13.0%. Ex. 1009, 35:12–21. Claim 2 of Leonard thus differs from claims 21 and 22 of the '862 patent in not disclosing that the dosage form contains the zoledronic acid amounts required by claims 21 and 22 of the '862 patent.

As also noted above, however, Leonard includes a general disclosure that its dosage forms can contain 0.5 µg to about 1000 mg of a drug (Ex. 1009, 9:49–51), and also discloses that zoledronic acid is one of the drugs that can be included in its dosage forms (*id.* at 6:13–37). Thus, as Petitioner contends, the range of suitable amounts of drug in its dosage forms entirely overlaps the ranges recited in claims 21 and 22 of the '862 patent.

Further, consistent with Petitioner's optimization contentions, Leonard discloses that, "[a]s will be appreciated by those skilled in the art, the actual amount of drug compound used will depend on, among other things, the potency of the drug, the specifics of the patient and the therapeutic purpose for which the drug is being used." Ex. 1009, 9:45–49.

Given Leonard's disclosure that its dosage form may contain zoledronic acid in amounts overlapping the amounts recited in claims 21 and 22 of the '862 patent, and given Leonard's disclosure that skilled artisans would be able to determine suitable amounts of zoledronic for use in its dosage forms, Petitioner persuades us, by a preponderance of the evidence, that an ordinary artisan would have considered the dosage forms recited in claims 21 and 22 of the '862 patent obvious.

5. Analysis—Obviousness of Claim 25 in view of Leonard

We determine that Petitioner has shown by a preponderance of the evidence that claim 25 is unpatentable for obviousness in view of Leonard.

Claim 25 of the '862 patent recites "[t]he dosage form of claim 17, wherein at least 10% of the weight of the dosage form is zoledronic acid." Ex. 1001, 28:27–28.

Petitioner contends that, even if Leonard does not expressly disclose compositions containing the percentage of zoledronic acid recited in claim 25, the dosage form recited in claim 25 would have been obvious in view of Leonard's disclosure of an example including 47.8 % active ingredient. Pet. 51. In addition, Petitioner contends, because an ordinary artisan would have considered it a routine matter to optimize the amount of zoledronic acid for use in Leonard's dosage forms, dosage forms having zoledronic acid percentages encompassed by claim 25 would have been obvious. *See id.* at

52–53 (citing Ex. 1005 ¶¶ 128, 132, 133 (Wilson Decl.)).

In response, Patent Owner cites to its previous contentions in relation to the anticipation ground, discussed above, that Leonard fails to explain with sufficient specificity what ingredients were present in the dosage forms described in Example 17. PO Resp. 41 (“For the same reasons asserted above in Sections II(C)(1) and II(C)(2) respectively, claims 21, 22, and 25 are not obvious over Leonard.”).

In this instance, we find that the preponderance of the evidence supports Petitioner’s position. Because Patent Owner does not address Petitioner’s optimization rationale for the obviousness of claim 25, Patent Owner’s reliance on its arguments in relation to anticipation is insufficient to show that Petitioner failed to establish the obviousness of claim 25.

In addition, as noted above, claim 2 of Leonard recites a pharmaceutical dosage form, which contains zoledronate as the sole active agent, and which has a bioavailability of 2.5% to 13.0%. Ex. 1009, 35:12–21. Claim 2 of Leonard thus differs from claim 25 of the ’862 patent in not disclosing the dosage form as containing the zoledronic acid percentage required by claim 25.

As also noted above, however, and consistent with Petitioner’s optimization contentions, Leonard discloses that, “[a]s will be appreciated by those skilled in the art, the actual amount of drug compound used will depend on, among other things, the potency of the drug, the specifics of the patient and the therapeutic purpose for which the drug is being used.” Ex. 1009, 9:45–49.

As Petitioner notes, moreover, Leonard discloses that its dosage forms may have a broad range of ratios of its drug in relation to its other

ingredients. *Id.* at 9:53–55 (“In one embodiment, the drug and the enhancer are present in a ratio of from 1:100000 to 10:1 (drug:enhancer).”).

Given Leonard’s disclosure that its dosage forms may have a broad range of ratios of its drug in relation to its other ingredients, and given Leonard’s disclosure that skilled artisans would be able to determine suitable amounts of zoledronic for use in its dosage forms, Petitioner persuades us, by a preponderance of the evidence, that an ordinary artisan would have considered the dosage form recited in claim 25 of the ’862 patent obvious.

H. Obviousness—Leonard and the Merrion Poster (Claims 17–30)

Petitioner contends that the Merrion Poster describes the same formulations as taught in Leonard, and provides additional detailed data regarding the administration of those formulations, further demonstrating that Leonard’s formulations have bioavailabilities within the range recited in claim 17. Pet. 53–55. Petitioner contends that, because the references relate to the same formulations and share an author/inventor, an ordinary artisan would have been motivated to combine their disclosures, and would have had a reasonable expectation that the formulations described therein would have bioavailabilities within the range recited in claim 17. *Id.* at 56.

As discussed above, we agree with Patent Owner that Petitioner has not shown that the Merrion Poster qualifies as prior art to the claims of the ’862 patent. Accordingly, although we expressly note our determination above as to the obviousness of claims 17–30 over Leonard alone, we determine that Petitioner has not shown by a preponderance of the evidence that the combined disclosures of Leonard and the Merrion Poster, as advanced in the Petition, would have rendered claims 17–30 of the ’862 patent obvious.

I. Obviousness—Fox, Laslett, Leonard, and the Merrion Poster (Claims 2–16)

1. Fox (Ex. 1007)

Fox discloses a “method for the treatment of pain . . . which comprises administering an effective amount of a bisphosphonate, e.g. zoledronic acid or salts or hydrates thereof, to the patient.” Fox, Abstract.

Fox discloses that, “[p]referably the invention is used for the direct treatment of pain in diseases and medical conditions in which bisphosphonates are used to inhibit osteoclast activity. . . . Examples of such diseases and conditions include . . . osteoarthritis [and] RA [rheumatoid arthritis]” *Id.* ¶ 10.

Fox discloses that its “most preferred bisphosphonate” is zoledronate “or a pharmacologically acceptable salt thereof or any hydrate thereof.” *Id.* ¶ 63. Fox discloses that “[e]specially preferred pharmaceutically acceptable salts are those where one, two, three or four, in particular one or two, of the acidic hydrogens of the bisphosphonic acid are replaced by a pharmaceutically acceptable cation, in particular sodium, potassium or ammonium, in first instance sodium.” *Id.* ¶ 64.

Fox discloses:

Preferably, the pharmaceutical compositions are adapted to oral or parenteral (especially intravenous, intraarterial or transdermal) administration. Intravenous and oral, first and foremost intravenous, administration is considered to be of particular importance. Preferably the bisphosphonate active ingredient is in the form of a parenteral, most preferably an intravenous form.

The particular mode of administration and the dosage may be selected by the attending physician taking into account the particulars of the patient, especially age, weight, life style, activity level, hormonal status (e.g. postmenopausal) and bone

mineral density as appropriate. Most preferably, however, the bisphosphonate is administered intravenously.

Id. ¶¶ 72–73.

2. *Laslett (Ex. 1008)*

Laslett discloses a study with an objective of comparing “the effect of a single infusion of zoledronic acid (ZA) with placebo on knee pain and bone marrow lesions (BMLs).” Ex. 1008, 1322 (Abstract).

Laslett discloses:

A [previous] study investigating the effect of risedronate [a different bisphosphonate] on cartilage loss in knee OA [osteoarthritis] suggested that risedronate 50 mg weekly may prevent an increase in BML size, although this was not statistically significant. While the effect of bisphosphonates on BMLs could be a class effect, bisphosphonates given intravenously appear to have greater treatment effects, at least, for osteoporosis.

Therefore, this study aimed to compare the effect of a single infusion of zoledronic acid (ZA) 5 mg with placebo on knee pain and BMLs over 12 months in participants with a pain intensity score >40 mm on a visual analogue scale (VAS) and a prevalent knee BML.

Id. at 1322 (citations omitted).

In Laslett’s study, adults “aged 50–80 years (n=59) with clinical knee osteoarthritis and knee BMLs were randomised to receive either ZA (5 mg/100 ml) or placebo. . . . Pain and function were measured using a visual analogue scale (VAS) and the knee injury and osteoarthritis outcome score (KOOS) scale.” *Id.* at Abstract.

“Participants (n=59) received an identical intravenous infusion of 100 mg of fluid, containing ZA (5 mg in normal saline) or placebo (normal saline), given by one nurse at the Menzies Institute.” *Id.* at 1323.

Laslett discloses that “VAS pain scores were significantly reduced in the ZA group compared with placebo after 6 months (−14.5 mm, 95% CI −28.1 to −0.9) but not after 3 or 12 months. Changes on the KOOS scales were not significant at any time point.” *Id.* at 1322 (Abstract).

Laslett concludes that “ZA reduces knee pain and areal BML size and increases the proportion improving over 6 months. Treatment of osteoarthritis may benefit from a lesion specific therapeutic approach.” *Id.*

3. *The Parties’ Contentions*

Petitioner contends that an ordinary artisan would have been motivated by Fox and Laslett to treat knee pain with zoledronate, as required by independent claim 2 of the ’862 patent. Pet. 59–62. Petitioner contends that, given Fox’s teaching that said treatment can be performed by oral administration, and further given the advantages of oral zoledronate administration taught in Leonard, an ordinary artisan would have considered it obvious to orally administer the dosage forms taught in Leonard and the Merrion Poster to treat knee pain, thereby administering the dosage form required by claim 2. *Id.* at 62–67.

Petitioner identifies teachings in Fox, Laslett, Leonard, and the Merrion Poster purporting to show the obviousness of the features recited in claims 3–16, which all depend from claim 2. *Id.* at 67–77.

Patent Owner contends, for a number of reasons, that an ordinary artisan would not have been motivated to administer zoledronate to treat knee pain, as required by claim 2 and its dependent claims. PO Resp. 57–68.

As discussed above, we agree with Patent Owner that Petitioner has not shown that the Merrion Poster qualifies as prior art. Nonetheless, except

as to claims 3 and 4 discussed below, Petitioner’s challenge to claims 2–16 of the ’862 patent relies on Leonard and the Merrion Poster as disclosing the same feature of claims 2–16, a zoledronic acid-containing dosage form having a bioavailability encompassed by the claims. We, therefore, evaluate the parties’ contentions in relation to this ground based on the relevant disclosures in Fox, Laslett, and Leonard, and to the exclusion of the teachings in the Merrion Poster.

4. Analysis—Obviousness of Claim 2 in view of Fox, Laslett, and Leonard

We determine that Petitioner has shown by a preponderance of the evidence that claim 2 is unpatentable for obviousness in view of Fox, Laslett, and Leonard.

Section 103 provides that a claim is unpatentable “if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” 35 U.S.C. § 103.

Claim 2 of the ’862 patent recites a method of treating knee pain by orally administering, to a human, a dosage form in which zoledronate is the only required therapeutically active agent, and which contains no therapeutically active agents other than zoledronate, Compound 1, or Compound 2. *See* Ex. 1001, 25:65–26:35. Claim 2 recites that “the bioavailability of zoledronic acid in the dosage form is from about 1.1% to about 4%.” *Id.* at 26:39–40.

The dosage form administered in the process of claim 2 is identical to the dosage form recited in claim 17 of the ’862 patent. As discussed above in relation to claim 17, the preponderance of the evidence supports

Petitioner's contention that Leonard describes, as well as renders obvious, a dosage form meeting all of the limitations of the dosage form recited in claim 2 of the '862 patent. Thus, claim 2 of the '862 patent differs from Leonard in that Leonard does not orally administer its dosage form to a human to treat knee pain.

As seen above, however, Fox teaches that oral administration of zoledronate was a suitable method of treating pain resulting from osteoarthritis in humans. See Ex. 1007, Abstract; *id.* ¶¶ 10, 72 (Fox). As also noted above, moreover, Laslett discloses that zoledronate was effective in treating osteoarthritis-related knee pain in human subjects. Ex. 1008, 1322 (Laslett).

Given Laslett's teaching that zoledronate was effective for treating osteoarthritis-related knee pain, as well as Fox's teaching that oral administration of zoledronate was a suitable method of treating pain resulting from osteoarthritis, and further given the teaching in Leonard that its oral formulation achieves plasma concentrations of zoledronate comparable to concentrations achieved intravenously (*see, e.g.*, Ex. 1009, 28:62–67), Petitioner persuades us that an ordinary artisan had a good reason for, and a reasonable expectation of success in, orally administering the dosage form of Leonard to treat knee pain. Petitioner, therefore, also persuades us that it has shown by a preponderance of the evidence that the treatment method of claim 2 of the '862 patent would have been obvious in view of Fox, Laslett, and Leonard.

Patent Owner's arguments do not persuade us to the contrary. Patent Owner contends that multiple bioavailability ranges may be derived from the data shown in Table 17 of Leonard, including ranges that do not overlap, and

are significantly higher than, the range recited in claim 2 of the '862 patent. PO Resp. 58–61.

As discussed above, however, the bioavailability range of 2.5% to 13.0% of the dosage form disclosed in claim 2 of Leonard (see Ex. 1009, 35:21–21) significantly overlaps the bioavailability range of about 1.1% to about 4% recited in claim 2 of the '862 patent. Thus, that the data in Leonard's Table 17 might be interpreted as teaching dosage forms not encompassed by claim 2 of the '862 patent does not persuade us that Leonard fails to describe or suggest an oral zoledronic acid dosage form meeting the requirements of claim 2 of the '862 patent.

In addition, as seen above, Table 17 of Leonard describes a distribution of bioavailability values resulting from administration of a 20 mg tablet containing zoledronic acid as the sole active ingredient, and the data includes a value that falls within the range recited in claim 2. *See id.* at 29:40–60 (Table 17 disclosing ratio of 0.507 at lower end of 90% confidence interval of ratio of oral versus intravenous absorption). And, as noted above, Leonard teaches that its oral formulation achieves plasma concentrations of zoledronate comparable to concentrations achieved intravenously. *See id.* at 28:62–67.

Patent Owner contends that an ordinary artisan would not have been motivated to administer Leonard's dosage forms encompassed by claim 2 of the '862 patent, because the artisan would only have been motivated to administer the dosage forms having the highest bioavailabilities disclosed in Leonard, which would be higher than the range recited in claim 2. PO Resp. 61–66.

We do not find this argument persuasive. As our reviewing court has explained, a “finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed by the patent applicant is the preferred, or most desirable, combination.” *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004).

Thus, even assuming for argument’s sake that Leonard discloses oral dosage forms of higher and lower potency, and that the most potent forms would be preferred, that does not negate the fact that Leonard’s zoledronic acid dosage forms encompassed by claim 2 of the ’862 patent were disclosed as providing a therapeutic benefit. Given Laslett’s teaching that zoledronic acid was effective for treating osteoarthritis-related knee pain, as well as Fox’s teaching that oral administration of zoledronic acid was a suitable method of treating pain resulting from osteoarthritis, Patent Owner does not persuade us that an ordinary artisan lacked motivation to treat knee pain by administering Leonard’s zoledronic acid oral dosage forms encompassed by claim 2 of the ’862 patent.

In sum, for the reasons discussed, Petitioner persuades us that it has shown by a preponderance of the evidence that the process recited in claim 2 of the ’862 patent would have been obvious in view of Fox, Laslett, and Leonard.

5. Analysis—Obviousness of Claims 3 and 4 in view of Fox, Laslett, and Leonard

As discussed above, we agree with Patent Owner that Petitioner has not shown that the Merrion Poster qualifies as prior art. Petitioner’s sole obviousness challenge to claims 3 and 4 of the ’862 patent relies extensively on specific disclosures in the Merrion Poster, however. *See* Pet. 68–70. We

determine, therefore, that Petitioner has not shown by a preponderance of the evidence that the process recited in claims 3 and 4 of the '862 patent would have been obvious to an ordinary artisan.

6. Analysis—Obviousness of Claims 5–7 and 10–16 in view of Fox, Laslett, and Leonard

As to claims 5–7 and 10–16, which all depend from claim 2, Petitioner identifies disclosures in Leonard purporting to teach or suggest each of the features of the dosage forms required by those claims. Pet. 71–77. Patent Owner does not assert error in Petitioner's contentions regarding claims 5–7 and 10–16. See PO Resp. 57–68.

Having reviewed the cited portions of Fox, Laslett, and Leonard in light of the contentions by Petitioner and in light of the absence of specific controverting argument or evidence from Patent Owner, we find that Petitioner has shown by a preponderance of the evidence that claims 5–7 and 10–16 are unpatentable for obviousness in view of Fox, Laslett, and Leonard.

7. Analysis—Obviousness of Claims 8 and 9 in view of Fox, Laslett, and Leonard

We determine that Petitioner has shown by a preponderance of the evidence that claims 8 and 9 are unpatentable for obviousness in view of Fox, Laslett, and Leonard.

Claim 8 of the '862 patent recites “[t]he method of claim 2, wherein the dosage form is administered in an amount such that a monthly dose of zoledronic acid is about 50 mg to about 300 mg.” Ex. 1001, 26:58–60.

Claim 9 of the '862 patent recites “[t]he method of claim 2, wherein the dosage form is administered in an amount such that a monthly dose of zoledronic acid is about 200 mg to about 300 mg.” *Id.* at 26:61–63.

Petitioner cites ¶¶ 75–77 of Fox as disclosing a wide range of zoledronic acid dosages (0.15 mg to 1,500 mg) that an ordinary artisan would have readily calculated as entirely overlapping the dosages of claims 8 and 9 of the '862 patent, assuming the dose would be administered to a 75 kg human. Pet. 71–72 (citing Ex. 1005 ¶¶ 138–144 (Wilson Decl.); Ex. 1003 ¶ 93 (Bruehl Decl.)). In addition, Petitioner contends, it would have been obvious to optimize the zoledronic acid dosage, in light of the teachings in Leonard. *Id.* at 72–73 (citing Ex. 1003 ¶¶ 95–98).

Patent Owner contends that the disclosure at ¶¶ 75–77 of Fox does not relate to zoledronic acid specifically, and that ¶ 78 of Fox, which does relate specifically to zoledronic acid, discloses a range outside that recited in claims 8 and 9 of the '862 patent. PO Resp. 66–68.

We find that the preponderance of the evidence supports Petitioner's position. We first note that Patent Owner does not address or explain why, nor do we discern why, Petitioner failed to provide an adequate evidentiary basis for concluding that it would have been obvious to optimize the dosage of zoledronic acid administered to treat knee pain, and thereby arrive at the dosages recited in claims 8 and 9.

In that regard, we note Dr. Bruehl's undisputed supporting testimony (Ex. 1003 ¶¶ 93–98), as well as the teaching in Leonard that "[a]s will be appreciated by those skilled in the art, the actual amount of drug compound used will depend on, among other things, the potency of the drug, the specifics of the patient and the therapeutic purpose for which the drug is being used." Ex. 1009, 9:45–49.

As to the dosage ranges in Fox, we acknowledge that Fox initially discloses that a single dose of its bisphosphonate active ingredient of from

0.002-20.0 mg/kg may be administered to a warm-blooded animal weighing approximately 75 kg, and that the dose may be administered monthly. Ex. 1007 ¶¶ 75–77. We note that Patent Owner does not assert error, nor do we discern error, in the calculations of Petitioner’s witnesses that this corresponds to monthly dosages of 0.15 mg to 1,500 mg, which entirely overlaps the dosages recited in claims 8 and 9 of the ’862 patent. See Ex. 1005 ¶¶ 138–144 (Wilson Decl.); Ex. 1003 ¶ 93 (Bruehl Decl.).

We acknowledge, as Patent Owner contends, that subsequent to disclosing the broader dosage range, Fox discloses that, preferably, its bisphosphonic acid derivatives are administered at dosages that inhibit bone resorption and treat Paget’s disease, tumour induced hypercalcemia, or osteoporosis, “[f]or example, for the preferred nitrogen-containing bisphosphonates, e.g. zoledronic acid and salts thereof, doses of bisphosphonate in the range from about 0.5 to about 20 mg, preferably from about 1 to about 10 mg, may be used for treatment of human patients.” Ex. 1007 ¶ 78.

Fox, however, does not state that the zoledronic acid dosages listed in ¶ 78 are monthly dosages. We are not persuaded, therefore, that the dosages in ¶ 78 are at odds with, or exclusive of, the broader dosage range set forth ¶ 75.

In sum, the preponderance of the evidence supports Petitioner’s contention that Fox discloses a zoledronic acid dosage range for treating pain that entirely overlaps the dosage ranges recited in claims 8 and 9 of the ’862 patent, and also supports Petitioner’s contention that it would have been obvious to optimize the zoledronic acid dosage administered to treat knee pain, and thereby arrive at a dosage encompassed by claims 8 and 9.

We determine, therefore, that Petitioner has shown by a preponderance of the evidence that claims 8 and 9 of the '862 patent would have been obvious to an ordinary artisan.

III. CONCLUSIONS—GROUNDS PRESENTED IN PETITION (ORIGINAL CLAIMS)

To summarize, for the reasons discussed above, we determine that:

(A) Petitioner has shown by a preponderance of the evidence that claims 2–30 of the '862 patent are unpatentable under 35 U.S.C. § 112(a) for lack of enablement;

(B) Petitioner has not shown by a preponderance of the evidence that claims 3 and 4 of the '862 patent are unpatentable under 35 U.S.C. § 112(b) for indefiniteness;

(C) Petitioner has shown by a preponderance of the evidence that claims 17–20, 23, 24, and 26–30 are unpatentable under 35 U.S.C. § 102(a)(1) as anticipated by Leonard;

(D) Petitioner has not shown by a preponderance of the evidence that claims 21, 22, and 25 are unpatentable under 35 U.S.C. § 102(a)(1) as anticipated by Leonard;

(E) Petitioner has shown by a preponderance of the evidence that claims 17–30 are unpatentable under 35 U.S.C. § 103 for obviousness over Leonard;

(F) Petitioner has shown by a preponderance of the evidence that claims 2 and 5–16 are unpatentable under 35 U.S.C. § 103 for obviousness over Fox, Laslett, and Leonard; and

(G) Petitioner has not shown by a preponderance of the evidence that claims 3 and 4 are unpatentable under 35 U.S.C. § 103 for obviousness over Fox, Laslett, and Leonard.

IV. MOTION TO AMEND

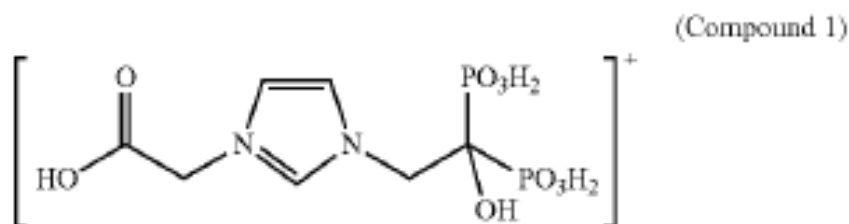
Contingent on our determination that claims 2–30 of the '862 patent are shown to be unpatentable, Patent Owner filed a Corrected Motion to Amend. Paper 33. As discussed above, we determine that Petitioner has shown by a preponderance of the evidence that claims 2–30 are unpatentable. Accordingly, we now consider Patent Owner's Motion to Amend.

A. The Proposed New Claims

Petitioner proposes substituting new claims 31–56 for claims 2–30, discussed above. Mot. to Amend 2.

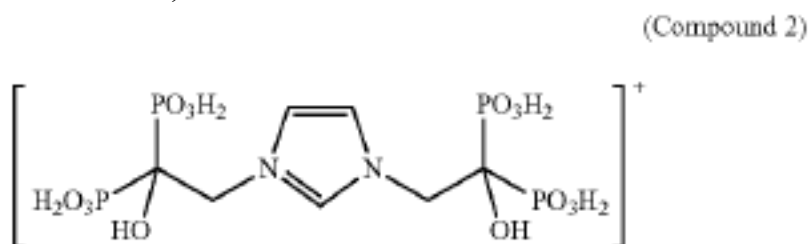
New claim 31, proposed as a substitute for original claims 2 and 15, reads as follows, with underlining to show inserted material, and *double brackets* showing deleted material, as compared to claim 2:

31. A method of treating knee pain comprising
fasting a human being for at least one hour, wherein the
human being suffers from knee pain,
orally administering a dosage form to ~~[[a]]~~ the human
being ~~[[suffering from knee pain]]~~,
then fasting the human being for at least one hour after
orally administering the dosage form,
wherein the dosage form comprises:
a) zoledronic acid; or
b) one of the following:
1) zoledronic acid and



in an amount that is less than 0.1% w/w and greater than 0% w/w;

2) zoledronic acid and



in an amount that is less than 0.1% w/w and greater than 0% w/w;

or

3) zoledronic acid and a combination of Compound 1 in an amount that is less than 0.1% w/w and greater than 0% w/w, and Compound 2 in an amount that is less than 0.1% w/w and greater than 0% w/w;

wherein the dosage form is free of therapeutically active agents that are not zoledronic acid, Compound 1, or Compound 2;

wherein any amount in % w/w is based upon the total weight of zoledronic acid, Compound 1, and Compound 2; and

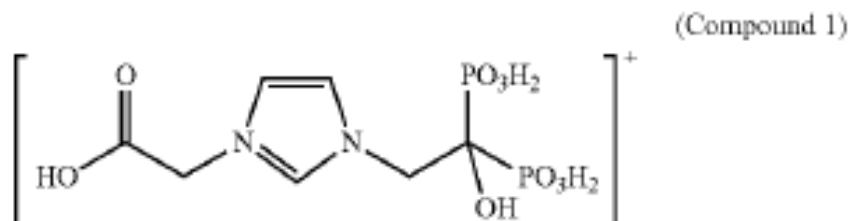
wherein the bioavailability of zoledronic acid in the dosage form is from [[about]] 1.1% to [[about 4%]] 2.3%.

Paper 33, App'x, 1–4.

New claim 45, proposed as a substitute for original claims 17, 24, and 25, reads as follows, with underlining to show inserted material, and *double*

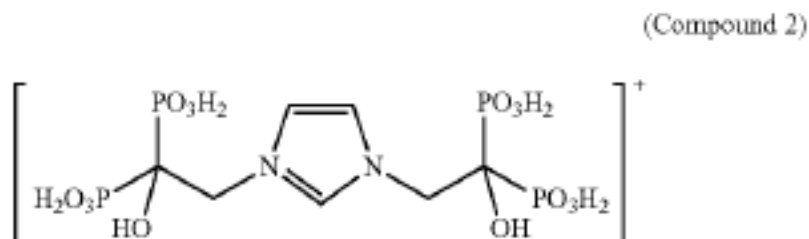
brackets showing deleted material, as compared to claim 17:

17. A pharmaceutical dosage form comprising:
a) zoledronic acid; or
b) one of the following:
1) zoledronic acid and



in an amount that is less than 0.1% w/w and greater than 0% w/w;

- 2) zoledronic acid and



in an amount that is less than 0.1% w/w and greater than 0% w/w;

or

- 3) zoledronic acid and a combination of Compound 1 in an amount that is less than 0.1% w/w and greater than 0% w/w, and Compound 2 in an amount that is less than 0.1% w/w and greater than 0% w/w;

wherein the dosage form is free of therapeutically active agents that are not zoledronic acid, Compound 1, or Compound 2;

wherein the dosage form is suitable for oral administration to a human being;

wherein any amount in % w/w is based upon the total weight of zoledronic acid, Compound 1, and Compound 2; and

wherein the bioavailability of zoledronic acid in the dosage form is from [[about]] 1.1% to [[about 4%]] 2.3% [[in a human being]] as determined by: 1) fasting a human subject for 10 hours, and then 2) orally administering the dosage form to the human subject, and then 3) fasting the human subject for 4 hours.

Paper 33, App'x, 6–8.

Petitioner contends that the proposed new claims are unpatentable for lack of written description and lack of enablement. Paper 38, 2–8. In addition, Petitioner contends that all of the proposed new claims are unpatentable for obviousness in view of the prior art cited in the Petition. *Id.* at 8–10.

Further, Petitioner contends that proposed new claims 45–53, 55, and 56 are unpatentable for obviousness in view of Hanna.¹³ *See id.* at 11–17.

Lastly, Petitioner contends that proposed new claims 31–44 are unpatentable for obvious over Fox, Laslett, Hanna, and Pazianas.¹⁴ *Id.* at 17–25.

B. Statutory/Regulatory Requirements for Proposed New Claims

In a post-grant review proceeding, a motion to amend must meet the following statutory and regulatory requirements: (1) the amendment must propose a reasonable number of substitute claims; (2) the amendment must

¹³ WO 2011/097269 A1 (published Aug. 11, 2011) (Ex. 1079).

¹⁴ Michael Pazianas et al., *Eliminating the need for fasting with oral administration of bisphosphonates*, 9 THERAPEUTICS AND CLINICAL RISK MANAGEMENT 395–402 (2013) (Ex. 1030).

not enlarge the scope of the claims of the patent or introduce new matter; and (3) the amendment must respond to a ground of unpatentability involved in the review. *See* 35 U.S.C. § 326(d); 37 C.F.R. § 42.221.

Petitioner does not dispute that Patent Owner's Motion to Amend proposes a reasonable number of substitute claims, nor does Petitioner dispute that the Motion to Amend responds to a ground of unpatentability involved in this review. Reviewing the amended claims, we find that the Motion to Amend complies with both of those requirements.

As to the statutory requirement under § 326(d) that the amendment may not introduce new matter, Patent Owner indicates where it believes each element of the proposed new claims finds support in the original specification. Paper 33, App'x, 1–10. Petitioner does not assert error in relation to Patent Owner's citations to the original specification.

Petitioner, however, contends that the proposed new claims are unpatentable for lack of written description. Paper 38, 2–5. This challenge implicates the threshold statutory requirement of § 326(d) that the amendment may not introduce new matter.

For the reasons discussed below, Petitioner does not persuade us that the proposed new claims fail to comply with the written description requirement. We determine, therefore, that the proposed new claims do not violate § 326(d) by introducing new matter.

C. Patentability of Proposed New Claims 31–56

1. Written Description

We determine that the preponderance of the evidence does not support Petitioner's challenge to proposed new claims 31–56 for unpatentability based on lack of written description.

Petitioner contends that proposed new claims 31–56 are unpatentable for lack of written description because none of the new bioavailability ranges recited in the claims finds support in the original disclosure. Paper 38, 2–3.

Petitioner contends, in addition, that proposed new claims 36–38 and 48–50 are unpatentable for lack of written description because none of the new dosage ranges recited in those claims finds support in the original disclosure. *Id.* at 3–5.

In *TurboCare Div. of Demag Delaval Turbomachinery Corp. v. General Elec. Co.*, 264 F.3d 1111, 1118 (Fed. Cir. 2001), our reviewing court explained as follows:

The written description requirement and its corollary, the new matter prohibition of 35 U.S.C. § 132, both serve to ensure that the patent applicant was in full possession of the claimed subject matter on the application filing date. When the applicant adds a claim or otherwise amends his specification after the original filing date . . . , the new claims or other added material must find support in the original specification.

The test for determining whether a specification is sufficient to support a particular claim “is whether the disclosure of the application relied upon ‘reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.’” *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983)).

Thus, “[i]t is not necessary that the application describe the claim limitations exactly, but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes

including those limitations.” *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976) (citation omitted).

Proposed new independent claims 31 and 45 narrow the zoledronic acid bioavailability of the recited dosage form to a range of from 1.1% to 2.3%. Paper 33, App’x, 11, 13–14.

Patent Owner cites ¶ 72 of the original specification (Ex. 2027) as support for this limitation. *Id.* at App’x 4, 8.

Paragraph 72 of the original specification does not expressly describe the bioavailability range recited in new claims 31 and 45. *See* Ex. 2027 ¶ 72. Paragraph 72, however, does recite numerous bioavailability ranges that include among them the upper and lower endpoints of the range recited in new claims 31 and 45:

For example, the oral bioavailability of zoledronic acid can be about 0.01% to about 5%, about 0.01% to about 4%, about 0.1% to about 3%, about 0.1% to about 2%, about 0.2% to about 2%, about 0.2% to about 1.5%, about 0.3% to about 1.5%, about 0.3% to about 1%, about 0.1% to about 0.5%, about 0.3% to about 0.5%, about 0.5% to about 1%, about 0.6% to about 0.7%, about 0.7% to about 0.8%, about 0.8% to about 0.9%, about 0.9%, about 1% to about 1.1%, **about 1.1%** to about 1.2%, about 1.2% to about 1.3%, about 1.3% to about 1.4%, about 1.4% to about 1.5%, about 1.5% to about 1.6%, about 1.6% to about 1.8%, about 1.8% to about 2%, about 1% to about 3%, about 1% to about 2%, about 1.5% to about 3%, about 2% to about 3%, or about 1.8% **to about 2.3%**.

Id. (emphasis added).

Given the disclosure in ¶ 72 of the original specification, we find that Patent Owner has established that, at the time the ’862 patent’s application was filed, the inventor possessed dosage forms having an oral zoledronic acid bioavailability of from 1.1% to 2.3%, as recited in new independent

claims 31 and 45. *Cf. Wertheim*, 541 F.2d at 265 (holding claim reciting solids content range of 35–60% supported by specification’s disclosure of range of 25–60% and specific embodiments of 36% and 50%).

In addition, given the disclosure in ¶ 72 of the original specification of bioavailability ranges having lower endpoints of 1.3% and 1.5%, we find that Patent Owner has established that, at the time the ’862 patent’s application was filed, the inventor possessed dosage forms having the bioavailability ranges recited in new dependent claims 42, 43, 53, and 54.

Similarly, given the disclosure in ¶ 66 of the original specification of monthly dosing, and zoledronic acid dosage ranges having lower endpoints of 20 mg, 50 mg, and 200 mg, and upper endpoints of 500 mg and 300 mg, we find that Patent Owner has established that, at the time the ’862 patent’s application was filed, the inventor possessed dosage forms having the dosage rates and amounts recited in new dependent claims 36–38 and 48–50.

We acknowledge, but are not persuaded by, Petitioner’s contention that the multiple ranges in the ’862 patent’s original specification fail to provide “blaze marks” sufficient to identify the specific subject matter the inventor considered to be his invention. Paper 38, 4 (citing *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326–27 (Fed. Cir. 2000)).

In *Purdue*, the patentees “pick[ed] a characteristic possessed by two of their formulations, a characteristic that [was] not discussed even in passing in the disclosure, and then [made] it the basis of claims that cover not just those two formulations, but any formulation that has that characteristic.” *Id.* at 1327. Here, in contrast, although possession of the claimed ranges is evidenced by viewing numerous ranges disclosed in the ’862 specification, the specification does much more than discuss those

ranges in passing, but instead makes it clear that each of the ranges is contemplated as part of the dosage forms of the disclosed invention.

In sum, for the reasons discussed, we find that Patent Owner has established that, at the time the '862 patent's application was filed, the inventor possessed all of the subject matter recited in proposed new claims 31–56.

2. Enablement of Proposed New Claims 31–56

a. The Parties' Contentions

Patent Owner contends that because the proposed new claims are limited to oral dosage forms, and because the oral bioavailability range in the new claims removes the modifier “about” from the new bioavailability range, and narrows the bioavailability range to 1.1% to 2.3%, new claims 31–56 are “fully enabled by the specification for all the reasons and evidence presented by Patent Owner in defense of the larger range in the Patent Owner Response.” Paper 33, 13.

Petitioner contends that proposed new claims 31–56 are unpatentable for lack of enablement because the '862 patent specification “does not disclose a single example of a pharmaceutical formulation having the newly claimed bioavailability, and does not report any bioavailability data associated with any dosage form.” Paper 38, 1.

Petitioner also reiterates its contention that it was known in the art that zoledronic acid has less than 1% oral bioavailability, and that the alleged improvement of 84% seen in dogs in the '669 publication (Ex. 2005) would not provide the full range of bioavailability required by new claims 31–56. *Id.* at 6–7. Petitioner contends that the prior art cannot be relied on to supplement the absence of specific teachings in the '862 patent specification.

Id.

Patent Owner contends that the '862 patent discloses the novel aspects of the claimed invention—in particular the use of the disodium salt form of zoledronic acid to deliver a higher than expected bioavailability in the absence of extraneous enhancing agents—which is all that is required to enable a claimed invention. Paper 42, 1–6. Moreover, Patent Owner contends, a skilled artisan could have identified all dosage forms of zoledronic acid, routinely tested them, and readily determined which forms had bioavailabilities within the range recited in the new claims. *Id.* at 3–7.

b. Analysis

We determine that the preponderance of the evidence supports Petitioner's contention that proposed new claims 31–56 are unpatentable for lack of enablement.

In particular, despite the narrowed bioavailability range of 1.1% to 2.3% in proposed new claims 31–56, we find that our enablement analysis as to claims 31–56 parallels our analysis as to claims 2–30 discussed above.

As Petitioner contends, and as noted above, the '862 patent specification includes no working examples of preparing any dosage form. Although working examples are not required for enablement, *see, e.g., In re Vaeck*, 947 F.2d at 497, beyond the absence of working examples, the '862 patent does not include any detailed descriptions of specific dosage forms, including the particular ingredients included therein, that illustrate specifically how to prepare a dosage form that meets the bioavailability requirements of claims 31–56.

As also discussed above, Exhibits 1027–1030 support Petitioner's contention that ordinarily skilled artisans would have understood zoledronic

acid generally to have an oral bioavailability of 1% or less, and this contention is further supported by the Hanna reference (Ex. 1079), discussed in further detail below. See Ex. 1079, 3 (“According to the US Food and Drug Administration (FDA) Summary Basis of Approval (SBA) for zoledronic acid, the poor oral bioavailability (approximately 1%), is partially due to its poor permeability in the GI tract.”).

Although, as Patent Owner contends, the ’862 patent discloses that the disodium salt can be used to enhance the oral bioavailability of zoledronate as much as 200% as compared to the diacid form (Ex. 1001, 7:35–42), the ’862 patent does not disclose with any specificity the bioavailability of any disodium salt form of zoledronate. Nor does the ’862 patent describe specifically the preparation of any dosage form containing a zoledronate disodium salt.

As noted above, Patent Owner relies on the alleged capacity of a skilled artisan to prepare and routinely test the known disodium salt forms of zoledronic acid and thereby determine which dosage forms have bioavailabilities falling within the claimed range. See Paper 42, 1–7. However, the sole evidence advanced by Patent Owner that a skilled artisan would be successful in using the disodium salt form to increase the zoledronic acid bioavailability above 1% is the dog study in the ’669 publication (Ex. 2005), which undisputedly at best provides a bioavailability value of 1.84%. See PO Resp. 11.

As noted above, to “be enabling, the specification of a patent must teach those skilled in the art how to make and use ***the full scope of the claimed invention*** without undue experimentation.” *Trustees of Boston University v. Everlight Electronics*, 896 F.3d at 1362 (internal quotations

omitted; emphasis added).

Here, the highest bioavailability value shown by Patent Owner as being attainable using the disodium salt form of zoledronic acid, 1.84%, falls significantly short of the highest value of 2.3% recited in proposed new claims 31–56, and Patent Owner advances no specific persuasive evidence suggesting that values higher than 1.84% would be attainable through routine experimentation. We note, moreover, that while Patent Owner relies on the dog data in the '669 publication to demonstrate the capacity of disodium salts to increase zoledronic acid's bioavailability above 1% (see PO Resp. 11), Patent Owner alleges in relation to the Hanna reference discussed below that the “dog data is . . . irrelevant for obviousness purposes. . . . There has been no showing of how the absolute bioavailability of a dog would correlate to absolute bioavailability in a human.” Paper 42, 12.

In sum, given the unrebutted evidence that skilled artisans would have understood zoledronic acid generally to have an oral bioavailability of 1% or less, and given the absence of specific guidance in the '862 patent specification directing skilled artisans to a particular set of ingredients that provides dosage forms having the 1.1% to 2.3% zoledronic acid bioavailability values recited in proposed new claims 31–56, Petitioner persuades us that the '862 patent specification does not provide a disclosure that would have enabled a skilled artisan, without undue experimentation, to make a dosage form having the full bioavailability range required by claims 31–56.

3. *Obviousness of Proposed New Claims 45–56 over Hanna*
a. *Hanna (Ex. 1079)*

Hanna “pertains to improvement of the aqueous solubility and permeability of poorly permeable and sparingly water soluble drug compounds through generating novel crystalline forms of such drugs.” Ex. 1079, 1.

As an example of a poorly soluble drug, Hanna discloses that zoledronic acid is “a third generation bisphosphonate which far exceeds the previous generations in terms of efficacy” and notes that “[m]uch effort has been taken to generate novel oral formulations of zoledronic acid through crystallization and metal salt formation to improve its aqueous solubility, permeability, and subsequent oral bioavailability.” *Id.* at 2, 3.

Hanna discloses that “[a]ccording to the US Food and Drug Administration (FDA) Summary Basis of Approval (SBA) for zoledronic acid, the poor oral bioavailability (approximately 1%), is partially due to its poor permeability in the GI tract.” *Id.* at 3.

Hanna discloses that its invention “is directed towards generating new forms of APIs [active pharmaceutical ingredients], e.g., zoledronic acid, with improved physicochemical properties, such as improved aqueous solubility, rate of dissolution, and, particularly, improved permeability resulting in enhanced bioavailability.” *Id.* at 4–5.

In particular, Hanna discloses that its invention “is directed in part to pharmaceutical compositions with increased permeability. In one aspect increased permeability is achieved through the addition of a coformer to a pharmaceutical composition comprising an API, wherein the coformer is an amino acid.” *Id.* at 16.

Hanna discloses that numerous different drugs (“APIs”) may be combined with amino acids to increase their permeability, among them zoledronic acid. *Id.* at 18–19.

Hanna discloses that amino acids can increase the oral bioavailability of drugs by at least 10%, up to three-fold, as compared the bioavailability in the absence of the amino acid:

In one embodiment the increase in oral bioavailability is at least 10%. In another embodiment the increase in oral bioavailability is at least 25%. In another embodiment the increase in oral bioavailability is at least 50%. In another embodiment the increase in oral bioavailability is at least 75%. In another embodiment the increase in oral bioavailability is at least two fold. In another embodiment the increase in oral bioavailability is at least three fold.

Id. at 19–20.

Hanna also discloses that the bioavailability of bisphosphonic acids, such as zoledronic acid, can be increased to a bioavailability of at least 3%, and as high as 10%. *Id.* at 34.

Hanna also discloses that the bioavailability of zoledronic acid, specifically, can be increased to a bioavailability of at least 3%, and as high as 8%. *Id.* at 47.

b. The Parties’ Contentions

Petitioner contends, based on Hanna’s disclosure that zoledronic acid has an oral bioavailability of about 1%, and based on Hanna’s disclosure that the baseline bioavailability of drugs such as zoledronic acid can be increased from 10% to five-fold, that Hanna discloses dosage forms having a zoledronic acid bioavailability range that entirely overlaps the range recited in proposed new claim 45. Paper 38, 11–12. Petitioner contends that the fasting regimen recited in new claim 45 in relation to the bioavailability

determination corresponds to the FDA's zoledronic acid bioavailability determination disclosed at page 3 of Hanna. *See id.* Petitioner contends, therefore, that Hanna renders the dosage form of claim 45, and its dependent claims, obvious. *See id.* at 11–17.

Patent Owner contends that Hanna does not teach or suggest a dosage form having bioavailability values within the range recited in any of proposed new claims 31–56, because the disclosures in Hanna relating specifically to zoledronic acid teach higher bioavailability values than recited in claims 31–56. Paper 42, 9–12.

c. Analysis

We determine that the preponderance of the evidence supports Petitioner's contention that proposed new claims 45–56 are unpatentable for obviousness in view of Hanna.

Independent claim 45 recites a dosage form, suitable for oral administration, which contains zoledronic acid. Paper 33, App'x, 13–14.

Claim 45 recites that “the bioavailability of zoledronic acid in the dosage form is from 1.1% to 2.3% as determined by: 1) fasting a human subject for 10 hours, and then 2) orally administering the dosage form to the human subject, and then 3) fasting the human subject for 4 hours.” *Id.* at 14.

As noted above, Hanna discloses that, “[a]ccording to the US Food and Drug Administration (FDA) Summary Basis of Approval (SBA) for zoledronic acid,” zoledronic acid has an oral bioavailability of “approximately 1%.” Ex. 1079, 3.

Petitioner contends, and Patent Owner does not dispute, that the FDA's oral bioavailability determination for zoledronic acid disclosed on

page 3 of Hanna corresponds to the determination method recited in claim 45. *See* Paper 38, 11–12 (citing Ex. 1076 ¶ 52 (Wilson Reply Decl.)).

In addition, in his supporting testimony, Dr. Wilson cites to Exhibit 1082, a document entitled “Guidance for Industry[;] Food-Effect Bioavailability and Fed Bioequivalence Studies” dated 2002. Ex. 1082, cover sheet. The document states that it was issued by the FDA. *See id.* As Dr. Wilson testifies, Exhibit 1082 states that “[f]ollowing an overnight fast of at least 10 hours, subjects should be administered the drug product with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose.” Ex. 1082, 6. Accordingly, Petitioner persuades us that the FDA’s oral bioavailability determination for zoledronic acid disclosed on page 3 of Hanna corresponds to the determination method recited in claim 45, and that it would have been obvious to use that method to determine zoledronic acid bioavailability.

The baseline zoledronic acid oral bioavailability of 1% disclosed by Hanna is less than the 1.1% to 2.3% recited in claim 45. However, as Petitioner contends, and as noted above, Hanna discloses that amino acids can be used to increase the baseline oral bioavailability of poorly absorbed drugs, including zoledronic acid, by at least 10%, up to three-fold. Ex. 1079, 19–20.

As Petitioner contends, Hanna more broadly discloses that a “coformer” may be used to increase the oral bioavailability of drugs by at least 10%, up to five fold (*id.* at 9), and lists zoledronic acid among drugs amenable to that improvement (*id.* at 11).

Given the baseline oral bioavailability of about 1% for zoledronic acid disclosed in Hanna, and given Hanna’s disclosure of increasing the baseline

oral bioavailability of drugs, including zoledronic acid, by at least 10%, up to three-fold, and even five-fold, Petitioner persuades us that Hanna suggests preparing an oral dosage form that contains zoledronic acid, with an oral bioavailability ranging of from 1.1% to 5%.

As noted above, where “a claimed range overlaps with a range disclosed in the prior art, there is a presumption of obviousness. . . . The presumption can be rebutted if it can be shown that the prior art teaches away from the claimed range, or the claimed range produces new and unexpected results.” *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d at 1311 (citation omitted).

In this instance, the zoledronic acid oral bioavailability range of 1.1% to 5% effectively taught by Hanna entirely overlaps the bioavailability range of about 1.1% to about 2.3% recited in proposed new claim 45. Petitioner persuades us, therefore, that it is proper to presume that the dosage form recited in claim 45 would have been obvious to an ordinary artisan.

We are not persuaded that Patent Owner has rebutted the presumption of obviousness as to claim 45. Patent Owner contends that, because Hanna discloses zoledronic acid oral bioavailability ranges higher than the range recited in claim 45, an ordinary artisan would not have been motivated to prepare a zoledronic acid-containing oral dosage form having an oral bioavailability within the range recited in claim 45. Paper 42, 9–12.

We acknowledge Hanna’s disclosure, noted above, that the oral bioavailability of bisphosphonic acids, such as zoledronic acid, can be increased to at least 3%, and as high as 10% (Ex. 1079, 34), as well as Hanna’s disclosure that the bioavailability of zoledronic acid, specifically, can be increased to a bioavailability of at least 3%, and as high as 8% (*id.* at

47). We acknowledge also that those bioavailabilities are above the range recited in proposed new claim 45.

We acknowledge, as Patent Owner contends, that Hanna's disclosure at page 9 of using a coformer to increase the bioavailability of drugs by at least 10%, up to five-fold, relates to a list of drugs that includes as many as 135 drugs, including zoledronic acid. Paper 42, 10–11.

We acknowledge that Hanna's disclosure at pages 19–20 of using an amino acid to increase the bioavailability of drugs by at least 10%, up to three-fold, also relates to a list that includes as many as 135 drugs, including zoledronic acid. *See id.*

As our reviewing court has explained, however, “in a section 103 inquiry, the fact that a specific [embodiment] is taught to be preferred is not controlling, since ***all disclosures of the prior art, including unpreferred embodiments, must be considered.***” *Merck & Co. v. Biocraft Labs. Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (internal quotations omitted; emphasis added); *see also DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (“A reference does not teach away . . . if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.” (internal quotations omitted)).

We are not persuaded, therefore, that it is proper to ignore, or that an ordinary artisan would have ignored, the broader disclosures in Hanna at pages 9 and 19–20, teaching that the baseline oral bioavailability of drugs, including zoledronic acid, may be increased by at least 10%, up to three-fold, and even five-fold, using certain ingredients. The fact that the increases in bioavailability disclosed at pages 9 and 19–20 are taught as

being applicable to as many as 135 drugs does not negate Hanna's express teaching that zoledronic acid is among the drugs whose bioavailability can be increased by at least 10%, up to three-fold, and even five-fold, resulting in zoledronic acid bioavailability values undisputedly encompassed by claim 45. *See Merck v. Biocraft*, 874 F.2d at 807 (species claim held obvious where it recited one of 1200 possible combinations of embodiments disclosed by reference and where reference suggested no preference for claimed embodiment).

In that regard, we note that Hanna's introductory disclosure repeatedly refers to zoledronic acid, and no other drug specifically, as being exemplary of poorly soluble drugs to which Hanna's bioavailability-increasing techniques are applicable. *See Ex. 1079*, 2–5. Thus, although perhaps not expressed as a preference, viewing Hanna as whole, an ordinary artisan would have been particularly motivated to apply Hanna's bioavailability-increasing techniques, including those increasing bioavailability by at least 10%, up to three-fold, and even five-fold (*Ex. 1079*, 9–20), to zoledronic acid.

Patent Owner contends that an ordinary artisan would not have considered Hanna's disclosure of the 1% baseline oral bioavailability of zoledronic acid, also disclosed in Exhibits 1027–1030, to be reliable, because of the absence of supporting data in the references. *Paper 42*, 11–12.

It might be true, as Patent Owner contends, that olpadronate, tiludronate, and etidronate had reported bioavailabilities of 3–4%, 6%, and 3%, respectively. *See id.* at 12 (citing *Ex. 2034* ¶¶ 2–9; *Ex. 2041* at 493; *Ex. 2036* at 1; *Ex. 2038* at 1).

Patent Owner, however, directs us to no specific evidence supporting its assertion that an ordinary artisan only would have relied on Hanna's disclosure of the 1% baseline oral bioavailability of zoledronic acid if the reference included supporting data. Nor does Patent Owner identify any specific evidence suggesting that an ordinary artisan would have considered the 1% baseline oral bioavailability of zoledronic acid disclosed in Hanna to be inaccurate or unreliable. By itself, the fact that similar, yet different, compounds such as olpadronate, tiludronate, and etidronate might have oral bioavailabilities higher than 1% does not persuade us that an ordinary artisan would have considered the 1% value disclosed in Hanna to be inaccurate or unreliable.

In sum, for the reasons discussed, we determine that the preponderance of the evidence supports Petitioner's contention that proposed new claim 45 is unpatentable for obviousness in view of Hanna.

As to claims 46–56, which all depend from claim 45, Petitioner identifies disclosures in Hanna purporting to teach or suggest each of the features of the dosage forms required by those claims. Paper 38, 13–17. Patent Owner does not assert error in Petitioner's contentions regarding claims 46–56. See Paper 42, 9–12.

Having reviewed the cited portions of Hanna in light of the contentions by Petitioner, and in light of the absence of specific controverting argument or evidence from Patent Owner, we determine that the preponderance of the evidence supports Petitioner's contention that proposed new claims 46–56 are unpatentable for obviousness in view of Hanna.

4. *Obviousness of Proposed New Claims 31–44 over Fox, Laslett, Hanna, and Pazianas*

a. *Pazianas (Ex. 1030)*

Pazianas is an article discussing the development of an enteric-coated delayed released formulation of risedronate. Ex. 1030, 395 (abstract).

Pazianas discloses:

Oral bisphosphonates are poorly absorbed (usually less than 1% for nitrogen-containing bisphosphonates) and when taken with food or beverages create complexes that cannot be absorbed. For this reason, they must be taken on an empty stomach, and a period of up to 2 hours must elapse before the consumption of any food or drink other than plain water.

Id.

b. *The Parties' Contentions*

Petitioner contends that an ordinary artisan would have been motivated by Fox and Laslett to administer zoledronic acid orally to treat knee pain, as recited in proposed new claim 31. Paper 38, 17–19.

Petitioner contends that an ordinary artisan would have been motivated to administer the zoledronic acid according to the fasting regimen taught by Pazianas, thereby also administering the drug according to the fasting regimen required by claim 31. *Id.* at 19–20.

Petitioner contends that an ordinary artisan seeking to treat knee pain by orally administering zoledronic acid, as taught by Fox and Laslett, would have considered it obvious to administer Hanna's oral dosage forms, having improved bioavailability encompassed by claim 31. *Id.* at 21–22.

Patent Owner does not directly address Petitioner's challenge to claims 31–44 based on the combination of Fox, Laslett, Hanna, and Pazianas, other than advancing the arguments, discussed above, traversing

Petitioner's contention that Hanna renders obvious an oral dosage form having a zoledronic acid bioavailability of 1.1% to 2.3%. *See generally* Paper 42.

c. Analysis

We determine that the preponderance of the evidence supports Petitioner's contention that proposed new claims 31–44 are unpatentable for obviousness in view of Fox, Laslett, Hanna, and Pazianas.

Independent claim 31 recites a method of treating knee pain in a human by orally administering a dosage form that contains zoledronic acid having a bioavailability of 1.1% to 2.3%. Paper 33, App'x, 11–12.

Independent claim 31 recites that the human being suffering from knee pain must fast for at least one hour before the zoledronic acid-containing dosage form is administered, and also fast for at least one hour after the dosage form is administered. *Id.* at 11.

As discussed above in relation to claim 45, we find that the preponderance of the evidence shows that Hanna teaches and/or suggests an oral dosage form having a zoledronic acid bioavailability of 1.1% to 5%. In other words, the preponderance of the evidence shows that Hanna teaches and/or suggests an oral dosage form encompassed by proposed new claim 31. Hanna differs from new claim 31 in not administering that dosage form to treat knee pain.

As discussed above, however, Fox teaches that oral administration of zoledronate was a suitable method of treating pain resulting from osteoarthritis in humans. *See* Ex. 1007, Abstract; *id.* ¶¶ 10, 72 (Fox). As also discussed above, moreover, Laslett discloses that zoledronate was effective in treating osteoarthritis-related knee pain in human subjects. Ex.

1008, 1322 (Laslett).

Given Laslett's teaching that zoledronate was effective for treating osteoarthritis-related knee pain, as well as Fox's teaching that oral administration of zoledronate was a suitable method of treating pain resulting from osteoarthritis, and further given the teachings in Hanna that its formulations have an increased zoledronic oral bioavailability as compared to zoledronic acid's baseline bioavailability, Petitioner persuades us that an ordinary artisan had a good reason for, and a reasonable expectation of success in, orally administering the dosage forms of Hanna to treat knee pain.

Although none of Fox, Laslett, or Hanna appears to expressly describe orally administering zoledronic acid according to the fasting regimen required by claim 31, Pazianas discloses that, because bisphosphonates like zoledronic acid are poorly absorbed after oral administration, "they must be taken on an empty stomach, and a period of up to 2 hours must elapse before the consumption of any food or drink other than plain water." Ex. 1030, 395 (abstract). Accordingly, Petitioner persuades us that an ordinary artisan, prompted by the teachings of Fox, Laslett, and Hanna to administer Hanna's oral dosage form, would also have had a good reason for, and a reasonable expectation of success in, following the fasting regimen taught in Pazianas when orally administering the drug.

In sum, for the reasons discussed, Petitioner persuades us that the combination of Fox, Laslett, Hanna, and Pazianas would have provided ample reason for, and a reasonable expectation of success in, performing a process having all of the steps and features required by proposed new independent claim 31. Patent Owner does not persuade us to the contrary.

As noted above, Patent Owner does not directly address Petitioner's challenge to claim 31 based on the combination of Fox, Laslett, Hanna, and Pazianas, other than advancing the arguments, discussed above, traversing Petitioner's contention that Hanna renders obvious an oral dosage form having a zoledronic acid bioavailability of 1.1% to 2.3%. *See generally* Paper 42. As discussed above in relation to claim 45, we do not find those arguments persuasive.

Accordingly, for the reasons discussed, we determine that the preponderance of the evidence supports Petitioner's contention that proposed new claim 31 is unpatentable for obviousness in view of Fox, Laslett, Hanna, and Pazianas. As to claims 32–44, which all depend from claim 31, Petitioner identifies disclosures in Hanna purporting to teach or suggest each of the features of the dosage forms required by those claims. Paper 38, 22–25. Patent Owner does not assert error in Petitioner's contentions regarding claims 32–44. *See* Paper 42, 9–12.

Having reviewed the cited portions of Hanna in light of the contentions by Petitioner, and in light of the absence of specific controverting argument or evidence from Patent Owner, we determine that the preponderance of the evidence supports Petitioner's contention that proposed new claims 32–44 are unpatentable for obviousness in view of Fox, Laslett, Hanna, and Pazianas.

V. CONCLUSIONS—MOTION TO AMEND AND UNPATENTABILITY CHALLENGES TO PROPOSED NEW CLAIMS

To summarize, for the reasons discussed above, we determine that:

(A) Patent Owner's Motion to Amend complies with the applicable statutory and regulatory requirements;

(B) The preponderance of the evidence does not show that proposed new claims 31–56 are unpatentable for lack of written description;

(C) The preponderance of the evidence shows that proposed new claims 31–56 are unpatentable for lack of enablement;

(D) The preponderance of the evidence shows that proposed new claims 45–56 are unpatentable for obviousness in view of Hanna; and

(E) The preponderance of the evidence shows that proposed new claims 31–44 are unpatentable for obviousness in view of Fox, Laslett, Hanna, and Pazianas.

In light of the above conclusions, Patent Owner’s Motion to Amend is *denied*.

VI. PATENT OWNER’S MOTION TO EXCLUDE

A. *The Laslett Article (Ex. 1008)*

Patent Owner moves to exclude the Laslett article for lack of authentication under Federal Rules of Evidence (FRE) 901 and 902, and as hearsay under FRE 801 and 802. Paper 46, 1–2. We deny Patent Owner’s motion to exclude the Laslett article.

As Petitioner contends (Paper 48, 2), FRE 902(6) provides that “[p]rinted material purporting to be a newspaper or periodical” “require[s] no extrinsic evidence of authenticity in order to be admitted.”

Contrary to Patent Owner’s contention that there is nothing to suggest that the Laslett Article was part of a periodical, the bottom of each page of the article includes a footer reading “*Ann Rheum Dis* 2012;71:1322–1328” and the pages of the article are consecutively numbered 1322–1328. See Ex. 1008, 1322–1328.

Because the Laslett article, therefore, purports on its face to be an article in the periodical “Annals of Rheumatic Disease” Patent Owner does not persuade us that it lacks authentication under FRE 902(6). As to hearsay, because the Laslett article is submitted for what it describes to an ordinary artisan, as opposed to the truth of the described subject matter, Patent Owner does not persuade us that the Laslett article is properly excluded under FRE 801 or 802. We, therefore, deny Patent Owner’s motion to exclude the Laslett article.

B. Exhibits 1027–1030

Patent Owner moves to exclude Exhibits 1027–1030 for lack of authentication and as hearsay. Paper 46, 2–3. We deny Patent Owner’s motion to exclude Exhibits 1027–1030.

Exhibit 1027 is published PCT application having International Publication Number WO 2011/014781 A1. Ex. 1027, cover page. We, therefore, agree with Petitioner that Exhibit 1027 is self-authenticating under Rule 902(5) as a publication purporting to be issued by a public authority. Accordingly, we deny Patent Owner’s motion to exclude Exhibit 1027 for lack of authentication.

As to Exhibits 1028–1030, the first page of each of those exhibits includes information indicating them to be articles in periodicals, including the name, volume number, and pages of the periodical, and each page includes a page number at the bottom corresponding to the pages recited on the first page. *See generally* Exs. 1028–1030. In addition, each page of Exhibits 1029 and 1030 includes a footer with the name and volume number of the periodical, and Exhibit 1028 includes a header on each alternating page that has the name and volume number of the periodical. *See generally*

Exs. 1028, 1029, and 1030. Because Exhibits 1028–1030 are, therefore, admissible under FRE 902(6), we deny Patent Owner’s motion to exclude them for lack of authentication.

In addition, because Exhibits 1027–1030 are submitted for what they describe to an ordinary artisan, as opposed to the truth of the described subject matter, Patent Owner does not persuade us that Exhibits 1027–1030 are properly excluded as hearsay. We, therefore, deny Patent Owner’s motion to exclude Exhibits 1027–1030.

C. The Merrion Poster

Patent Owner moves to exclude the Merrion Poster for a number of reasons. Paper 46, 3–7. As discussed above, Patent Owner persuades us that the Merrion Poster does not qualify as prior art to the claims of the ’862 patent. We, therefore, dismiss as moot Patent Owner’s motion to exclude the Merrion Poster.

D. Wilson Reply Declaration, § VII.B (Ex. 1076)

Patent Owner moves to exclude Dr. Wilson’s testimony in relation to the Hanna reference (Ex. 1079), pursuant to 37 C.F.R. § 42.61(c). Paper 46, 8–9. We deny Patent Owner’s motion to exclude § VII.B of Exhibit 1076.

As Patent Owner concedes (*id.* at 8, n.2), § 42.61(c) governs the admissibility of the truth of data presented in the specification or drawing of a United States patent application or patent. The Hanna reference, however, is a published PCT Application, and not the specification or drawing of a United States patent application or patent. *See* Ex. 1079, cover sheet. We, therefore, deny Patent Owner’s motion to exclude § VII.B of Exhibit 1076.

E. The Butler Affidavit (Ex. 1081)

Patent Owner moves to exclude the Butler Affidavit as untimely. Paper 46, 9–10. We deny Patent Owner’s motion to exclude the Butler Affidavit.

As discussed above, Petitioner submitted the Butler Affidavit along with its Reply, in response to Patent Owner’s contention that the Merrion Poster does not qualify as prior art. As discussed above, we find that Petitioner’s new rationale for qualifying the Merrion Poster as prior art (online availability), which relies on the Butler affidavit, is not properly advanced for the first time in Petitioner’s Reply.

Nonetheless, as noted above, Patent Owner’s contentions that the Merrion Poster failed to qualify as prior art were first advanced in the Patent Owner’s Response. Accordingly, although we agree with Patent Owner that the Butler Affidavit should not be considered as part of a new theory of unpatentability advanced for the first time in Petitioner’s Reply, Patent Owner does not persuade us that the Butler was untimely, for the purposes of its admissibility as evidence.

F. Wargin Cross-Examination Testimony (Ex. 1083)

Patent Owner moves to exclude a number of portions of Dr. Wargin’s cross-examination testimony as being outside the scope of his direct testimony, and as being irrelevant. Paper 46, 10–13. Because our decision does not rely on Dr. Wargin’s cross-examination testimony, we dismiss Patent Owner’s motion to exclude Dr. Wargin’s cross-examination testimony as moot.

VII. ORDER

In consideration of the foregoing, it is
ORDERED that claims 2–30 of the '862 patent are held unpatentable;
FURTHER ORDERED that Patent Owner's Contingent Motion to
Amend is *denied*;

FURTHER ORDERED that Patent Owner's Motion to Exclude is
denied-in-part and *dismissed-in-part* as moot;

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GRÜNENTHAL GMBH,
Petitioner,

v.

ANTECIP BIOVENTURES II LLC,
Patent Owner.

Case PGR2017-00022
Patent 9,408,862 B2

Before TONI R. SCHEINER, FRANCISCO C. PRATS, and
GRACE KARAFFA OBERMANN, *Administrative Patent Judges*.

OBERMANN, *Administrative Patent Judge, concurring*.

The touchstone of enablement is whether undue experimentation would have been required to practice the claimed invention. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). At the outset, I agree with the majority that Leonard anticipates many claims of the '862 patent, including independent claim 17, and that Hanna alone or in combination with other prior art references would have made obvious the subject matter of the proposed substitute claims. That circumstance appears inconsistent with the further conclusion that the degree of detail provided in the specification is inadequate to enable the claims in view of the state of the prior art as revealed, for example, by the disclosures of Leonard and Hanna. *See Invitrogen*

Corp. v. Clontech Labs., Inc., 429 F.3d 1052, 1070–71 (Fed. Cir. 2005) (“The scope of enablement ... is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.” (quoting *Nat’l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999))).

Petitioner bears the burden of proving “by way of testimony or documentary evidence the amount of experimentation needed” and, on that point, opinion testimony suggesting that the required effort “would be ‘difficult’ and ‘complicated’ is not sufficient” to establish undue experimentation. PO Resp. 6 (citing *Cephalon, Inc. v. Watson Pharmaceuticals, Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013)). I find critically significant that Petitioner does not distinguish experiments that would have been “routine” from those that would have been “non-routine” or undue. PO Resp. 9; *see* Pet. 19–25, 30–31; Reply 1–7; Paper 38, 5–8. At best, Petitioner directs us to opinion testimony that an ordinarily skilled artisan would have had “to perform various pre-clinical and clinical studies” to carry out the claimed invention. Pet. 31 (citing Ex. 1005 ¶ 89).

Petitioner stops short of arguing, much less proving, that those studies would have required more than a routine exercise of ordinary skill in the art. *Id.* Patent Owner, by contrast, advances persuasive evidence that completing those studies would have fallen squarely within the ambit of “routine” experimentation—evidence that Petitioner has not refuted effectively. PO Resp. 12–14 (citing Ex. 2022, 84:16–23 (deposition of Petitioner’s own witness, Dr. Wilson, testifying that conducting such studies would have been “routine”)); Paper 42, 3–4 (citing Ex. 2022, 81:11–84:23), 3 n.2 (citing Ex. 1035), 6–7 (citing Ex. 1067 ¶ 21); *see also* Reply 8 (Petitioner, declining to dispute that an ordinarily skilled artisan

would have been equipped to perform “a routine bioavailability test” as disclosed in Leonard).

I concur only in the result that the original and proposed amended claims are unpatentable as anticipated by or obvious over the asserted prior art references and that original claims 3 and 4 are not proven indefinite. I respectfully disagree that Petitioner has established by a preponderance of the evidence that any original or proposed substitute claim is unpatentable for lack of enablement.

PGR2017-00022
Patent 9,408,862 B2

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