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Paper 48
Entered: April 29, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GRÜNENTHAL GMBH,
Petitioner,

v.

ANTECIP BIOVENTURES II LLC,
Patent Owner.

Case PGR2018-00001
Patent 9,539,268 B2

Before TONI S. SCHEINER, GRACE KARAFFA OBERMANN, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges.*

OBERMANN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
Determining that Claims 3–30 are Unpatentable
35 U.S.C. § 328(a)

I. INTRODUCTION

This is a post-grant review of claims 3–30 of U.S. Patent No. 9,539,268 B2 (Ex. 1001, "the '268 patent"). Prior to institution of review, Patent Owner filed a statutory disclaimer of claims 1 and 2. Paper 13; Ex. 2008. We instituted review of claims 3–30 based on the grounds stated in the Petition (Paper 2, "Pet."). *See* Paper 17 ("Dec."), 2, 8–9, 38. Thereafter, in timely sequence, Patent Owner filed a Response (Paper 22, "Resp."), Petitioner filed a Reply (Paper 36), and Patent Owner filed a Surreply (Paper 39). This decision resolves also Petitioner's Motion to Exclude Evidence (Paper 40) and Patent Owner's Motion to Exclude Evidence (Paper 42). We held a final oral hearing on February 7, 2019. Paper 47 ("Tr."). The Board has jurisdiction under 35 U.S.C. § 6. We issue this Final Written Decision pursuant to 35 U.S.C. § 328(a).

A. Related Proceedings

The parties identify no related administrative or judicial proceedings. Pet. 4; Paper 3, 1. According to Petitioner, "[t]he '268 patent is a continuation of the application that issued as Patent Owner's U.S. Patent No. 9,408,862" ("the '862 patent"), noting that the two patents "have nearly identical specifications." Pet. 4. Petitioner states that it filed a post grant review of the '862 patent on May 8, 2017, PGR2017-00022 ("PGR022"). Pet. 4. The Board entered a final written decision in PGR022 on November 14, 2018, and Patent Owner filed a notice of appeal of that decision. PGR022, Papers 50, 52. Petitioner states also that a patent in a different family involving similar technology is under challenge in PGR2017-00008 ("PGR008"), which involves the same parties as this

proceeding. Pet. 4; *see also* Paper 3, 2. The Board entered a final written decision in PGR008 on June 22, 2018. PGR008, Paper 43.

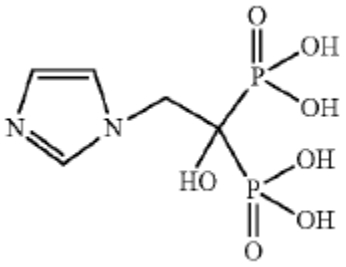
B. The '268 Patent (Ex. 1001)

The '268 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." Ex. 1001, 1:63–2:1. According to the '268 patent:

> An oral dosage form comprising a subject composition may be used to treat, or provide relief of, any type of pain including, but not limited to, inflammatory pain, arthritis pain, complex regional pain syndrome, lumbosacral pain, musculoskeletal pain, neuropathic pain, chronic pain, cancer-related pain, acute pain, postoperative pain, etc. In some instances, pain relief may be palliative, or pain relief may be provided independent of improvement of the disease or condition or the underlying cause of the disease or condition. For example, although the underlying disease may not improve, or may continue to progress, an individual suffering from the disease may experience pain relief. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising a subject composition wherein zoledronic acid is in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

Id. at 2:28–46.

The '268 patent discloses that zoledronic acid "is also referred to as zoledronate" and has the structure shown in the following figure:



Id. at 5:66–6:10. The figure above shows the molecular structure of zoledronic acid. *Id*.

The ’268 patent discloses:

> 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 7:65–8:5.

According to the ’268 patent:

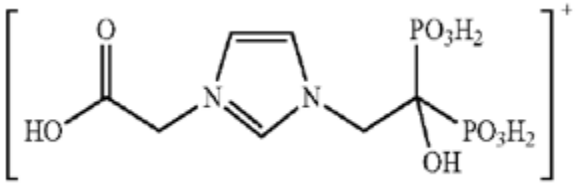
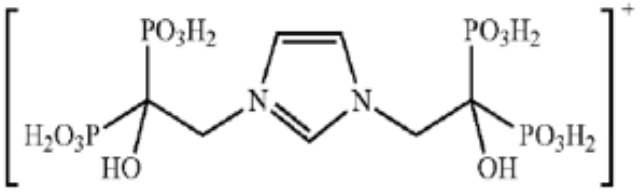
> Because of the improved bioavailability of the disodium salt a dosage form may contain, or a mammal, such as a human being, may receive, on a molar basis, less of the disodium salt form of zoledronic acid than would otherwise be administered of the diacid form of zoledronic acid. For example, a dosage form may contain, or a mammal may receive, at least about 10 mole % less, at least about 20 mole % less, at least about 40 mole % less, at least about 50 mole % less, and/or up to about 90 mole % less or 95 mole % less, of the disodium salt form as compared to the amount of the diacid form of zoledronic acid that would otherwise be administered, such as a molar amount that would be administered of zoledronic acid in the diacid form in order to achieve the same plasma levels of zoledronic acid.

Id. at 8:6–19.

The ’268 patent includes only one working example, which describes syntheses for compounds 1 and 2. *Id.* at 18:12–19:18 (Example 1). The ’268 patent contemplates multiple embodiments. *Id.* at 19:19–27:58.

C. The Challenged Claims

Claims 1 and 2 of the ’268 patent are disclaimed and no longer in dispute. Prelim. Resp. 3, Paper 13. Claims 3 and 23 are the remaining challenged independent claims of the ’268 patent and read as follows:

> 3. A method of treating arthritis comprising orally administering a dosage form to a human being suffering from arthritis, wherein the dosage form comprises:
>
> a) zoledronic acid in a salt or an acid form; or
>
> b) one of the following:
>
> 1) zoledronic acid in a salt or an acid form and
>
> 
>
> (Ion 1) in a salt form, in an amount that is less than 0.1% w/w and greater than 0% w/w; or
>
> 2) zoledronic acid in a salt or acid form and
>
> 
>
> (Ion 2) in a salt form, in an amount that is less than 0.1% w/w and greater than 0% w/w;
>
> or
>
> 3) zoledronic acid in a salt form or an acid form and a combination of Ion 1 in a salt form, in an amount that is less than 0.1 % w/w and greater

than 0% w/w, and Ion 2 in a salt form, 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 in a salt or acid form, Ion 1 in a salt form, or Ion 2 in a salt form;

wherein any amount in % w/w is based upon the total weight of zoledronic acid in a salt or an acid form, Ion 1, Ion 2, and any corresponding counter ions; and

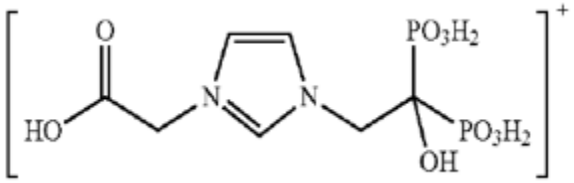
wherein the bioavailability of zoledronic acid in the dosage form is from about 1.1% to about 4%.

23. A pharmaceutical dosage form for oral administration comprising:

a) zoledronic acid in a salt form; or

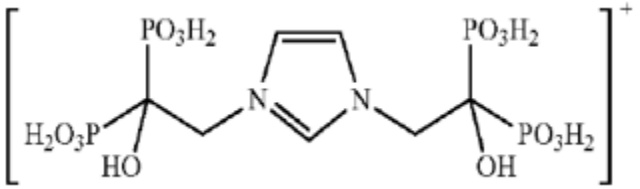
b) one of the following:

1) zoledronic acid in a salt or an acid form and



(Ion 1) in a salt form, in an amount that is less than 0.1% w/w and greater than 0% w/w;

2) zoledronic acid in a salt or an acid form and



(Ion 2) in a salt form, in an amount that is less than 0.1% w/w and greater than 0% w/w; or

> 3) zoledronic acid in a salt or an acid form and a combination of Ion 1 in a salt form, in an amount that is less than 0.1 % w/w and greater than 0% w/w, and Ion 2 in a salt form, 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 in a salt or acid form, Ion 1 in a salt form, or Ion 2 in a salt form;
>
> wherein any amount in % w/w is based upon the total weight of zoledronic acid in a salt or an acid form, Ion 1, Ion 2, and any corresponding counter ions; and
>
> wherein the bioavailability of zoledronic acid in the dosage form is from about 1.2% to about 4% in a human being.

Ex. 1001, 29:20–61, 30:56–32:3.

D. The Asserted Grounds of Unpatentability

As discussed above, Patent Owner filed a disclaimer of claims 1 and 2 of the ’268 patent; accordingly, we do not discuss claims 1 and 2, or the two grounds in the Petition directed solely to claims 1 and 2, in this decision. *See* 37 C.F.R. § 42.207(e) (“No post-grant review will be instituted based on disclaimed claims.”). The following chart identifies the challenges remaining in dispute following disclaimer of claims 1 and 2.

Claims	Statutory Basis	References
3–30	35 U.S.C. § 112(a) (lack of enablement)	
15	35 U.S.C. § 112(b) (indefiniteness)	

Claims	Statutory Basis	References
15–22	35 U.S.C. § 112(a) (lack of enablement)	
23	35 U.S.C. § 102 (anticipation)	Leonard
23	35 U.S.C. § 103 (obviousness)	Leonard
23–30	35 U.S.C. § 103 (obviousness)	Leonard, Aronhime, Merrion Poster
3–15	35 U.S.C. § 103 (obviousness)	Fox, Laslett, Leonard, Merrion Poster

The Petition is supported by a declaration of Stephen Bruehl, Ph.D. (Ex. 1003) and a declaration of Clive G. Wilson, Ph.D. (Ex. 1005). The Response is supported by a declaration of Dr. William Wargin (Ex. 2017).

II. ANALYSIS

As an initial matter, the parties agree that the '268 patent is eligible for post-grant review. Pet. 5–6; Tr. 40:1–6. We organize our analysis into three parts. First, we resolve the ordinary skill level in the art. Second, we address claim construction. Third, we consider whether claims 3–30 are unpatentable for lack of enablement under 35 U.S.C. § 112(a).

A. A Person of Ordinary Skill in the Art

Petitioner offers two different definitions pertaining to the person of ordinary skill in the art at the time of the invention: one for claims 3–22 and one for claims 23–30. Pet. 9–10. As to claims 3–22, Petitioner contends an ordinarily skilled artisan would have had "an M.D. or a Ph.D. in a pain-medicine-relevant discipline, such as clinical health psychology or

neuroscience, and at least 3-5 years of experience in the treatment of arthritis or related chronic pain conditions, or in the study of arthritis or related types of chronic pain." *Id.* at 9 (citing Ex. 1003 ¶¶ 27–31). Petitioner asserts an ordinarily skilled artisan would also have had "knowledge and experience in formulating pharmaceutical dosage forms and studying their pharmacokinetics, or have access to a person with such knowledge and experience." *Id.* at 9–10. As to claims 23–30, Petitioner contends that an ordinarily skilled artisan generally would have had "a Ph.D. in biochemistry, medicinal chemistry, pharmacology, pharmaceutics, or a related discipline, and at least 3–5 years of experience in formulating pharmaceutical dosage forms and studying their pharmacokinetics," but may have had less formal education and more work experience. *Id.* at 10.

Patent Owner counters that, as to claims 3–22, one of ordinary skill would have had "a degree related to drug development in the pain area, such as an M.D., a Pharm.D., or a Ph.D. in a drug development-related field, such as formulation or medicinal chemistry, biology, pharmacology, or pharmacokinetics, and experience in supervising, carrying out, or collaborating in animal or human testing, including off-label treatment of patients, related to drug development in the pain area." Resp. 10. As to claims 23–30, we understand Patent Owner to argue[1] that one would have had "a Ph.D. in pharmacokinetics, pharmacodynamics, pharmaceutics, pharmacology, biochemistry, chemistry, or a related discipline, or an M.D.,

[1] We determine that Patent Owner intends to mirror Petitioner's claim groupings, even though Heading II.B of Patent Owner's Response refers to "[c]laims 22–30" and the accompanying argument refers to "claims 17–30." Resp. 10. In any event, no combination of claim groupings would alter our ultimate decision that the specification does not enable claims 3–30.

and experience formulating pharmaceutical dosage forms and studying their pharmacokinetics." *Id.* at 10–11.

For purposes of this decision, we adopt Patent Owner's definitions; however, we would reach the same conclusion on enablement even under Petitioner's proposed levels of ordinary skill. In our view, moreover, the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding the ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

The Board interprets claims in 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) (2018).[2] Under that standard, we assign claim terms their ordinary and customary meaning as understood by one of ordinary skill in the art at the time of the invention, within the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only 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 no claim term requires express construction for purposes of this decision.

[2] A recent amendment to this rule does not apply here, because the Petition was filed before November 13, 2018. *See* "Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board," 83 Fed. Reg. 51,340 (Oct. 11, 2018) (amending 37 C.F.R. § 42.200(b) effective November 13, 2018).

C. Enablement—Claims 3–30

In this section, we assess whether the disclosure of the '268 patent specification is sufficient to permit the ordinarily skilled artisan to select, make, and use pharmaceutical dosage forms that enable the full scope of bioavailability ranges set forth in claims 3–30.[3] Pet. 16–27; Resp. 11–42; Reply 22–24; Surreply 15–20.

i. Analysis

In Petitioner's view, the '268 patent "specification does not teach" an ordinarily skilled artisan "how to make and use any dosage form having a zoledronic acid bioavailability within the claimed ranges." Pet. 16. In that regard, we find that claims 3–30 broadly embrace zoledronic acid in a salt or acid form, with or without the addition of one or more bioavailability-enhancing ingredients. Ex. 1001, claims 3 and 23 (the independent claims).

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) (listing non-exclusive factors to assist in making this determination). Petitioner addresses the *Wands* factors in its challenge to the claims. Pet. 17–27. We consider those factors below.

a. The Nature of the Invention, Level of Skill in the Art, and Unpredictability of the Art

Claims 3–30 are drawn to pharmaceutical dosage forms, or methods of administering those forms, comprising zoledronic acid of a specified bioavailability. Ex. 1001, 29:20–32:34 (claims 3–30); Pet. 18. Claim 3

[3] We decline to address a second enablement ground, based on area-under-the-curve limitations of claims 15–22, which stands or falls with our resolution of the instant enablement ground. Dec. 26–29.

"covers dosage forms wherein the zoledronic acid bioavailability is from about 1.1% to about 4%," and the remaining claims have that limitation, or more narrowly define a high endpoint of 3% bioavailability. *Id.*

The claimed invention, according to Dr. Wilson, Petitioner's witness, is within the unpredictable field of pharmaceutical formulations. Pet. 18 (citing Ex. 1005 ¶ 60). An ordinarily skilled artisan would have expected that "different dosage forms of the same drug may have different bioavailabilities" and, further, that "[v]arious properties of the active ingredient, including the crystal form, salt form, wettability, solubility, and particle size of the active ingredient, and the particular excipients and manufacturing process used to make the dosage form, can also have unpredictable effects on bioavailability." *Id.* at 18–19 (citing Ex. 1005 ¶ 60). Patent Owner does not dispute those factual contentions, and offers no reasons why Petitioner's witness, Dr. Wilson, is wrong in describing the relevant field as unpredictable. *See generally* Resp.; Surreply.

b. The State of the Prior Art

"Zoledronic acid and zoledronic acid salts were known in the art at least as early as 2000," and one asserted prior art reference, Aronhime, "disclosed eleven different disodium salt forms." Pet. 19 (citing Ex. 1034; Ex. 1035, 3:30–4:7, 8:22–11:1; Ex. 1005 ¶¶ 140–142). An ordinarily skilled artisan would have understood and expected that bisphosphonates, such as zoledronic acid, have poor bioavailability, and that, in the absence of enhancement, the bioavailability in a human would be 1% or lower. *Id.* at 19–20 (citing Ex. 1005 ¶¶ 66–67; Ex. 1027 ¶ 6; Ex. 1028, 184; Ex. 1029, 122, 124; Ex. 1030, 395–397).

Patent Owner confirms that an ordinarily skilled artisan would have "believed that the oral bioavailability in humans of *all* forms for zoledronic acid could not be above 1% without an enhancer." Resp. 1 (emphasis in original). "Without ingredients or other methods to enhance bioavailability," the ordinarily skilled artisan would have expected all dosage forms of zoledronic acid to have relatively low bioavailabilities that fall outside the ranges specified in the challenged claims. Pet. 20 (citing Ex. 1001, 13:57–59). The critical inquiry is whether the specification contains disclosure that, in the face of that expectation, would have guided the artisan to a selection of zolendronic acid dosage forms, with or without enhancers, sufficient to attain the full range of claimed bioavailabilities of at least 1.1% and up to 3% or 4%. Aronhime discloses at least 22 dosage forms of zoledronic acid, including eleven disodium salt forms. Pet. 23; Resp. 20. An ordinarily skilled artisan would have expected that those eleven disodium salt forms could have different properties, including different solubilities and bioavailabilities. Pet. 23 (citing Ex. 1034; Ex. 1035, 3:30–4:7; 8:22–11:1; Ex. 1005 ¶ 70).

c. The Breadth of the Claims, Lack of Guidance, and Absence of Working Examples

Claims 3–30 are "broad, covering any oral zoledronic acid dosage form having the claimed bioavailabilities." Pet. 20. The claims employ the transitional phrase "comprising" and, thus, are open to the inclusion of bioavailability-enhancing ingredients. *Id.*

The specification does not disclose any examples of zoledronic acid dosage forms and identifies no bioavailability-enhancing ingredients that may be added to improve zoledronic acid's bioavailability to at least 1.1%. Ex. 1005 ¶ 69; Pet. 21–22. Nor does the specification contain

pharmacokinetic data identifying any zoledronic acid dosage forms that will achieve a bioavailability in humans that falls within the scope of the claims. Ex. 1005 ¶¶ 64–65, 69; Pet. 21–22. On that point, even Dr. Wargin, Patent Owner's witness, agrees that the specification is silent:

Q. There is no actual data on any particular dosage form of zoledronic acid regarding bioavailability?

A. There is no actual data, that's true.

Ex. 1093, 89:17–22 (deposition transcript); Reply 18.

The '268 patent informs that "[t]he oral bioavailability of zoledronic acid may be enhanced by orally administering the zoledronic acid in the disodium salt form." Ex. 1001, 7:65–67. The '268 patent also informs that the disodium salt form of zoledronic acid "is much more soluble in water than the diacid form" and, therefore, "may be more bioavailable" or "more rapidly absorbed when taken orally as compared to the diacid form." Ex. 1001, 6:31–36. The claims, however, are not limited to the disodium salt form. Ex. 1001, 2:39–65, 3:9–13; Pet. 22; Ex. 1005 ¶ 68.

The specification acknowledges that the bioavailability of zoledronic acid may be as low as 0.01%. Ex. 1001, 14:8–11. Without providing any data or guidance for identifying workable dosage forms, the specification states that the bioavailability of zoledronic acid may be enhanced by as much as 200% by administering the diacid form. *Id*. at 7:67–8:5. However, Dr. Wargin, Patent Owner's witness, likened the belief "that some salt forms of oral zolendronic acid" could "provide oral bioavailability, without enhancers, to within the range of 1.1%" (the lowest bioavailability embraced by the claims) to a "belie[f] in 'fairies.'" Resp. 1 (quoting Ex. 2014, 137:21–138:8). The specification includes "hypothetical values" pertaining

to the bioavailability ranges that may be desired, but no actual data obtained from any dosage form, or any other information explaining how to make a dosage form having a bioavailability that falls within the claimed ranges. Ex. 1093, 129:7–130:10; *see* Reply 18–19; Ex. 1001, 8:20–35.

d. The Quantity of Experimentation Required

Petitioner contends that "the complete lack of guidance and information in the specification" results in a situation where the ordinarily skilled artisan "would not have known where to begin in trying to formulate a dosage form having the claimed bioavailabilities." Pet. 24–25 (citing Ex. 1005 ¶ 74). Patent Owner counters that the inventors disclosed a "disodium zoledronate tetrahydrate form"—not in the disclosure of the specification, but rather, in a "public reference that predates the" patent "and is presumed to be part of the [ordinarily skilled artisan's] knowledge." Resp. 31 (citing Ex. 1074).

Setting aside for a moment whether that extrinsic evidence can substitute for disclosure in the specification to provide enabling support for the inventive aspects of the claimed invention, we observe that the public reference advanced by Patent Owner describes the bioavailability of zoledronic acid in beagle dogs. Pet. 25; Ex. 1074, Fig. 8, ¶¶ 142–146 (U.S. Patent Publication No. 2014/0051669, reporting the results of a dog study). An ordinarily skilled artisan would have recognized that bioavailability in humans differs from bioavailability in beagle dogs due, for example, to differences in gastric pH and emptying rate. Pet. 25 (citing Ex. 1005 ¶ 105, Ex. 1087; Ex. 1088). Beagles have a more basic gut pH than humans, which may make acidic drugs like zoledronic acid more soluble and more bioavailable in beagles as compared to humans. *Id*. The beagle dog study,

therefore, would not have provided sufficient guidance to an ordinarily skilled artisan seeking to practice the full scope of the challenged claims, including the limitations that require dosage forms having a bioavailability of up to 3% or 4% in a human being. Resp. 31; Reply 20–21. Patent Owner's witness agrees that an ordinarily skilled artisan would not have understood bioavailability data obtained from dogs to correlate well to humans. Reply 21 (citing Ex. 1011, 34:4–19, 35:1–10).

Patent Owner further argues that the "specification tells an" ordinarily skilled artisan "that the recited range of about 1.1% to about 4% is achievable without using enhancers." Resp. 24 (citing Ex. 1001, 7:65–8:6, 13:62). That observation is not persuasive to show that the specification tells an ordinary artisan ***how*** to achieve the recited range. Even Dr. Wargin admits, "we don't know ***today*** whether any of the salt forms in Aronhime [aside from Form VII], if tested, would have a bioavailability within the ranges claimed in the '268 patent." Ex. 1093, 37:1–7 (emphasis added).

Dr. Wargin explains that ascertaining the bioavailability of a dosage form would have required a year's worth of effort and cost about one million dollars. Ex. 1093, 79:24–80:20. Patent Owner contends that such an endeavor would have been "routine," dismissing any difficulty involved in ascertaining which forms of zoledronic acid, and which bioavailability-enhancing ingredient (if any), would have been logical starting points for so expensive and time-consuming an exercise. *See* Surreply 19–20. Patent Owner argues that the testimony of its own witness should be discounted because it relates to a phase one study (*id*.), but a fair reading of the testimony reveals that the million-dollar figure and one-year time frame identified by Dr. Wargin would have applied to an ordinarily skilled

artisan's efforts to ascertain whether any given dosage form would exhibit "a bioavailability within the claimed range." Ex. 1093, 79:25–80:20; *see* Pet. 24–27 (and evidence cited therein); Reply 21 (and evidence cited therein).

Perhaps because the guidance provided within the four corners of the specification is so scant, Patent Owner looks outside the disclosure of the patent for information that may have guided an ordinarily skilled artisan's selection of dosage forms. Resp. 13–20, 31. "It is the specification," however, "not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genentech Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). On that point, we find it significant that Patent Owner's witness, Dr. Wargin, was unable to identify disclosure "in the '268 patent that says that the bioavailability of the disodium salt" form of "zoledronic acid actually falls within any of the claimed ranges." Ex. 1093, 89:24–90:3.

e. Weighing the Wands Factors

The specification provides no guideposts that would have illuminated a path toward even one dosage form that has a bioavailability that falls within the scope of any claim. *See, e.g.*, Ex. 1001, 29:20–61, 30:56–32:3. Unmodified zoledronic acid would have been understood to have an oral bioavailability of less than 1%. *See, e.g.*, Ex 1027[4] ¶ 6. The '268 patent specification discloses no working examples for any zoledronic acid dosage forms. Nor does the specification identify, with any particularity, a bioavailability-enhancing ingredient that would increase the oral

[4] Hanna et al., WO 2011/014781 A1, published February 3, 2011.

bioavailability of zoledronic acid from the art-recognized level of less than 1% to levels within the claimed ranges.

Patent Owner submits that an ordinarily skilled artisan could have taken "the salt and other forms of zoledronic acid identified in Aronhime" and "screened" each one "for solubility and dissolution rates using routine tests to eliminate the forms that have properties that are dissimilar to" a form used in the beagle studies reported in an extrinsic reference (namely, a "disodium zoledronate tetrahydrate form"). Resp. 20; Ex. 1074. Further, according to Patent Owner, that artisan could have performed "[b]ioavailability studies on a few remaining forms, far less than the 22 forms described in Aronhime, selected for their solubility and dissolution properties, again routine in nature," in order to "determine which forms fall within the range of the claims." *Id*.

In Patent Owner's view, the screening required "can be performed using a routine dog study or, alternatively, human clinical studies." *Id*. Where an ordinarily skilled artisan "could have identified and made all known forms of zoledronic acid as set forth in Aronhime, made oral dosage forms of those screened for higher solubility, and tested them to determine their bioavailability," Patent Owner contends that "practic[ing] the full scope of the claimed dosage forms" would have fallen within the ambit of "routine, not undue, experimentation." Resp. 23 (footnote omitted).

We disagree. Performing those steps to determine whether even one dosage form falls within the scope of the claimed bioavailability ranges would have required, according to Patent Owner's witness, about one million dollars and a year's worth of effort. Ex. 1093, 79:25–80:20 (testimony of Dr. Wargin); Pet. 24–27 (and evidence cited therein); Reply 21

(and evidence cited therein). Taking those steps with respect to "all known forms of zoledronic acid" (Resp. 23) to enable the practice of the full scope of the claims represents the epitome of undue experimentation.

On this record, we do not agree that an ordinarily skilled artisan "would understand that the '268 patent specification further identifies that with certain forms of zoledronic acid, one does not need to use an enhancer to achieve the bioavailabilities" required by the claims, including bioavailabilities as high as 3 or 4%. Resp. 27. Even if "the specification expressly tells [the ordinarily skilled artisan] that a disodium form of zoledronic acid can have an oral bioavailability in humans from about 1.1 to about 4%," that does not end the inquiry. *Id*. (citing Ex. 2017 ¶ 24). The central problem with Patent Owner's position, in that regard, is that the claims broadly include all forms of zoledronic acid, with or without an enhancer, and whether or not employed in the form of a disodium salt, as long as they meet the claimed bioavailability limitation. Not even Patent Owner argues, however, that all of those dosage forms, or even all known disodium salt forms, have a bioavailability above 1%. Resp. 20 ("It is believed that a significant number of the disodium salts, ***but not all***, will have solubility and dissolution properties that are similar to disodium zoledronate tetrahydrate"—a form identified in an extrinsic reference—"and thus are likely to have bioavailabilities within the range of the claims.") (emphasis added).

The specification includes no disclosure that explains how one may reliably distinguish dosage forms that fall within the scope of the claims from those that do not—short of preparing the forms and testing their bioavailability. The only example provided in the specification of the

’268 patent demonstrates the synthesis of compounds 1 and 2; it contains no guidance for selecting forms of zoledronic acid having the requisite bioavailability. Ex. 1001, 18:12 (Example 1). As to excipients, the specification teaches only that they may be determined by using standard pharmaceutical practice. *Id.* at 10:54–63.

As explained above, the art of pharmaceutical dosage formulation is unpredictable. *See supra* 11–12. Where an ordinarily skilled artisan would have understood that unmodified zoledronic acid has an oral bioavailability of less than 1%, that artisan could not have been expected to resolve, without any guidance, how to arrive at a dosage form having a bioavailability of 3% or 4%, without engaging in undue experimentation. Patent Owner’s counterview that ascertaining the workable dosage forms could be achieved through an exercise of ordinary skill in the art, without undue experimentation, is untenable. On this record, the specification does not enable claims 3–30.

ii. Conclusions on the Patentability of Claims 3–30

We determine that Petitioner demonstrates by a preponderance of the evidence that claims 3–30 are unpatentable for lack of enablement under 35 U.S.C. § 112(a). We decline to reach any other ground of unpatentability asserted in the Petition. *See Beloit Corp. v. Valmet Oy*, 742 F.2d 1421, 1423 (Fed. Cir. 1984) (finding an administrative agency is at liberty to reach a decision based on a single dispositive issue because doing so “can not only save the parties, the [agency], and [the reviewing] court unnecessary cost and effort,” but can “greatly ease the burden on [an agency] faced with a . . .

proceeding involving numerous complex issues and required by statute to reach its conclusion within rigid time limits").

III. MOTIONS TO EXCLUDE EVIDENCE

Patent Owner moves to exclude (1) portions of Dr. Wilson's testimony that pertains to data disclosed in Leonard; (2) the Merrion Poster; and (3) the Affidavit of Christopher Butler (Ex. 1094). Paper 40. We do not rely on that evidence in this decision. Petitioner moves to exclude paragraph 73 of Exhibit 2017. Paper 42. We do not rely on that evidence in this decision. Accordingly, we dismiss both motions as moot.

IV. CONCLUSION

Petitioner establishes by a preponderance of the evidence that claims 3–30 of the '268 patent are unpatentable for failure of the specification to enable the claims under 35 U.S.C. § 112(a).

V. ORDER

It is

ORDERED that claims 3–30 of the '268 patent are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence (Paper 40) is *dismissed as moot*;

FURTHER ORDERED that Petitioner's Motion to Exclude Evidence is *dismissed as moot*; and

FURTHER ORDERED that, because this is a Final Written Decision, any party to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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