Trials@uspto.gov
571.272.7822

Paper No. 10
Entered: December 11, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS-KABI USA LLC,
Petitioner,

v.

ASTRAZENECA AB,
Patent Owner.

Case IPR2017-01910
Patent 6,774,122 B2

Before GRACE KARAFFA OBERMANN, ZHENYU YANG, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

OBERMANN, *Administrative Patent Judge*.

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

I. INTRODUCTION

Petitioner Fresenius-Kabi USA LLC ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1, 2, 5, and 9 U.S. Patent No. 6,774,122 B2 (Ex. 1001, "the '122 Patent"). Paper 1 ("Pet."). AstraZeneca AB ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp.").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition and the Preliminary Response, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. Accordingly, we decline to institute an *inter partes* review of the '122 Patent.

A. Related Applications and Proceedings

The '122 Patent shares substantially the same specification with U.S. Patent Nos. 7,456,160 B2 ("the '160 Patent"), 8,329,680 B2 ("the '680 Patent"), and 8,466,139 B2 ("the '139 Patent), which are related as follows. The '139 Patent issued from Application No. 13/602,667 ("the '667 Application"), which is a continuation of Application No. 12/285,887 ("the '887 Application") (now the '680 Patent), which is a continuation of Application No. 10/872,784 ("the '784 Application") (now the '160 Patent), which is a continuation of Application No. 09/756,291("the '291 Application") (now the '122 Patent). This chain of continuations was first

filed on January 9, 2001, and each patent in the family claims benefit of foreign priority to applications filed April 12, 2000, and January 10, 2000.

According to the parties, the ’122 Patent has been the subject of numerous district court litigations. *See* Pet. 4–5; Paper 6, 2–3. According to Patent Owner, the related ’160, ’680, and ’139 Patents have also been involved in district court proceedings. Paper 6, 3.

Each of the four related patents have also been the subject of *inter partes* review proceedings filed by Mylan Pharmaceuticals, Inc. (“Mylan”). Of these, IPR2016-01316 on the ’122 patent, IPR2016-01324 on the ’160 patent, and IPR2016-01326 on the ’139 patent were terminated before we issued a decision regarding institution. In IPR2016-01325 (“the Mylan IPR”) on the ’680 patent, however, we issued a Decision denying institution (“Mylan Decision”), which Petitioner submits in this proceeding as Exhibit 1011 and discusses extensively in the Petition.

The ’122 patent and two related patents also have been the subject of petitions for *inter partes* review filed by InnoPharma Licensing, LLC: IPR2017-00904 on the ’122 patent, IPR2017-00900 on the ’680 patent, and IPR2017-00905 on the ’139 patent. We previously denied each of those petitions.

In addition to the instant Petition challenging claims of the ’122 Patent, Petitioner has submitted Petitions challenging claims of the ’139 Patent (IPR2017-01912) and the ’680 Patent (IPR2017-01913). These petitions are virtually identical to the three petitions filed by InnoPharma Licensing and denied by the Board in IPR2017-00900, IPR2017-00904, and IPR2017-00905, respectively. Paper 7, 3–4; *see id.* at 4 (“Petitioner copied verbatim the earlier-filed petitions, and supporting declarations, submitted

by InnoPharma Licensing.”). Petitioner filed requests for joinder with the respective *inter partes* reviews filed by InnoPharma (Paper 3), which we denied (Paper 7).

B. The ’122 Patent and Relevant Background

The Specification of the ’122 Patent discloses “an extended release pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant” [1] for the treatment of “benign or malignant disease[s]of the breast or reproductive tract, preferably treating breast cancer.” Ex. 1001, 10:56–11:22. Fulvestrant is also known in the art as ICI 182,780 or 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17-β-diol, and is the active ingredient in AstraZeneca’s FASLODEX product for “[t]reatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.” *Id*. at Abstract; 1:64–2:2; Ex. 1021,[2] 1, 13.

As of the filing date of the ’122 Patent, nonsteroidal antiestrogens, most particularly, tamoxifen, were used in the treatment of hormone-dependent breast cancers. *See* Ex. 1001, 1:16–32; Prelim. Resp. 19–20. In some hormone-dependent cancers, estrogen bound to estrogen receptors (ERs) stimulates tumor growth. *See* Pet. 12; Prelim. Resp. 19. Tamoxifen is a selective estrogen receptor modulator or SERM, meaning that it acts as an estrogen antagonist in these cancers, blocking the binding of estrogen to its receptors. Prelim Resp. 19–20. As of the filing date of the ’122 Patent,

---

[1] The Specification defines “extended release” to mean that “at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved.” *Id.* at 9:17–9.

[2] FASLODEX Prescribing Information, Rev. 11/2012.

however, researchers were seeking alternative treatments, including fulvestrant, for estrogen-dependent breast cancers because resistance to tamoxifen tends to develop over time, and because tamoxifen treatment could adversely affect bone and uterine tissue. *See* Ex. 1001, 2:11–31; Prelim. Resp. 19–21; Ex. 1015 ¶¶ 61–74. Unlike tamoxifen, fulvestrant is a "pure" antiestrogen or ERD (estrogen receptor downregulator), which does not display the partial ER agonist activity of tamoxifen. *See* Ex. 1001, 2:12–19; Ex. 1015 ¶¶ 61, 77.

The Specification discloses that intramuscular administration of fulvestrant in aqueous suspension results in a clinically insufficient release rate and "extensive local tissue irritation" because fulvestrant particles are present at the injection site. Ex. 1001, 8:36–46. And while the "solvating ability of castor oil for steroidal compounds is known" (*id*. at 5:19–24), a monthly depot injection made by dissolving fulvestrant in castor oil alone would require formulation volumes of at least 10 ml "to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate." *Id*. at 5:25–41. In addressing these problems, the '122 Patent states:

> With the addition of high concentrations of an alcohol concentrations of >50 $mgml^{-1}$ of fulvestrant in a castor oil formulation is achievable, thereby giving an injection volumes of <5 ml. . . . We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 $mgml^{-1}$. . . . The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents . . . is significantly lower than the solubility of fulvestrant in an alcohol. . . . [or] in castor oil.

Id. at 5:44–57 (referencing Tables 2 and 3); *see also id*. at 9:23–47 ("Table 3 shows . . . . the positive effect of benzyl benzoate on fulvestrant solubility in castor oil, despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.").

The Specification further discloses that "[s]imply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site." *Id.* at 9:20–22. But according to the inventors, in vivo testing of the castor oil-based formulations of the invention "surprisingly" demonstrates, "after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time." *Id.* at 8:29–32. In particular, Figure 1 shows release profiles after intramuscular injection into rabbits of 5% fulvestrant formulations comprising 10% ethanol, 10% benzyl alcohol and 15% benzyl benzoate made to volume with various oil components. *See id*. at 9:54–10:55, Fig. 1. The inventors conclude that "the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site." *Id*. at 10:52–55; *see id*. at Fig. 1 and Table 4, second half.

The Specification, thus, describes the extended release fulvestrant formulation of the invention as comprising

> Fulvestrant . . . in a ricinoleate vehicle,[3] a pharmaceutically acceptable nonaqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically

---

[3] The Specification defines ricineolate vehicles as castor oil and other oils having "at least 20% . . . of its composition as triglycerides of ricinoleic acid." *Id*. at 8:23–27; *see id*. at 5:47–53.

> significant[4] blood plasma fulvestrant concentration for at least 2 weeks.

Ex. 1001, 5:58–67. In preferred embodiments, the ricinolate vehicle is castor oil, the alcohol is a combination of ethanol and benzyl alcohol, and the non-aqueous ester solvent is benzyl benzoate. *Id*. at 7:12–31; 8:23–33.

C. Challenged Claims

Petitioner challenges claims 1, 2, 5, and 9 of the '122 Patent. Pet. 1. Claims 1 and 5 are independent. Claim 1 recites (paragraphing added):

> 1. A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intramuscular injection of a pharmaceutical formulation comprising
>
> fulvestrant,
>
> a mixture of 10% weight of ethanol per volume of formulation,
>
> 10% weight of benzyl alcohol per volume of formulation and
>
> 15% weight of benzyl benzoate per volume of formulation and
>
> a sufficient amount of a castor oil vehicle,
>
> whereby a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ is attained for at least 2 weeks after injection.

Ex. 1001, 12:55–65.

---

[4] The Specification explains that "therapeutically significant" blood plasma levels refer to "blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant [] achieved in the patient." *Id.* at 9:1–4.

Claim 5 is similar but in place of the "whereby" clause of claim 1, recites: "whereby the formulation comprises at least 45 mgml of fulvestrant." *Id*. at 13:15–16. Depending from claims 1 and 5, respectively, claims 2 and 9 specify that "the benign or malignant disease is breast cancer." *Id*. at 12:66–67, 14:13–14.

D. The Asserted Prior art and Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 8–9):

Ground	**Reference(s)**	**Basis**	**Claims**
1	Howell[5]	§ 103	1, 2, 5, and 9
2	Howell and McLeskey[6]	§ 103	1, 2, 5, and 9
3	Howell, McLeskey, and O'Regan[7]	§ 103	1, 2, 5, and 9

Petitioner also relies on the Declarations of Diane Burgess, Ph.D. (Ex. 1012), Richard Bergstrom, Ph.D. (Ex. 1013), Dorraya El-Ashry, Ph.D. (Ex. 1014), and Dr. Adrian Harris (Ex. 1015).

---

[5] Howell *et al.*, *Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer*, 74 BRIT. J. CANCER 300–308 (1996). Ex. 1007.

[6] McLeskey *et al.*, *Tamoxifen-resistant fibroblast growth factor transfected MCF-7 cells are cross-resistant in vivo to the antiestrogen ICI 182,780 and two aromatase inhibitors*, 4 CLIN. CANCER RESEARCH 697–711 (1998). Ex. 1008.

[7] O'Regan *et al.*, *Effects of the Antiestrogens Tamoxifen, Toremifene, and ICI 182,780 on Endometrial Cancer Growth*, Vol. 90 No. 20 J. NAT'L CANCER INST. 1552–58 (1998). Ex. 1009.

Patent Owner relies on the Declarations of Lisbeth Illum, Ph.D. (Ex. 2001), John F. R. Robertson, M.D. (Ex. 2002), and Ronald J. Sawchuk, Ph.D. (Ex. 2003).

The parties also discuss the Sawchuk § 1.132 Declaration[8] and the Gellert § 1.132 Declaration[9] submitted during the prosecution leading to the issuance of the '680 Patent. *See, e.g.*, Pet. 15–16; Prelim. Resp. 8–12.

Dr. El-Ashry, Dr. Illum, Dr. Robertson, and Dr. Sawchuk also opine on Exhibit 2043, the October 1, 2014, Declaration of Sandra McLeskey, Ph.D. *See* Ex. 1014 ¶ 3; Ex. 2001 ¶ 61; Ex. 2002 ¶ 150; Ex. 2003 ¶ 58.

E. Overview of the Asserted References

i. Howell (Ex. 1007)

Howell discloses the results of a clinical trial in which 19 patients with advanced breast cancer resistant to tamoxifen were administered fulvestrant as "a long-acting formulation contained in a castor oil-based vehicle by monthly i.m. injection (5 ml) into the buttock." Ex. 1007, 301;[10] *see also id.* at Abstract ("The agent was administered as a monthly depot intramuscular injection."). To investigate local and systemic toxicity, "the first four patients received escalating doses of [fulvestrant], starting with 100 mg in the first month and increasing to 250 mg i.m. from the second month onwards." *Id.* at 301. The remaining patients received 250 mg doses of

---

[8] Declaration under 37 C.F.R. § 1.132 of Ronald J. Sawchuk, dated January 13, 2012. Ex. 1019.

[9] Declaration under 37 C.F.R. § 1.132 of Paul Richard Geller, dated August 8, 2008. Ex. 1020.

[10] We refer, herein, to the original pagination of the cited references rather than to that supplied by the parties.

fulvestrant, intramuscularly, each month from the outset.[11] *Id*. Howell reports that "[t]hirteen (69%) patients responded (seven had partial responses and six showed 'no change' responses) to [fulvestrant], after progression on tamoxifen, for a median duration of 25 months." Ex. 1007, Abstract.

With respect to pharmacokinetics, Figure 2 of the reference shows fulvestrant serum concentration profiles over time during the first and sixth months of treatment. *Id.* at 303. Howell states that "continuous release of drug from the [fulvestrant] slow release formulation was shown throughout the one month dosing interval." *Id*. at 302. "[M]ean exposure to the drug increased slightly after multiple dosing. Mean C_{max} (which occurred on day 7) increased from 10.5 ng $m1^{-1}$ to 12.8 ng ml^{-1}, accompanied by increases in mean end-of-month concentrations from 3.1 ng $m1^{-1}$ to 5.6 ng $m1^{-1}$." *Id*.

In addressing the relationship between fulvestrant blood levels and efficacy, Howell states:

> This study represents the first investigation of long-term administration of the specific anti-oestrogen, ICI 182780, to patients with breast cancer and demonstrates that predicted therapeutic levels of ICI 182780, as judged from animal experiments . . . and our previous short phase I study (DeFriend *et al*., 1994b) can be achieved and maintained for 1 month following a single i.m. injection of the long-acting formulation used.
>
> * * *

[11] As Petitioner's expert, Dr. Burgess indicates, one of ordinary skill in the art would have understood that the concentration of fulvestrant in the castor oil-based vehicle was 50 mg/ml. Ex. 1012 ¶¶ 78, 83, 85. Howell is silent as to the presence or absence of other components in the formulation.

> From studies on inhibition of endometrial proliferation in the monkey and inhibition of tumour proliferation in a previous phase I study, it was predicted that serum levels of [fulvestrant] in the range of 2–3 ng $m1^{-1}$ were consistent with a therapeutic effect in patients with advanced breast cancer. However, a direct pharmacokinetic-pharmacodynamic link is not proven with the few patients studied to date. Serum drug concentrations in excess of this were observed with the 250 mg dose used in the present study for most of the first and all of the sixth month. However, there was evidence of drug accumulation after multiple dosing, such that after 6 months treatment there was an 80% increase in mean end of month drug levels and a 50% increase in the AUC compared with data from month 1. These data suggest that lower doses of the drug may be effective in maintaining therapeutic serum drug levels, although further clinical studies are required to confirm this hypothesis.

Id. at 305.

Howell concludes that fulvestrant "is well tolerated during long-term treatment and is active as an anti-tumour agent in patients with advanced breast cancer who have previously relapsed on tamoxifen." *Id*. at 306. However, "[a]t the dose used, there was accumulation of the drug over time and thus lower doses than those administered in this study may be as effective." *Id*.

ii. McLeskey (Ex. 1008)

McLeskey teaches that, in the treatment of clinical breast cancer, "conventional therapy is not usually curative," and can result in the "development of tamoxifen resistance, in which breast tumors previously growth-inhibited by tamoxifen become refractory." Ex. 1008, 697. Moreover, "early results for small numbers of tamoxifen-resistant patients have shown that only about 30–40% of such patients have a positive response to subsequent [fulvestrant] or aromatase inhibitor therapy." *Id*. at

698 (citing, inter alia, Howell). To explore the underlying mechanisms of acquired tamoxifen resistance, McLeskey employs a mouse model of tamoxifen-resistant breast cancer. *Id*., Abstract.

McLeskey notes that "FGFs [fibroblast growth factors] and their receptors have been shown to be present with high frequency in breast cancer specimens," and that there is "[e]vidence for a possible role for FGF signaling in the estrogen-independent growth of breast tumors." *Id*. at 698. McLeskey posits that, "[i]f FGF-mediated growth pathways bypass the ER pathway to affect growth directly, we would expect that [tumor] growth would be unaffected by hormonal treatments devoid of agonist activity." *Id*. McLeskey "therefore sought to determine the sensitivity of the estrogen-independent tumor growth of FGF-transfected MCF-7 cells to [fulvestrant] or aromatase inhibitors," by treating "ovariectomized tumor-bearing mice injected with fibroblast growth factor (FGF)-transfected MCF-7 breast carcinoma cells with the steroidal antiestrogen [fulvestrant] or one of two aromatase inhibitors." *Id*. at 698, Abstract.

With respect to the fulvestrant arm, McLeskey injects the tumor-bearing mice subcutaneously, once per week, with 5 mg doses of the drug at 50 mg/ml in an oil-based formulation. *Id*. at 698, Fig. 1. Depending on the experiment, the fulvestrant formulations comprise either ethanol and peanut oil (Fig. 1A), or "10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil" (Figs. 1B and 1C). *Id*. "These treatments did not slow estrogen independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice" (*id*. at Abstract)—a result McLeskey characterizes as "treatment failure." *Id*. at 706, *see id*. at 700–01.

Because fulvestrant and the aromatase inhibitors were "without effect" in these experiments, McLeskey "injected reproductively intact female mice for 2 weeks with these compounds at the same doses used in the above experiments to observe for activity in preventing effects of endogenous estrogens on the endometrium." *Id*. at 701–02. Upon examining the effect of these compounds on the uteri of the treated mice, McLeskey concludes that "these compounds retained activity, although they had no effect on tumor growth in our experiments." *Id*. McLeskey does not specify whether the peanut oil-based or the castor oil-based fulvestrant composition was used for this experiment. Nor does McLeskey address fulvestrant blood plasma levels, or otherwise provide pharmacokinetic data, for any experiment.

iii. O'Regan (Ex. 1009)

Noting that tamoxifen has been associated with an increased risk of endometrial cancers, O'Regan explores the effect of a tamoxifen derivative and fulvestrant in a mouse model of human endometrial cancer. *See* Ex. 1009, Abstract. With respect to fulvestrant, O'Regan reports that this compound "has shown promising results clinically in Europe, with high response rates of almost 70% in tamoxifen-failed, advanced breast cancer" (*id*. at 1553 (citing Howell)) and that "[c]linically, it must be given by depot intramuscular injection because of low oral potency" (*id*.). In the context of the mouse model, however, O'Regan administers fulvestrant by subcutaneous injection in peanut oil. *Id*.

O'Regan concludes that in the mouse model, "[fulvestrant] inhibits endometrial cancer, both in the presence and in the absence of estrogen, suggesting that it will prevent further tumor growth in patients with

tamoxifen-stimulated endometrial cancer." *Id*. at 1557. According to O'Regan, "[fulvestrant] should not be associated with an increase in endometrial cancer and could even be considered in the treatment of endometrial cancer." *Id*.

F. Prosecution History

As set forth in section I(A), above, the '122, '160, '680, and '139 Patents derive from a series of continuation applications (the '291, '789, '887, and '667 Applications, respectively) and share essentially the same Specification. Applicants first disclosed Howell during the prosecution of the '291 Application. *See* Ex. 1006, 461. The Examiner did not address Howell in any rejection, but argued that the then-pending claims were obvious because, inter alia, "combining one or more agents, which are known to be useful as commonly used solvents, such as benzyl benzoate, ethanol, castor oil, and benzyl alcohol, together and incorporated such combination with an estrogen derivatives, fulvestrant, would be reasonably expected to be useful in formulating a pharmaceutical composition." *Id*. at 508.

Applicants responded that one of ordinary skill in that art would not have used benzyl benzoate in view of "the very low solubility of fulvestrant in such ester," as shown in the Specification. *Id*. at 523–530. The Examiner found allowable subject matter in light of the "[u]nexpected increase of solubility of fulvestrant by adding 15% of benzyl benzoate into the composition with ethanol, benzyl alcohol, and castor oil . . . ." *Id*. at 540–541; *see also id*. at 572 (Examiner's Reasons For Allowance stating that "[t]he herein recited ratio of ethanol, benzyl alcohol, and benzyl benzoate is demonstrated to have unexpected increase of solubility of fulvestrant.").

Addressing a similar argument during the prosecution of the ’784 Application, Applicants relied on the Gellert § 1.132 Declaration. Ex. 1046, 150–181; *see id*. at 182–496; Ex. 1020. Dr. Gellert testified that, although it was known to use benzyl benzoate in castor oil-based formulations, an experienced formulator

> would have expected that benzyl benzoate would *not* act as a co-solvent for fulvestrant in castor oil because the solubility of fulvestrant in benzyl benzoate was significantly lower than its solubility in castor oil. . . . [and] would have been expected to *decrease, rather than increase*, the solubility of fulvestrant in the resulting castor oil/benzyl benzoate mixture.

Ex. 1020 ¶¶ 18–20, 24. According to Dr. Gellert, the inventors’ discovery “that the addition of benzyl benzoate to the castor oil/alcohol mixture actually increases the solubility of fulvestrant such that more fulvestrant could be dissolved in a given volume of formulation, was unexpected and truly surprising.” *Id*. ¶ 25. In allowing the ’160 Patent to issue, the Examiner stated that “the unexpected solubility and the bioavailability of using the specific solvent mixture as recited have been demonstrated.” Ex. 1046, 729.

During the prosecution of the ’887 Application, Applicants disclosed that, in connection with an attempt by Teva Parenteral Medicines Inc. to gain approval of a generic 50 mg/ml fulvestrant injection, Teva had alleged that the claims of the then-issued ’122 and ’160 Patents were invalid as obvious over, inter alia, McLeskey and Howell. Ex. 1042, 295–99. Howell and McLeskey were then the subject of an Examiner Interview. *See id.* at 336–37. Subsequent to the interview, the Examiner entered a rejection under § 103 over McLeskey in combination with three other references. *Id*.

at 313–15. In responding to that rejection, Applicants amended the independent claims (now claims 1 and 9) to recite a formulation comprising "about 50 $mgml^{-1}$ of fulvestrant; about 10% w/v of ethanol; about 10% w/v of benzyl alcohol," and "about 15% w/v of benzyl benzoate," wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration "for at least four weeks." *See id*. at 335; Ex. 3001.[12] Applicants also relied extensively on arguments set forth in the Sawchuk § 1.132 Declaration. Ex. 1042, 339–55; *see id* at 357–83; Ex. 1019.

Dr. Sawchuk testified that the cited references provide no motivation to select the disclosed castor oil formulation for intramuscular administration. Ex. 1019, ¶¶ 31–41. McLeskey, for example, "did not disclose plasma or blood levels of fulvestrant in mice after subcutaneous administration of either the peanut oil or the castor oil compositions" and, thus presents "no information regarding the rate and/or extent of absorption of fulvestrant from the subcutaneous injection site." *Id*. ¶ 32. Dr. Sawchuk further testified that "*McLeskey* concluded that treatment with fulvestrant (ICI 182,780), using either of the disclosed compositions was not effective in that it 'did not slow estrogen-independent growth or prevent metastasis of tumors'" in the mouse model and, thus, would not have informed one of ordinary skill in the art "about the usefulness of either fulvestrant formulation when administered subcutaneously to a mouse for the treatment of cancerous tumors." *Id*. ¶ 33; *see also id*. ¶ 34 (noting that although

[12] Exhibit 1042, pages 334–356, contains the comments section of Applicants' January 17, 2012, submission and omits internally numbered pages 2–6, setting forth the claim amendments. For completeness, we provide a copy of those amendments as Ex. 3002.

McLeskey demonstrated that fulvestrant had activity in mice uteri, the reference did not specify which formulation was used in that experiment). Dr. Sawchuk concluded that

> because of the lack of fulvestrant efficacy and the absence of pharmacokinetic data in *McLeskey*, one of ordinary skill in the art would have been unable to conclude whether either of the two fulvestrant *McLeskey* compositions (peanut oil or castor oil) was able to deliver a dose of fulvestrant that had an antitumour therapeutic effect in the mice when administered subcutaneously, nor any insight about fulvestrant absorption characteristics (rate and extent) when administered via the *intramuscular route* in any species, including humans.

Id. ¶ 35.

Expanding on that conclusion, Dr. Sawchuk testified that "one of ordinary skill in the art would not have had a reasonable expectation that the *McLeskey* castor oil composition would have been effective when given as an intramuscular injection" (*id*. ¶ 69) because (1) the composition of a formulation can have a significant effect on efficacy (*id*. ¶¶ 57–69), and (2) because "results from subcutaneous administration in general, and including those included in *McLeskey*, cannot be extrapolated to intramuscular administration," either with respect to side effects or efficacy (*id*. ¶ 42–43).

Quoting the Specification's assertion that "[s]imply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site," Dr. Sawchuk stated that "suitable experiments are needed to determine the pharmacokinetic performance of any candidate formulation(s)." *Id*. ¶ 62. To illustrate the unpredictability in the prior art, Dr. Sawchuk discussed three published examples illustrating that "the intramuscular and subcutaneous administration of a drug to the same animal or human may

produce very different plasma level curves, and therefore very different pharmacologic effects." *Id*. ¶¶ 42–56. According to Dr. Sawchuk, these references[13]

> show that there are significant differences in the rate and extent of absorption of a drug given by the intramuscular and subcutaneous route, even when given to the same animals in a crossover study. As a result, it cannot be predicted a priori whether intramuscular or subcutaneous dosing will result in more rapid and/or complete drug absorption, as examples of both cases are found in the scientific literature.

Id. ¶ 53.

Dr. Sawchuk also testified that one of ordinary skill in the art would have understood that the components in McLeskey's castor oil formulation are implicitly described in terms of volume/volume percent units, which differ substantially from the weight/volume percentages of the claimed invention. *See id*. ¶¶ 16–30. Upon reviewing several prior art sources in which formulations were disclosed in a % v/v basis, Dr. Sawchuk testified that "one of ordinary skill in the art would have concluded that the composition [of McLeskey] was described in terms of volume/volume percent units (% v/v)." *Id*. ¶ 21. Based on the proposition that McLeskey implicitly disclosed a formulation based on volume/volume percent units, Dr. Sawchuk calculated the amount of each component in weight/volume

---

[13] Guerrini et al., *Pharmacokinetics of probenecid in sheep*, 8(2) J. VET. PHARMACOL. THER. 128–135 (1985) (Ex. 1042 at 549–556); Lavy et al., *Pharmacokinetics of clindamycin HCl administered intravenously, intramuscularly and subcutaneously to dogs*, 22(4) J. VET. PHARMACOL. THER. 261–265 (1999) (Ex. 1042 at 482–486); Ismail, *Disposition kinetics of difloxacin after intravenous, intramuscular and subcutaneous administration in calves*, 31(4) VET. RES. COMMUN. 467–476 (2007) (Ex. 1042 at 487–496).

percent units. *Id*. ¶¶ 23–28 (referencing Table 1). Based on these calculations, Dr. Sawchuk concluded that "*McLeskey* described a composition containing about 8.1% w/v ethanol, about 16.8 % w/v benzyl benzoate, and about 10.4% w/v benzyl alcohol in a castor oil vehicle." *Id*. ¶ 29.

Without citing any one argument as dispositive, the Examiner withdrew the obviousness rejection "in view of the arguments along with the declaration of Dr. Sawchuk filed 1/17/2012" (Ex. 1042, 650) and allowed the '680 Patent to issue (*id.* at 717–19).

II. ANALYSIS

A. Person of Ordinary Skill in the Art.

The parties propose similar, albeit non-identical, definitions of one of ordinary skill in the art, both of which are consistent with the high level of ordinary skill demonstrated by the prior art asserted in the Petition. *See* Pet. 18; Prelim. Resp. 20. Discerning no present conflict between the parties' proposals, we rely on the level of ordinary skill in the art of developing and treating hormone-dependent diseases of the breast as demonstrated by the prior art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard).

Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

In the Mylan IPR, we determined the meaning of several claim terms of the '680 Patent. *See* Ex. 1011, 15–18. The parties contend that the terms of the '122 Patent claims should be interpreted in accord with our prior construction. Pet. 18–19; Prelim. Resp. 20. For the reasons set forth in the Mylan Decision, we agree. *See* Ex. 1011, 16–18.

C. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417. We are, nevertheless, cautioned not to "rel[y] on hindsight reasoning to piece together elements to arrive at the claimed invention." *In re NTP, Inc.* 654 F.3d 1279, 1299 (Fed. Cir. 2011) ("Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of

prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." (internal quotations and citations omitted)). Thus, a finding of obviousness, "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). Accordingly, a party petitioning the Board for a determination of obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

D. Asserted Grounds

We next turn to the three grounds of invalidity asserted in the Petition: whether the subject matter of claims 1, 2, 5, and 9 of the '122 patent would have been obviousness to a person of ordinary skill in the art at the time of the invention over (1) Howell; (2) Howell and McLeskey; or (3) Howell, McLeskey, and O'Regan. Pet. 9. Given the overlap between these grounds, we consider them together.

i. The Petition's Use of the Prior Mylan Decision as a Roadmap

As explained above in Section I(F), Howell and McLeskey previously were considered during prosecution of related patents. Further, all three asserted references (Howell, McLeskey, and O'Regan) were raised, and found insufficient to support institution of a trial, in the Mylan IPR. *See* Mylan IPR, Paper 2, 5, 40 (Mylan's petition, raising Howell and McLeskey

in grounds and O'Regan as background art). Petitioner contends that the "Petition cures [] gaps in the record" created in the Mylan IPR, and alleges that "[f]our differences" distinguish the instant Petition from the unsuccessful Mylan petition. Pet. 10.

There is no doubt that the Petition was prepared using our prior Mylan Decision as a roadmap in an attempt to cure deficiencies that led to our denial of trial in the Mylan IPR. *Id*. at 9–12. The Petition repeatedly refers to our Mylan Decision, and is structured to address deficiencies that we identified in the record of the prior proceeding. *See id. passim*. Patent Owner requests that we exercise our discretion to deny the Petition on the basis that it uses a previous Board decision "as a 'roadmap' to address challenges that were advanced, unsuccessfully," in the Mylan IPR. Prelim. Resp. 6 (quotation omitted). The Mylan IPR, however, involved a different petitioner (Mylan) and a different patent (the related '680 patent). Based on the particular facts of this case, we decline to issue a discretionary denial and, instead, consider the Petition on its merits.

Nevertheless, we approach this case cognizant that the '680 patent (at issue in the Mylan IPR) and the '122 patent (at issue here) share essentially the same disclosure and conclude with similar patent claims. *Compare* Mylan IPR, Ex. 1001 *with* Ex. 1001. We recognize, moreover, that our prior Mylan Decision addressed essentially the same factual inquiry centered on essentially the same disclosures of the same asserted prior art references. We accept, therefore, Petitioner's view that the nub of this dispute is whether "[f]our differences" set forth in the Petition overcome the shortcomings that we previously identified in the Mylan Decision. Pet. 10;

see Ex. 1011, 19–30 (Mylan Decision, including our prior analysis of essentially the same issues raised in the instant Petition).

Accordingly, we address in turn below each of the "[f]our differences" identified in the instant Petition: whether the instant Petition (1) changes the obviousness analysis by emphasizing Howell—and not McLeskey—as the appropriate starting point for the combination; (2) includes persuasive "new evidence," consisting of supporting declarations and alleged admissions, that cures deficiencies and gaps in the record of the Mylan IPR; (3) adequately addresses the Sawchuk § 1.132 Declaration; and (4) "fills every [other] deficiency" in the record created in the Mylan IPR, as identified in the Mylan Decision. Pet. 10–12.

ii. New Emphasis on Howell as the Starting Point

The first "difference" between the instant Petition and Mylan's petition relates to the order of consideration of the asserted prior art references. Pet. 10. Petitioner asserts that the instant Petition materially changes the obviousness inquiry by emphasizing Howell—and not McLeskey—as the appropriate starting point for the combination. *Id*. We are not persuaded that the alleged change in emphasis justifies a result different from that obtained in the Mylan IPR.

A change in emphasis does not alter the content of the combined teachings of the prior art. Howell discloses the results of a clinical trial in which 19 patients with advanced breast cancer resistant to tamoxifen were administered fulvestrant as "a long-acting formulation contained in a castor oil-based vehicle by monthly i.m. injection (5 ml) into the buttock." Ex. 1007, 301. Howell does not identify or suggest inclusion of any other excipient. *Id*. Like Howell, O'Regan suggests an intramuscular injection of

fulvestrant but does not disclose or suggest the inclusion of any particular excipient or solvent. Ex. 1009, 1553. The challenged claims, by contrast, require a fulvestrant formulation that includes 10% weight of ethanol per volume, 10% weight of benzyl alcohol per volume, and 15% of benzyl benzoate per volume in a castor oil vehicle. Ex. 1001, claims 1, 2, 5, and 9.

McLeskey conducted experiments in which the fulvestrant formulations comprised either ethanol and peanut oil (Fig. 1A), or "10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil" (Figs. 1B and 1C). Ex. 1008, 698, Fig. 1. As we did in the Mylan Decision, we accept for the purposes of this decision that McLeskey discloses the claimed formulation. Ex. 1011, 23, 27.

As we observed in the Mylan IPR, however, "[i]t is not enough for Petitioner to establish that castor-oil based intramuscular injections of fulvestrant were known; the evidence must provide a reason for one of skill in the art to administer [the claimed] fulvestrant formulation"—which includes specific concentrations of three required excipients in castor oil—"'intramuscularly' to" achieve a therapeutically significant blood plasma concentration or dosage "for 'treating a hormonal dependent benign or malignant disease of the breast or reproductive tract,' as recited in the challenged claims." *Id*. at 29.

As an initial matter, we are not persuaded that the Petition adopts a new approach by focusing on Howell as the starting point for the combination. Pet. 10, 19–23. In the Mylan Decision, we expressly considered the combination of Howell and McLeskey—using Petitioner's preferred perspective of starting with Howell. Prelim. Resp. 15 (quoting Ex. 1011, 22). Specifically, in the Mylan Decision, we considered whether

an ordinary artisan, seeking an appropriate formulation of fulvestrant "in light of Howell[] . . . would have been immediately drawn to McLeskey." Ex. 1011, 22. We determined that an ordinary artisan would not have been drawn to McLeskey, given that the reference describes its own results as a "treatment failure." *Id*. at 27; Ex. 1008, 706.

Approaching the inquiry from the perspective of Howell does not cure the deficiencies in the combined disclosures of the asserted prior art. Howell teaches only "a long-acting formulation contained in a castor oil-based vehicle." Ex. 1007, 301. It does not disclose any information about excipients used in the formulation, much less suggest the use of the claimed excipients in the specified weight-to-volume ratios. *Id*.

The Petition attempts to fill that gap with declaration testimony. Pet. 37–40 (citing Ex. 1020 (the Gellert § 1.132 Declaration), Ex. 1012 (Dr. Burgess's declaration), Ex. 1015 (Dr. Harris's Declaration)). Specifically, relying on the Gellert § 1.132 Declaration, the Petition posits that benzyl alcohol and ethanol would have been recognized "as the best co-solvent candidates for raising the fulvestrant solubility to the 45 mg/mL target." Pet. 40 (quoting Ex. 1020 ¶ 21). Critically lacking, however, is a rational explanation why or how an ordinary artisan would have arrived at the target of "45 mg/mL" in the absence of the disclosure of the '122 patent. *Id*.; *see* Ex. 1001, claim 5 (specifying the 45 mg/mL target). In that regard, as Patent Owner points out, the Gellert § 1.132 Declaration is not prior art. Prelim. Resp. 40 (citing Ex. 2001 ¶¶ 104–121, 156–166; Ex. 2003 ¶¶ 61, 63, 64). Instead, it "sets forth the inventors' own unpublished data and experimentation" and uses "data generated by the inventors" to explain

"how the inventors themselves were surprised by the result of their work." *Id*. (citing Ex. 1020 ¶¶ 13, 16, 20, 21; Ex. 1046, 729).

In addition, according to Petitioner, an ordinary artisan would have been motivated to add benzyl benzoate as another co-solvent to the formulation because "castor oil, benzyl alcohol, and ethanol could not solubilize fulvestrant at the target 50 mg/ml concentration." Pet. 40 (citing Ex. 1020 ¶ 16). On that point, however, Petitioner fails to address Dr. Gellert's testimony that an "experienced formulator" would have expected the addition of benzyl benzoate "to *decrease, rather than increase*, the solubility of fulvestrant in the resulting castor oil/benzyl benzoate mixture." Ex. 1020 ¶ 20. Petitioner may not selectively rely on portions of the Gellert §1.132 Declaration that buttress its argument but ignore another part of the same document that undermines its contention.

Furthermore, citing the testimony of Dr. Burgess, the Petition states that benzyl benzoate would have been recognized as "the third best co-solvent for solubilizing fulvestrant." Pet. 40 (citing Ex. 1012 ¶ 113). When we turn to the testimony cited in support of that factual proposition, however, the cited evidence does not substantiate the assertion stated in the Petition. *Compare* Pet. 40 (citing Ex. 1012 ¶ 113) *with* Ex. 1012 ¶ 113. Finally, the Petition argues, without citation to any evidence, that "there was a reasonable probability of success because the prior art taught that benzyl benzoate would improve the solubility of fulvestrant in castor oil." Pet. 42. On this record, the Petition fails to show sufficiently that an ordinary artisan, starting from Howell's formulation of fulvestrant in castor oil, would have been led to include in the formulation a combination of benzyl alcohol,

ethanol, and benzyl benzoate in the weight-to-volume ratios required by each challenged claim of the ’122 patent.

On that point, the instant Petition does little to improve the record developed in the Mylan IPR. Even when the subject is single-reference obviousness over Howell alone, the Petition relies on subjective witness testimony that is supported by the same objective proof (the disclosure of McLeskey) that was raised, and found insufficient, in the Mylan IPR. Pet. 43–45 (claim chart for obviousness based on Howell alone, directing us to, *inter alia*, Ex. 1012 ¶¶ 88–92, Ex. 1015 ¶¶ 144–166 (Dr. Burgess and Dr. Harris, relying on McLeskey for the claimed combination and ratio of excipients)). We address in the next section whether the Petition raises new declaration testimony and alleged admissions that cure the deficiencies identified in the Mylan Decision, regarding the sufficiency of McLeskey.

iii. New Declaration Testimony and Alleged Admissions

The second asserted “difference” between the instant Petition and Mylan’s petition is the sufficiency of new declaration testimony and alleged admissions advanced by Petitioner. As an initial matter, we observe that the most reliable evidence on point consists of the disclosures of the asserted prior art references. The new evidence, consisting of declaration testimony and alleged admissions, cannot work to change the words of the prior art or establish a disclosure that is not reflected there.

In that regard, Petitioner comes forward with declaration testimony of Dr. El-Ashry, a co-author of McLeskey, which attempts to recast McLeskey’s “treatment failure” as successful. Ex. 1008, 706; Pet. 23–25, 57 (arguing that “fulvestrant worked exactly as intended in McLeskey”) (citing Ex. 1014 ¶¶ 44–49). In Petitioner’s view, the purpose of McLeskey was to

test whether fulvestrant successfully abrogated all estrogen activity, and reliably blocked tumor growth, in certain cell lines. *Id.* at 23–25 (citing Ex. 1014 ¶¶ 38, 39, 45, 50–52). Citing the testimony of Dr. El-Ashry, Petitioner asserts that an ordinary artisan would not have discounted McLeskey's self-proclaimed "treatment failure" (Ex. 1008, 706) solely because those cell lines were resistant to fulvestrant. Pet. 25 (citing Ex. 1014 ¶¶ 50–52).

As Patent Owner points out, however, this testimony relies on one experiment in McLeskey that involved powdered—not oil-based—fulvestrant. Prelim. Resp. 50 (citing Pet. 24; Ex. 1014 ¶ 45, 52; Ex. 1008, 707, Fig. 8; Ex. 2002 ¶¶ 93, 161–162). Accordingly, we agree with Patent Owner that this new testimony does not address the Board's question of *in vivo* bioavailability, which requires an oil-based fulvestrant formulation. *Id.* (citing Ex. 1011, 28; Ex. 2162, 28; Ex. 2001 ¶¶ 176, 185, 234–243); *see* Ex. 1046, 729 (Examiner's finding that "the unexpected solubility and the bioavailability of using the specific solvent mixture as recited have been demonstrated").

Patent Owner asserts that Petitioner attempts to rewrite the plain disclosure of McLeskey, by raising opinion testimony directed to what the McLeskey authors may have "hoped" to achieve. Prelim. Resp. 18 (citing Pet. 56–57). We agree. As Patent Owner points out, the testimony of Dr. El-Ashry "reverses McLeskey's conclusion of 'treatment failure' . . . and instead claims it was a 'successful treatment.'" *Id.* at 5. We accord little weight to the testimony of Dr. El-Ashry, which was executed nearly two decades after McLeskey was published, because it runs counter to the

statement of McLeskey within its four corners—"treatment failure," which was reported at or near the time of the experiments. Ex. 1008, 706.

The information presented in the Petition does not show sufficiently that a person of ordinary skill in the art reasonably would have predicted, from the combined disclosures of the asserted prior art references, that the claimed formulation would effectively treat hormone-dependent disease when administered via intramuscular injection. *See* Ex. 1008, 698, 700–701, 706, Fig. 1 (McLeskey, the only reference that discloses the claimed formulation, disclosing no efficacy or pharmacokinetics data from which an ordinary artisan could predict that the formulation would effectively treat hormone-dependent disease when administered via intramuscular injection); Prelim. Resp. 34–35 (citing Ex. 2002 ¶¶ 95–97, 163; Ex. 2001 ¶¶ 55, 60, 68–74, 242; Ex. 2003 ¶¶ 89–90, 118–119, 133–135, 145).

McLeskey discloses no data related to the ability of any formulation to deliver fulvestrant to the blood following intramuscular injection. *See generally* Ex. 1008; Prelim. Resp. 33–34 (and evidence cited therein). At best, McLeskey shows that weekly subcutaneous injections of an undisclosed fulvestrant formulation resulted in changes to mouse uterine tissue —thereby suggesting at least some level of drug in the blood following subcutaneous injections. Ex. 1008, 702. McLeskey, however, does not identify the formulation that resulted in changed mouse uterine tissue, and does not report any data on fulvestrant blood plasma levels or pharmacokinetic data. *Id*.

Petitioner makes no attempt to address five background references, cited in the Mylan Decision, which we previously relied upon in determining "that the intramuscular and subcutaneous administration of a drug to the

same animal or human may produce very different plasma level curves, and therefore very different pharmacologic effects." *See* Ex. 1011, 30. As it did in the Mylan IPR, Patent Owner, by contrast, comes forward with abundant and persuasive evidence on that point. Prelim. Resp. 55–56 (citing Ex. 1019 ¶¶ 43–54; Ex. 2001 ¶¶ 226–233).

Petitioner suggests that Howell provides the data that we previously found lacking in McLeskey. Pet. 55, 57–58. But the Petition does not identify evidence sufficient to show how or why one would have extrapolated Howell's fulvestrant-in-castor oil results to a formulation (such as that disclosed in McLeskey) that includes ethanol, benzyl alcohol, and benzyl benzoate. *Id*. Howell cautions against extrapolation, warning that any positive responses may have been an artifact of stopping tamoxifen treatment. Prelim. Resp. 23 (citing Ex. 1007, 7; Ex. 2002 ¶¶ 69, 89, 108).

The Petition argues that "Howell expressly discloses the claimed therapeutically significant blood plasma levels" of fulvestrant. Pet. 31. On the contrary, Howell discloses that "a direct pharmacokinetic-pharmacodymanic link [was] not proven with the few patients studied to date" and, further, reports that "[t]here were no significant differences in drug kinetics between responders and non-responders." Prelim. Resp. 27 (quoting Ex. 1007, 4, 6). Howell, moreover, discloses that, "[a]t the dose used [250 mg], there was accumulation of the drug over time." Ex. 1007, 306. Reasonably interpreting Howell as suggesting that the 250 mg dose may be too high, Patent Owner notes that three subsequent clinical trials, including those conducted by Howell, used lower [125 mg or 50 mg] doses. *See* Prelim. Resp. 27–28 (citing Ex. 2002 ¶¶ 81-83, 118, 133; Exs. 2028–2030).

Other evidence advanced by Patent Owner shows that higher dosing was not thought to correspond to an increase in clinical benefit and could, in fact, increase unwanted off target effects. Prelim. Resp. 25–26 (citing Ex. 2002 ¶¶ 119–33; Ex, 2010, 4; Ex. 2085, 3; Ex. 2111, 1; Ex. 2140, 9; Ex, 2142, 3–5; Ex. 2143, 2; Ex. 2144, 1; Ex. 2147, 1; Ex. 2150, 1; Ex. 2151, 1). On this record, the evidence supports Patent Owner's contention that the higher dosing necessary to achieve the therapeutically significant blood plasma limitations of the challenged claims represented "a break in philosophy from conventional endocrine therapies" that was not suggested by Howell. *Id*. at 25 (citing Ex. 2002 ¶¶ 81–88, 115–135).

The Petition further relies on alleged "admissions" to show that the prior art would have led an ordinary artisan to reasonably expect that the claimed formulation would successfully treat hormone-dependent disease when administered by intramuscular injection. For example, the Petition argues that the Gellert § 1.132 Declaration includes "admissions" suggesting that success was predictable (Pet. 16–17, 34–43), but none of the formulations discussed by Dr. Gellert included all four claimed excipients—much less all four in the claimed weight-to-volume ratios required by each challenged claim. Prelim. Resp. 29 (citing Ex. 1020 ¶¶ 14–15, 23; Ex. 1001, Table 1; Ex. 2001 ¶¶ 106–121, 155–166).

Petitioner also argues that Patent Owner "admitted" that Howell "utilized the same long-acting castor-oil based formulation" later sold and claimed by Patent Owner. Pet. 20. In support of that proposition, however, Petitioner directs us to a document published in 2003—well after the priority date of the '122 patent. *Id*. (citing Ex. 1044). In an analysis under 35 U.S.C. § 103, the critical inquiry is what the combined disclosures of the prior art

would have suggested to an ordinary artisan at the time of the invention. Howell discloses only "a long-acting formulation contained in a castor oil-based vehicle," without any disclosure or suggestion of any other excipient. Prelim. Resp. 24 (quoting Ex. 1007, 2). We are not persuaded that the document published in 2003 (Ex. 1044) bolsters the disclosure of Howell or otherwise compensates for the lack of disclosure in the combined disclosures of the prior art. Prelim. Resp. 34–35 (citing Ex. 2002 ¶¶ 95–97, 163; Ex. 2001, ¶¶ 55, 60, 68–74, 242; Ex. 2003 ¶¶ 89–90, 118–119, 133–135, 145). We find unpersuasive the Petition's use of extrinsic evidence in an attempt to rewrite the disclosure of Howell.

Other prior art references do not fill that gap. McLeskey concludes that its fulvestrant formulations were "treatment failure[s]." *Id*. at 35 (citing Ex. 1008, 4–6, 10). And like Howell, O'Regan (which is not "new" but was raised in the Mylan IPR (*see* Mylan IPR, Paper 2, 40)) includes no relevant data, no information about excipients, and no disclosure from which one would have reasonably predicted that the claimed formulation would successfully treat hormone-dependent disease when administered via intramuscular injection. Ex. 1009, 1553.

iv. New Treatment of Evidence in the Sawchuk § 1.132 Declaration

The third asserted "difference" between the instant Petition and Mylan's unsuccessful prior petition relates to the Petition's treatment of the evidence contained in the Sawchuk § 1.132 Declaration. Pet. 11; *see* Ex. 1019 (the Sawchuk § 1.132 Declaration). The Gellert § 1.132 Declaration (Ex. 1020) was submitted to the Examiner as an attachment to the Sawchuk § 1.132 Declaration. The combined evidence of those declarations previously was considered during related patent prosecution and

during the Mylan IPR. Twice the Office determined that this evidence was sufficient to show that the combination of excipients required by the challenged claims was nonobvious at the time of the invention. Prelim. Resp. 9–11 (citing Ex. 1042, 295–300, 313, 334–383, 717–719 (related prosecution history); Ex. 1011, 29–30 (Mylan Decision). Accordingly, this third "difference" asserted in the Petition relates not to a gap in the record, but to an effort to undercut evidence that the Office repeatedly has found persuasive in related proceedings. Pet. 11.

Relying on witness testimony, Petitioner contends that the Sawchuk § 1.132 Declaration is inconsistent with the Gellert § 1.132 Declaration. *Id*. at 11, 16–18, 56, 57. Patent Owner responds with a detailed explanation of why the Sawchuk § 1.132 Declaration and the Gellert § 1.132 Declaration are consistent with each other, and a showing that the claimed formulation of fulvestrant would have been unobvious at the time of the invention. Prelim. Resp. 9–18, 37–42 (and citations therein).

We are not persuaded that this raises a genuine issue of material fact that justifies institution of trial. *Compare* Pet. 11, 16–18, 56, 57 *with* Prelim. Resp. 9–18, 37–40. The Gellert § 1.132 Declaration "is hardly 'new', it was submitted during prosecution, and both cited and attached to the Sawchuk declaration—which was itself cited in Mylan's Petition." Prelim. Resp. 39–40. And the Petition raises old arguments in connection with the Sawchuk § 1.132 Declaration. For example, the Petition argues that results based on subcutaneous injection of one formulation of fulvestrant would have been predictive of results obtained for the intramuscular injection of a different formulation. Pet. 57–58. Patent Owner, by contrast, directs us to persuasive evidence that, even when the same formulation is compared via

subcutaneous versus intramuscular injection, the release profiles and tolerability results would have been unpredictable. Prelim. Resp. 29–30 (citing Ex. 2001 ¶¶ 227–233; Ex. 2121, 1; Ex. 1111, 2).

We are not persuaded that any results reported in Howell or O'Regan, relating to the intramuscular injection of unidentified fulvestrant formulations, would have prompted an ordinary artisan to apply McLeskey's subcutaneous formulation (including the claimed excipients) as an intramuscular injection with a reasonable expectation of success in treating hormone-dependent disease. Only McLeskey suggests the claimed combination of excipients, and McLeskey reports "treatment failure" in subcutaneous experiments. Ex. 1008, 706. Notwithstanding Petitioner's argument that therapeutically significant "serum concentrations" of fulvestrant were an inherent property of McLeskey's formulation, the Petition fails to show sufficiently that the combined disclosures of the prior art would have prompted an ordinary artisan to administer McLeskey's formulation by intramuscular injection to treat hormone-dependent disease with a reasonable expectation of success. Pet. 57–58 (quoting *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012)).

The Petitioner's new treatment of the Sawchuk § 1.132 Declaration does little to undercut the persuasiveness of that document. Pet. 11, 16–18, 56–59. As we did in the Mylan Decision, we find that the Sawchuk § 1.132 Declaration persuasively demonstrates that "one of ordinary skill in the art would not have had a reasonable expectation that the McLeskey castor oil composition would have been effective when given as an intramuscular injection." Ex. 1011, 29–30; Prelim. Resp. 11–12 (citing Ex. 1019 ¶¶ 37–

41, 57–68 (Sawchuk § 1.132 Declaration); Ex. 2001 ¶¶ 120–121, 244–250 (Illum Declaration); Ex. 2003 ¶¶ 60–75 (additional Sawchuk declaration)).

Patent Owner, by contrast, comes forward with new evidence that bolsters our prior finding in the Mylan Decision (Ex. 1011, 27) that it would have been understood at the time of the invention "that small changes in excipients could markedly affect a formulation's properties in muscle." Prelim. Resp. 33 (citing Ex. 2001 ¶¶ 87–94, 155, 177–180 (Illum Declaration)). Unlike Petitioner's new evidence, Patent Owner's new evidence is consistent with the disclosure of the '122 patent, which reports that other formulations of fulvestrant, when administered via intramuscular injection, showed "extensive local tissue irritation at the injection site as well as a poor release profile" that "appeared to be determined by the extent of inflammation/irritation present at the injection site." Ex. 1001, 8:38–44.

Accordingly, as in the Mylan IPR, we are persuaded, by paragraph 43 of the Sawchuk § 1.132 Declaration, that "[t]here is abundant evidence in the scientific literature that the intramuscular and subcutaneous administration of a drug to the same animal or human may produce very different plasma level curves, and therefore very different pharmacological effects" (other citations omitted). Ex. 1011, 30. As we did in the Mylan IPR, we find that the selection and concentration of excipients "can have significant and unpredictable effects on the pharmacokinetics, efficacy, and side effects (including post-administration precipitation reactions) when [fulvestrant is] administered intramuscularly." *Id.* at 27. The record in this case persuades us anew that solubility and blood plasma levels could not reasonably be predicted from a list of ingredients, and experimentation would have been required to determine the appropriate concentrations of

potential solvents useful to solubilize fulvestrant in an effective treatment for hormone-dependent disease when administered via intramuscular injection. Prelim. Resp. 11–12 (citing Ex. 1020 ¶¶ 16, 22–24; Ex. 1019 ¶¶ 57–68).

Petitioner does not show adequately that its treatment of the Sawchuk § 1.132 Declaration justifies a result different from that obtained in the Mylan IPR. Like Mylan, Petitioner argues that a formulation of fulvestrant with benzyl benzoate in castor oil "could" have been developed at the time of the invention, but fails to show adequately that an ordinary artisan reasonably would have expected the physiologic effects of the claimed formulation when administered to human patients by intramuscular injection. Pet. 42. As we stated in our Mylan decision,

> [w]hile one of ordinary skill in the art *could* have combined fulvestrant with benzyl alcohol, benzyl benzoate, ethanol, and castor oil in the amounts claimed, Petitioner has provided insufficient evidence that one of ordinary skill in the art would have reasonably expected the physiologic effects of the claimed combination upon intramuscular injection to human patients.

Ex. 1011, 28 (emphasis in original).

Accordingly, we find that the Petition's new treatment of the Sawchuk § 1.132 Declaration is insufficient to show that Petitioner is reasonably likely to prevail at trial on any challenged claim. Pet. 11.

v. Other Deficiencies Identified in the Mylan Decision

Given the lack of persuasiveness of the first three identified "differences" between the instant Petition and the Mylan petition, we need not address Petitioner's further attempts to cure other deficiencies in the record of the Mylan IPR. In this section, for completeness, we focus on the Petition's new emphasis on the O'Regan reference—which was cited in

Mylan's petition, but not in the Mylan Decision—and, in particular, whether Petitioner shows sufficiently that O'Regan cures the deficiencies in the combined disclosures of Howell and McLeskey. Pet. 9, 27, 33, 61–65.

As Patent Owner points out, in the Mylan IPR, O'Regan was not asserted in the grounds, but was raised as background evidence, reflecting the state of the art at the time of the invention. Prelim. Resp. 4; Mylan IPR, Paper 2, 40. O'Regan was advanced in the Mylan IPR for the exact same proposition as in this proceeding; namely, that fulvestrant "inhibits tamoxifen-stimulated breast cancer growth in mice" and that "[c]linically, it must be given by depot intramuscular injection because of low oral potency." Mylan IPR, Paper 2, 40 (citing Mylan IPR, Ex. 1013, 1–2); *compare* Pet. 26, 32 (citing Ex. 1009, 2).

Petitioner's new emphasis on O'Regan does not cure the deficiencies identified above in the disclosures of Howell and McLeskey. Petitioner does not direct us to O'Regan for any information regarding excipients in the fulvestrant formulation. Pet. 27, 33 (citing Ex. 1009, 2). Again, as we previously found in the Mylan Decision (Ex. 1011, 27), and based on the record developed in the instant proceeding, we find that even small changes in excipients would have been understood to markedly affect a formulation's properties in muscle. Prelim. Resp. 33 (citing Ex. 1033, 3; Ex. 2001 ¶¶ 87–94). Different fulvestrant formulations would have been understood to result in different plasma profiles and, as stated in the Specification of the '122 patent, other fulvestrant formulations showed extensive tissue irritation. *Id*. (quoting Ex. 1001, 8:42–44 ("[t]he release profile appeared to be determined by the extent of inflammation/irritation present at the injection site")).

In sum, on this record, Petitioner fails to show sufficiently that the subject matter of any challenged claim would have been obvious over the combined disclosures of Howell, McLeskey, and O'Regan. Accordingly, we deny the Petition.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has not shown there is a reasonable likelihood that it would prevail in proving the unpatentability of claims 1, 2, 5, and 9 of the '122 Patent.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner's request for *inter partes* review of claims 1, 2, 5, and 9 of the '122 Patent is denied and no *inter partes* review is instituted.

PETITIONER:

Imron T. Aly
Jason G. Harp
SCHIFF HARDIN LLP
ialy@schiffhardin.com
jharp@schiffhardin.com

PATENT OWNER:

Filko Prugo
Caitlin Hogan
Marc Pensabene
Carolyn Wall
O'MELVENY & MYERS LLP
fprugo@omm.com
chogan@omm.com
mpensabene@omm.com
cwall@omm.com