UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INNOPHARMA LICENSING, LLC,
Petitioner

v.

ASTRAZENECA AB,
Patent Owner

Case IPR2017-00900
Patent No. 8,329,680

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,329,680 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *ET SEQ.*

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Exhibit 1003	Proof of Service in *AstraZeneca Pharms. LP et al. v. InnoPharma, Inc.*, Case No. 1:16-cv-894 (D.N.J.)
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Exhibit 1106	*Remington's Pharmaceutical Sciences* 1538-39, 1545-50, 1686-88 (18th ed. 1990)
Exhibit 1107	Roberts, *Investigation of Cosolvent Effects on the Solvation of AOT Reverse Micelles in Supercritical Ethane*, 102 J. PHYS. CHEM. B 9074-80 (1998)
Exhibit 1108	Sawka, *Physiological Consequences of Hypohydration: Exercise Performance and Thermoregulation*, 24 MEDICINE & SCIENCE IN SPORTS & EXERCISE 657-70 (1992)
Exhibit 1109	Simmons, *The Laboratory Mouse: Selection and Management* 127-28 (1970)
Exhibit 1110	Ting, *Solubility of Naproxen in Supercritical Carbon Dioxide with and without Cosolvents*, 32 IND. ENG. CHEM. RES. 1471-81 (1993)
Exhibit 1111	Tse, *Bioavailability of Parenteral Drugs II. Parenteral Doses Other Than Intravenous and Intramuscular Routes*, 34 J. PARENTERAL DRUG ASSOCIATION 484-95 (1980)
Exhibit 1112	U.S. Patent No. 4,212,863

Exhibit 1113	USP 23 – NF 18, The United States Pharmacopeia – The National Formulary 13-14 (1995)

TABLE OF ABBREVIATIONS

7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)- triene-3,17β-diol .....Fulvestrant

Estrogen receptor……ER

Estrogen receptor-positive .....ER+ or ER-positive

Estrogen-receptor downregulators.....ERDs

Hormone-dependent.....HD

ICI 182,780.....Fulvestrant

Intramuscular .....IM

Percent volume in volume.....%v/v

Percent weight in volume.....%w/v

Person of ordinary skill in the art……POSA

Selective estrogen-receptor modulators.....SERMs

Subcutaneous .....SC

U.S. Food and Drug Administration.....FDA

U.S. Patent and Trademark Office.....PTO

Petitioner InnoPharma Licensing, LLC ("Petitioner" or "InnoPharma") requests *inter partes* review of claims 1-3 and 6 ("the challenged claims") of U.S. Patent No. 8,329,680 ("the '680 patent") (Ex. 1001) pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100.

I. INTRODUCTION

The challenged claims should never have issued. They relate to a specific method for treating breast cancer with fulvestrant—a compound for which all patent protection has expired. And they do so in a manner that was previously touted for its efficacy. Indeed, the Board already found that two prior art references—McLeskey and Howell—"disclose[] each individual element of the claimed invention" when it considered a petition for *inter partes* review of the '680 patent ("the Mylan '680 IPR"). Ex. 1011 at 0023. The sole question was whether Mylan had "adequately demonstrated" a motivation to combine the references or a reasonable expectation of success from that combination. *Id.* And the Board concluded that Mylan had not.

This Petition fills the gaps the Board identified and removes any doubt that there is a reasonable likelihood that the challenged claims are not patentable. It does so using new grounds, evidence, theories, and arguments that the Board has never considered. The Board should, therefore, institute this proceeding and cancel the claims that are stifling generic competition for breast cancer treatment.

The claimed treatment method requires: (1) a 50 mg/ml concentration of fulvestrant, (2) a formulation with four excipients—castor oil, ethanol, benzyl alcohol, and benzyl benzoate, (3) an IM injection, and (4) certain specified amounts of the drug in the body at least two weeks after injection. This treatment method was nothing new. Howell already reported "excellent" results from IM injections of a 50 mg/ml concentration of fulvestrant in a castor oil formulation that achieved the claimed blood concentrations for at least four weeks. And there was only one castor oil formulation in the prior art that had pharmaceutically acceptable excipients at levels previously approved by FDA and the ability to solubilize fulvestrant at the target 50 mg/ml concentration. That formulation was disclosed in McLeskey—and it is the exact same formulation recited in the challenged claims. A person motivated to achieve the promising results reported in Howell would necessarily use the McLeskey formulation.

With all the elements disclosed in on-point references that directly tie together, AstraZeneca attempted to rewrite history to introduce complexity that did not then exist. It was able to raise enough questions to avoid institution in the Mylan '680 IPR. It should not be so lucky this time. The Board identified the specific failures of proof that led to its decision—and they have been remedied here with new evidence that even includes a declaration from one of McLeskey's authors.

This time around, AstraZeneca's arguments should be rejected. They depend on revisionist history contradicted by contemporaneous evidence, including statements from AstraZeneca's own experts. For example, AstraZeneca now claims that the success of fulvestrant was unpredictable—but then, its experts described fulvestrant as a "very exciting drug" that was "a prime candidate" for further study as early as 1991.

AstraZeneca's arguments also rely on an ever-shifting story of what a POSA would do. One of its experts, for example, argues that a POSA would not have preferred a castor oil formulation, when another concedes that the only formulation a POSA would consider would be castor oil-based. The arguments also depend on theories that have been rejected by the Federal Circuit. AstraZeneca argues that its claims are saved because there was no conclusive proof of efficacy—even though the Federal Circuit has held that "conclusive proof of efficacy is not necessary to show obviousness." *Hoffmann-La Roche Inc. v. Apotex Inc*., 748 F.3d 1326, 1331 (Fed. Cir. 2014). Here, where the most fulsome fulvestrant study had shown positive results using the claimed method, there was a reasonable expectation of success.

The Board, therefore, should institute this proceeding and cancel the challenged claims as obvious.

II. NOTICES, STATEMENTS AND PAYMENT OF FEES

A. Real Party In Interest Under 37 C.F.R. § 42.8(b)(1)

InnoPharma Licensing, LLC, InnoPharma, Inc., and Pfizer Inc. are the real parties in interest. Additionally, out of an abundance of caution, Petitioner identifies each of Pfizer Australia Pty Ltd., Hospira Pty Ltd., and Hospira, Inc. as real parties in interest solely for this Petition and solely to the extent that Patent Owner contends that any of these separate legal entities should be named as real parties in interest in this IPR. Petitioner does not believe that Pfizer Australia Pty Ltd., Hospira Pty Ltd., and Hospira, Inc. are real parties in interest, but identifies them here as real parties in interest to avoid the potential expenditure of resources to resolve such a challenge. No unnamed entity is funding, controlling, or otherwise has an opportunity to direct or control this Petition or Petitioner's participation in any resulting IPR.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

AstraZeneca has asserted the '680 patent in the litigations listed below:

- *AstraZeneca Pharms. LP v. Agila Specialties, Inc.,* No. 1:15-cv-06039-RMB-KMW (D.N.J.) ("the Consolidated Fulvestrant Action");
- *AstraZeneca Pharms. LP v. InnoPharma, Inc.*, No. 1:16-cv-894-RMB-KMW (D.N.J.) ("the First InnoPharma Action");
- *AstraZeneca Pharms. LP v. InnoPharma Licensing LLC*, No. 1:16-cv-1962-

RMB-KMW (D.N.J.) (part of the Consolidated Fulvestrant Action);

- *AstraZeneca Pharms. LP v. Sandoz Inc.*, No. 1:14-cv-03547-RMB-KMW (D.N.J.);
- *AstraZeneca Pharms. LP v. Sagent Pharms., Inc.*, No. 1:14-cv-05539-RMB-KMW (D.N.J.) and 1:14-cv-7358-EEC (N.D. Ill.);
- *AstraZeneca Pharms. LP v. Glenmark Pharms. Inc., USA*, No. 1:15-cv-615 (D.N.J.);
- *AstraZeneca Pharms. LP v. Teva Pharms. USA, Inc*., No. 1:15-cv-7889-RMB-KMW (D.N.J.)
- *AstraZeneca Pharms. LP v. Mylan Pharms. Inc.*, No. 1:15-cv-7009-RMB-KMW (D.N.J.);
- *AstraZeneca Pharms. LP v. Dr. Reddy's Laboratories, Inc.*, No. 1:17-cv-926-RMB-KMW (D.N.J.);
- *AstraZeneca Pharms. LP v. Mylan Institutional LLC*, No. 1:16-cv-4612-RMB-KMW (D.N.J.).

Petitioner's parent company, InnoPharma, Inc., was a party to the First InnoPharma Action, and was served with a Complaint no earlier than February 26, 2016. *See* Exs. 1002-1003. That Complaint was dismissed without prejudice on April 21, 2016. Ex. 1004. InnoPharma Licensing, LLC is a party to the Consolidated Fulvestrant Action, and was first served with a Complaint on April 7,

2016. Ex. 1005.

On June 29, 2016, Mylan filed the Mylan '680 IPR. The Board denied institution, although it concluded that "each individual element of the claimed invention" was taught by the cited references. Ex. 1011 at 0023. As explained below, *see* Section IV, the grounds for unpatentability in this Petition are different from those presented in the Mylan '680 IPR and rely on different references, evidence, and claim constructions.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

InnoPharma designates lead and back-up counsel as noted below. Powers of attorney pursuant to 37 C.F.R. § 42.10(b) accompany this Petition.

Lead Counsel	Backup Counsel
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D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Please address all correspondence to counsel at the addresses above. Petitioner consents to electronic service by email at: mpacella@wileyrein.com and khessler@wileyrein.com.

E. Grounds for Standing Under 37 C.F.R. § 42.104(a)

Pursuant to 37 C.F.R. § 42.104(a), InnoPharma certifies that the '680 patent

is available for *inter partes* review, and that Petitioner is not barred or estopped from requesting *inter partes* review based on the grounds herein.

F. Fees Under 37 C.F.R. § 42.103

Petitioner concurrently submits fees of $23,000. If more fees are necessary to accord this Petition a filing date, authorization is granted to charge the same to Deposit Account No. 50-1129.

III. IDENTIFICATION OF CHALLENGE UNDER 37 C.F.R. § 42.104(b)

InnoPharma requests cancellation of the challenged claims as unpatentable under 35 U.S.C. § 103. This Petition, supported by the accompanying Declarations of Dr. Diane Burgess (Ex. 1012), Dr. Richard Bergstrom (Ex. 1013), Dr. Dorraya El-Ashry (Ex. 1014), and Dr. Adrian Harris (Ex. 1015), demonstrates that there is a reasonable likelihood that the challenged claims are not patentable.

Pursuant to 37 C.F.R. §§ 42.22(a) and 42.104(b)(1)-(2), this challenge is based on the following references, all of which are prior art under 35 U.S.C. § 102(b):

1. **Howell (Exhibit 1007)**, *Pharmacokinetics, pharmacological and anti-tumor effects of the Specific anti-oestrogen ICI 182780 in women with advanced breast cancer*, BRITISH J. OF CANCER, 74, pp. 300-308, published in 1996—about 4 years before the January 2000 priority date of the '680 patent. Howell is cited on the face of the '680 patent but was not used during prosecution to substantively reject

the claims.

2. **McLeskey (Exhibit 1008)**, *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, published in 1998.

3. **O'Regan (Exhibit 1009)**, *Effects of the Antiestrogens Tamoxifen, Toremifene, and ICI 182,780 on Endometrial Cancer Growth*, 90 J. NAT'L CANCER INST. No. 20 1552–1558, published in 1998. O'Regan was not cited during prosecution of the '680 patent.

4. **DeFriend (Exhibit 1038)**, *Investigation of a New Pure Antiestrogen (ICI 182780) in Women with Primary Breast Cancer*, 54 CANCER RESEARCH 408–414 (1994), published in 1994.

As explained below, InnoPharma requests that the Board cancel the challenged claims based on the following grounds:

Ground 1: Claims 1, 2, 3, and 6 are obvious over Howell;

Ground 2: Claims 1, 2, 3, and 6 are obvious over Howell and McLeskey;

Ground 3: Claims 1, 2, 3, and 6 are obvious over Howell, McLeskey, and O'Regan; and

Ground 4: Claims 2 and 6 are obvious over Howell, McLeskey, O'Regan, and DeFriend.

IV. INNOPHARMA'S GROUNDS OF UNPATENTABILITY ARE DISTINCT FROM THOSE PRESENTED BY MYLAN

This Petition does not duplicate the Mylan IPRs. It relies on three new grounds of unpatentability—Grounds 1, 3, and 4—which are by definition not "the same or substantially the same" as the Mylan grounds. 35 U.S.C. § 325(d). And the fourth ground—Ground 2—is also substantially different, because it is based on new evidence and argument, including the specific evidence that the Board found missing.

Ground 2 seeks cancellation of the claims as obvious over Howell and McLeskey, a combination that the Board found "discloses each individual element of the claimed invention." Ex. 1011 at 0023. The Board nonetheless declined to institute review in the Mylan IPR—but clarified that its decision was the result of specific gaps in the record. In particular, Mylan had not "adequately demonstrated" a motivation to combine the references or a reasonable expectation of success from that combination. *Id.* This Petition cures these gaps.

Four differences highlight the distinctions between this Petition and the Mylan IPRs. *First*, this Petition changes the obviousness analysis by arguing that Howell—and not McLeskey—is the appropriate starting point. Howell closely mirrors the challenged claims and called for a castor oil-based vehicle that a POSA would necessarily have looked to McLeskey to find. As a result, the Board's

concern that Mylan did not "adequately address why one of ordinary skill in the art would have selected McLeskey's castor oil-based formulation as a starting point…" *id.* at 0024, is inapplicable here.

Second, this Petition provides new evidence to answer questions the Board found were not resolved by the Mylan IPRs. For example, the attached Declaration of Dr. El-Ashry—an author of McLeskey and the lead ER expert on the project—corrects misrepresentations of McLeskey made by AstraZeneca that were left unrebutted in the Mylan IPRs. *See* Ex. 1014. Also attached are admissions made by Dr. Paul Gellert, AstraZeneca's formulation scientist, that Mylan did not provide, but that confirm that a POSA would have taken certain routine steps as of the priority date. *See* Ex. 1020.

Third, this Petition, unlike the Mylan IPRs, addresses each point raised by AstraZeneca's expert, Dr. Sawchuk, during prosecution of the '680 patent, *see infra* §§ V(2); IX(B), and so cannot be criticized for "fail[ing] to adequately address the expert testimony and the other evidence cited in the Sawchuk § 1.132 Declaration…. " *See* Ex. 1011 at 0027.

Fourth, this Petition fills every deficiency that the Board identified in the Mylan '680 IPR. Ex. 1011 at 0023. Included are reasons why the claims are obvious despite McLeskey's alleged "treatment failure," *see infra* § VIII(A)(2); Ex. 1012 ¶88; Ex. 1014 ¶¶54-58; McLeskey's supposed lack of efficacy or

pharmacokinetics data, *see infra* § VIII(A)(4), Section (B)(3)(a); Ex. 1012 ¶¶217-20; Ex. 1013 ¶¶177-89; the claimed lack of predictability of formulation components, *see infra* § VIII(B)(3); Ex. 1012 ¶¶204-11, 215-20; Ex. 1013 ¶¶177-89; the purported inability to extrapolate between SC and IM injections, *see infra* § VIII(B)(3)(b), Section IX(A)(2); Ex. 1012 ¶¶212-13; Ex. 1013 ¶¶187-88; Ex. 1015 ¶¶154-56, 195-200; and the ostensibly inadequate expectation of achieving the claimed blood plasma levels over weeks, *see infra* § VIII(B)(3)(a); Ex. 1012 ¶¶217-20; Ex. 1013 ¶¶177-89.

This Petition thus presents new evidence and arguments, and provides at least two new rationales for combining Howell and McLeskey that are supported by Federal Circuit law. It is substantially different from the Mylan IPRs and should be instituted.

V. OVERVIEW OF THE '680 PATENT AND PROSECUTION HISTORY

A. The '680 Patent

The '680 patent relates to a method of treating hormone-dependent breast cancer using a sustained release formulation of fulvestrant, but it does not claim the fulvestrant compound. Ex. 1001 at 12:41–14:21. As the '680 patent concedes, fulvestrant was patented more than a decade before the '680 patent, and is no longer subject to patent protection. *Id.* at 2:31-44.

Fulvestrant belongs to a class of compounds known as steroidal antiestrogens, which work by binding to—or "antagonizing"—ERs found on breast cancer cells. *Id.* at 1:29-37. By antagonizing these receptors, fulvestrant prevents them from being stimulated by estrogen, and thus stops a known trigger of tumor growth. *Id.*

Steroidal antiestrogens have long been known to be efficacious against "many benign and malignant diseases of the breast and reproductive tract." *Id.* at 1:23-28. "The rationale for [their] design and testing" was first described in the 1980s. *Id.* at 1:47-50. Accordingly, there is extensive literature about formulation techniques for steroidal antiestrogens. The '680 patent, for example, states that "there are a number of sustained release steroidal formulations which have been commercialized," including formulations that could achieve an extended release for as long as 8 weeks. *Id.* at 2:54-66.

Many of the prior art formulations include the same excipients recited in the challenged claims—benzyl benzoate, benzyl alcohol, and ethanol. *Id.* at 2:61-64. And the '680 patent itself cites at least six prior art formulations that used castor oil. *Id.* at Table 1. In its words, castor oil had been known to have a "greater solvating ability" for steroidal compounds since at least 1964—nearly forty years before the '680 patent's earliest priority date. *Id.* at 5:48-53.

And more than a decade before that priority date, AstraZeneca's initial

formulations of fulvestrant were published. In 1988, for example, U.S. Patent No. 5,183,814 ("Dukes '814") described a formulation that taught the same concentration of fulvestrant (50 mg/ml) and many of the same excipients (castor oil, benzyl alcohol) recited years later in the challenged claims. *Id.* at 3:63-4:66.

Given this crowded art, AstraZeneca's purported point of novelty in the '680 patent was the supposed "surprising" discovery that adding benzyl benzoate increased the solubility of fulvestrant. *Id.* at 6:8-16. But benzyl benzoate was known in the art to enhance steroid solubility: indeed, each of the commercially available castor oil-based formulations referenced in the '680 patent included benzyl benzoate. Ex. 1001 at Table 1. There was, therefore, nothing "surprising" about benzyl benzoate.

B. The Prosecution History of the '680 Patent

Throughout prosecution, the PTO recognized that numerous aspects of the claims were obvious. Indeed, the PTO rejected the claims twice on obviousness grounds before they finally issued. First, the PTO found that the formulation and excipients were all well within the purview of a POSA:

- "One of ordinary skill in the art ***would have been motivated to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein***

claimed weight percent, with fulvestrant…."[1] Ex. 1042 at 0254;

- "Benzyl benzoate is ***known to be effective*** as solvent for steroidal compounds." *Id.*;
- "[C]ombining…benzyl benzoate, ethanol, castor oil, and benzyl alcohol, together and incorporat[ing] such combination with…fulvestrant, would be ***reasonably expected to be useful in formulating a pharmaceutical composition***." *Id.*;

In response to this first rejection, AstraZeneca cancelled its claims, replaced them with new claims, and tried to explain why the new claims did not suffer from the same flaws. *Id.* at 0279, 0288. Tellingly, AstraZeneca did not dispute the finding that the excipients were well-known. Instead, it argued that the addition of benzyl benzoate to the excipients was surprising because it would have been expected to reduce solubility of fulvestrant, *id.* at 0292-93.

The PTO rejected the claims again, this time finding that it would have been obvious to a POSA "to employ fulvestrant in [McLeskey], in the herein claimed dosing regimen and dosage, for treating hormonal dependent diseases such as breast cancer and postmenopausal symptoms." *Id.* at 0314. The PTO also recognized that many other aspects of claims were obvious:

[1] Unless otherwise noted, all emphases are added.

- "Employing ***Mc[L]eskey's formulation of fulvestrant for intramuscular administration would be seen as obvious*** since administering a relative large volume of fulvestrant (5ml) would not be appropriate for subcutaneous administration." *Id.*
- "[T]he optimization of result effect parameters (e.g., ***dosing regimen***, weight ratio of the actives and the excipients) is ***obvious as being within the skill of the artisan***." *Id.* at 0314-15.
- "[T]he herein claimed serum concentration is ***considered to be an inherent effect of the formulation of fulvestrant***." *Id.* at 0315.

After this second rejection, AstraZeneca submitted declarations from Drs. Ronald Sawchuk and Paul Gellert, which took contradictory positions. *See* Ex. 1019; Ex. 1020. Significantly, it was Dr. Gellert, not Dr. Sawchuk, who had substantial formulation experience and was directly involved in AstraZeneca's formulation of fulvestrant. Ex. 1020 ¶¶1-2. Dr. Gellert's declaration, as a result, provides the far more probative evidence about how a POSA "would likely have approached the task of developing a sustained release suitable for human use for a steroid composition such as fulvestrant in about early 2000." *Id.* ¶3.

The inconsistencies between the declarations are many. For example, Dr. Sawchuk claims that "the *McLeskey* ***castor oil composition*** would have been among the ***least favored compositions***…." Ex. 1019 ¶41. Dr. Gellert instead

concluded "the experienced formulator ***would have selected castor oil as the oil vehicle***…." Ex. 1020 ¶17. Dr. Sawchuk also believed that an oil suspension would have been "among ***the most favored formulations*** to select for further development," Ex. 1019 ¶41, when Dr. Gellert found that "suspensions…were ***not an acceptable option for fulvestrant***," Ex. 1020 ¶13. Dr. Sawchuk believed IM administration was unpredictable, Ex. 1019 ¶49), when Dr. Gellert conceded that a POSA would have targeted IM administration, Ex. 1020 ¶11.

And Dr. Sawchuk admitted that he had "***not performed a search*** for fulvestrant compositions known in the art," Ex. 1019 ¶37, when Dr. Gellert explained that a POSA "***would have conducted a literature review***." Ex. 1020 ¶14. Given these repeated contradictions and Dr. Sawchuk's lack of formulation expertise, Dr. Sawchuk's testimony is entitled to little to no weight. *See Covidien LP v. Ethicon Endo-Surgery, Inc.*, IPR2013-00209, Paper 28 at 11 (June 9, 2014).

The PTO ultimately withdrew its obviousness rejection in light of the Sawchuk Declaration, but it did so without analyzing its contradictions with Dr. Gellert's declaration. Ex. 1042 at 0650. The PTO also did not consider any of the specific Grounds presented in this Petition.

VI. LEVEL OF ORDINARY SKILL IN THE ART

A POSA as of the January 2000 priority date would have an advanced degree in pharmaceutics, pharmacy, chemistry, medicine, or a related field, with at

least three years of experience in analyzing the pharmacokinetics of drug formulations, developing and formulating dosage forms, and/or clinically treating or researching hormone dependent diseases of the breast. Ex. 1012 ¶¶43-44; Ex. 1013 ¶¶63-64; Ex. 1014 ¶¶17-18; Ex. 1015 ¶¶18-19. An individual need not have every qualification enumerated above. A multi-disciplinary team consisting of individuals with different skills and experience could suffice.

VII. CLAIM CONSTRUCTION

A claim subject to *inter partes* review receives the "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b). Throughout this Petition, InnoPharma applies the broadest reasonable construction.

A. "Achieves"

For purposes of this proceeding, "achieves" should be construed to mean that **"the concentration of fulvestrant in a patient's blood plasma is at or above the specified minimum concentration for the specified time period."** Ex. 1011 at 0018; Ex. 1001 at 12:54-64.

B. "Therapeutically Significant"

For purposes of this proceeding, "therapeutically significant" need not be expressly construed, which is consistent with the Board's analysis in the Mylan '680 IPR. Ex. 1001 at 9:24-28; *see* Ex. 1017 at 0033.

C. "Wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ / [8.5 $ngml^{-1}$] for at least four weeks"

For purposes of this proceeding—and consistent with the Board's guidance in the Mylan '680 IPR—these phrases should be interpreted as limitations. Ex. 1017 at 0033-0034.

VIII. SCOPE AND CONTENT OF THE PRIOR ART

A. The Prior Art Discloses All Limitations of the Challenged Claims

1. Howell Closely Matches the Claimed Invention

The Board recognized that Howell tracks the challenged claims. Ex. 1011 at 0021-0022. For good reason: AstraZeneca financially sponsored Howell, and two of its authors were AstraZeneca employees. Ex. 1007 at 0001, 0007. Moreover, AstraZeneca later admitted that Howell—published about 4 years before the '680 patent's priority date—utilized ***the same long-acting castor oil-based formulation that AstraZeneca has claimed***. *See* Ex. 1044 at 0001-0002 (confirming after approval of Faslodex® that Howell utilized the "the current long-acting formulation" in the 1996 study).

Howell thus teaches a castor oil-based vehicle with the ***same*** injection volume (5 ml), the ***same*** fulvestrant concentration (50 mg/ml), the ***same*** route of administration (IM), and the ***same*** sustained release profile as the challenged claims. Ex. 1007 at 0002, 0004 ("ICI 182780 was administered as a long-acting

formulation contained in a castor oil-based vehicle by monthly i.m. injection (5 ml) into the buttock."). In fact, Howell describes the release profile using the language that AstraZeneca now contends is covered by the claims. *Compare id.* at 0006 (concentration could be "***achieved and maintained*** for 1 month…") *with* Ex. 1017 at 0030 ("concentration[s] [were]…***achieved and maintained*** for prolonged periods of time"). A POSA would have arrived at the claimed methods by routine experimentation.

The results from Howell were indisputably promising. Ex. 1015 ¶¶127-32. Howell reported a "***high response rate*** after tamoxifen failure," with 69% patients responding to the treatment. Ex. 1007 at 0005-0007. Howell also reported that "[n]o ***serious drug-related adverse events occurred*** in any of the 19 patients treated with ICI 182780" and that the "long-acting formulation of ICI 182780 used in this study appeared ***well tolerated locally***…." *Id.* at 0004. The results of Howell were so positive that AstraZeneca's own expert witness, Dr. Robertson, touted it as "result[ing] in a ***high response rate*** and a ***long median duration of remission***." Ex. 1043 at 0001. Similarly, another AstraZeneca expert, Dr. Osborne, described Howell's 69% response rates as "***much higher than you would expect from other forms of second-line hormonal therapies***." Ex. 1034 at 0001.

AstraZeneca's attempt to back away from these admissions should be rejected. *First*, AstraZeneca and its expert, Dr. Robertson, attempted to reduce the

study's touted 69% response rate by excluding patients who did not experience a change in tumor size over the course of the study. Ex. 1017 at 0036; Robertson Decl. ¶174. But Dr. Robertson explained why it was so important to include those patients in the response rate when the Howell results were published:

> Dowsett and co-workers point out that use of the no-change category of response to endocrine therapy is uncommon. We showed that if patients had no change of their tumour growth for at least 6 months their final duration of response and overall survival did not differ significantly from that in patients who had a partial remission…. Thus, we feel that it is ***important to recognise the no-change category of response since it is clinically relevant***.

Ex. 1045 at 0002.

Second, AstraZeneca and Dr. Robertson claimed that the consensus was to treat the results of Howell "with care." But Dr. Robertson again had a different view when Howell was published. *Id.* at 0001. He responded to the argument "that the high response rate we reported…should be interpreted with care" by stating that the results instead "suggest that this hypothesis [that fulvestrant may be better than other endocrine therapies] is ***worth pursuing***." *Id.* at 0001-0002.

Third, AstraZeneca asserted that Howell was too "small" of a study to assess whether fulvestrant was efficacious. Ex. 1017 at 0035. But Howell was much

more ambitious, describing the "aims of the study" as "assess[ing] the long-term efficacy and toxicity of the specific anti-oestrogen ICI 182780 in patients with advanced breast cancer…." Ex. 1007 at 0001. Regardless, AstraZeneca fails to explain why a POSA would discount this study because of its size.

Fourth, AstraZeneca dismissed Howell because the patients were "highly selected." Ex. 1017 at 0035-36. But in Howell, "highly selected" meant that the patients had "advanced breast cancer resistant to tamoxifen." Ex. 1007 at 0002. This selection made sense, as the aim of the study was to assess fulvestrant treatment in patients with advanced breast cancer. *Id.* at 0001.

2. McLeskey Discloses the Claimed Formulation and Was Not a "Treatment Failure"

The Board already accepted that "McLeskey discloses the same formulation as recited in the present claims" based on the record in the Mylan '680 IPR. Ex. 1011 at 0023. The Board's conclusion is unsurprising: McLeskey received "preformulated" fulvestrant ***directly from AstraZeneca***. Ex. 1008 at 0002.

With McLeskey directly on-point, AstraZeneca tried to discount it in the Mylan IPRs as being a "treatment failure[]." Ex. 1017 at 0035. It was not. This Petition includes new evidence provided by Dr. El-Ashry—co-author and lead ER expert on the project— explaining that a POSA would understand that fulvestrant performed successfully and as intended in McLeskey. Ex. 1014.

The purpose of McLeskey was to better understand why certain types of ER+ breast cancers were resistant to known ER antagonists such as tamoxifen. *Id.* ¶38. By understanding the mechanism of resistance, clinicians could more effectively treat ***both*** hormone-dependent and hormone-independent breast cancer. *Id.* ¶¶65-66. For example, a patient with hormone-independent cancer will likely be resistant to antiestrogen therapy, thus, a skilled researcher would need to understand both mechanisms to effectively treat such a patient.

Prior to the study, the McLeskey authors had hypothesized that a growth factor known as fibroblast growth factor ("FGF") may be "replacing estrogen as a…stimulus for tumor growth" in these treatment-resistant cancer cells. Ex. 1008 at 0001. To confirm that hypothesis, the McLeskey authors injected "MCF-7"—the most popular human cell line used in breast cancer research—into mice lacking ovaries. *Id.* However, the McLeskey authors modified that cell line to overexpress the FGF thought to be stimulating tumor growth. Ex. 1014 ¶39. This modified cell line is referred as the "FGF-transfected MCF-7 cell line." *Id.* ¶39.

To test whether it was, in fact, FGF and not estrogen that was stimulating tumor growth, the McLeskey authors administered the best-known and efficacious antiestrogens at the time—which included fulvestrant—to "***abrogate all estrogenic activity***" in the FGF-transfected MCF-7 cell line. Ex. 1008 at 0010. As McLeskey acknowledges, fulvestrant was known at the time to be a "pure antiestrogen" that

could successfully inhibit growth. Ex. 1008 at 0004; Figures 4, 5.

Fulvestrant did its job. Ex. 1017 at 0035. Indeed, Figure 8 of McLeskey confirms that fulvestrant was successfully blocking ERs in the FGF-transfected MCF-7 cell line. Ex. 1014 ¶¶ 45, 50, 52. This was known to be the mechanism by which fulvestrant treated hormone-dependent breast cancer. Ex. 1015 ¶¶83, 85. That success allowed the McLeskey authors to reliably conclude that tumor growth was being stimulated by FGF and not by estrogen. *Id.* ¶50.

Therefore, and as Dr. El-Ashry explains, a POSA would not have discounted McLeskey solely because the FGF-transfected MCF-7 cell lines were resistant to fulvestrant. *Id.* ¶¶50-52. As the McLeskey authors concluded, the cell line was resistant because the modifications they introduced caused the ER to be ***entirely bypassed*** in the FGF-mediated tumor growth pathway. *Id.* ¶51. Thus, the outcome in McLeskey was not due to fulvestrant, but rather a consequence of FGF overexpression. *Id.* ¶58.

AstraZeneca's remaining criticisms of McLeskey are equally meritless. *First*, AstraZeneca has claimed that a POSA would conclude that the formulations disclosed in McLeskey would only be administrable to animals because the testing was performed on mice. Ex. 1017 at 0035. But the formulations that AstraZeneca relies on to support its argument—tamoxifen pellets and an oral letrozole gavage—are not the formulation at issue here. Rather, these are formulations of drugs that

are typically administered orally in the clinical setting and necessarily need to be specially formulated for administration to mice.[2] Ex. 1014 ¶¶60-61. A POSA would have understood that the other formulation in McLeskey—the oil-based formulation at issue here—would be appropriate for human use. *Id.* ¶60. Indeed, the formulation was obtained ***preformulated*** from AstraZeneca, a company specializing in human pharmaceuticals. Ex. 1008 at 0002.

Second, AstraZeneca argues that a POSA would have disregarded McLeskey because it focused on hormone-independent breast cancer. Ex. 1017 at 0034, 0053. This argument misunderstands both McLeskey and the nature of breast cancer research and treatment. Ex. 1014 ¶¶65-66. A POSA would have already known that fulvestrant is an effective treatment for hormone dependent breast cancer. Ex. 1015 ¶¶83, 85. The POSA would not discount that evidence based on McLeskey, which utilized fulvestrant in a modified, overexpressed cell line as a control. Ex. 1014 ¶¶39, 50.

Moreover, in order to effectively treat breast cancer, the POSA must

[2] Oral solid dosage forms have to be given to mice in their food and water, which introduces dosing uncertainty and variability. Ex. 1014 ¶¶59-60. Thus, mice typically receive different formulations of oral drugs than those administered to humans to in order to eliminate that variability problem. *Id.* ¶60.

understand ***both*** the hormone-dependent and hormone-independent pathways to select the appropriate treatment and accurately predict patient response. *Id.* ¶¶65-66. A POSA would not have ignored research directed toward one type of cancer particularly in the context of fulvestrant, which was a known second line therapy. Understanding the mechanism of resistance to treatment would have, therefore, been crucial in determining whether treatment by fulvestrant was appropriate. *Id.* ¶¶65-66. The POSA would not discount that evidence based on McLeskey, which utilized fulvestrant in a modified, overexpressed cell line as a control.

3. O'Regan Confirms the Route of Administration

O'Regan was never considered during the prosecution of the '680 patent. To the extent that there was any question concerning the proper route of administration for fulvestrant in humans—despite the fact that Howell used IM administration with success—O'Regan answered it. Indeed, O'Regan disclosed that "[***c***]***linically***, [fulvestrant] ***must be given by depot intramuscular injection*** because of low oral potency." Ex. 1009 at 0002. Importantly, O'Regan drew this conclusion despite the fact that she injected fulvestrant subcutaneously in mice in her study. *Id.*

4. DeFriend Discloses Dose-Dependent Pharmacokinetics

DeFriend was also never considered during the prosecution of the '680 patent. DeFriend teaches that a dose of fulvestrant equivalent to about 500

mg/month is highly effective at inhibiting ER in human patients and showed no toxicity. Ex. 1038 at 0002-5. DeFriend shows that an 18 mg/day (equivalent to 500 mg/month) dose achieves higher serum concentrations and better inhibition of ER than a 6 mg/day dose, demonstrating that the efficacy of fulvestrant is dose dependent. *Id.*

B. AstraZeneca's Attempts to Detract From These Prior Art Teachings Fail

In its preliminary response to the Mylan IPRs, AstraZeneca relied on untenable arguments. In addition to the flawed arguments detailed above, *see* Section VIII(A), AstraZeneca has asserted that: (1) a POSA—despite recognizing that fulvestrant was ***"excellent"*** and ***"much better than tamoxifen"***—would have ignored fulvestrant as a treatment option; (2) absolute proof of efficacy in humans is required; and (3) vague "unpredictability" about fulvestrant precluded its further development. These arguments uniformly fail.

1. AstraZeneca's Purported "Lead Compound" Analysis is Inapplicable

In the Mylan '680 IPR, the Board properly disregarded AstraZeneca's attempt to re-cast fulvestrant as a "tainted" drug that was apparently inferior to "at least 15 other more promising candidates" and would not have served as a starting point for a POSA. Ex. 1017 at 0039-0040. AstraZeneca's argument is contrary to the law and facts.

Legally, the Federal Circuit has rejected AstraZeneca's argument. In *Purdue Pharma*, the patentee argued that a POSA "would not have selected tramadol out of the myriad other possible active ingredients for use in a once-daily formulation." *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 982 (Fed. Cir. 2010). The Court disagreed, finding that the prior art's disclosure of tramadol "as one of fourteen different opioid analgesics" had "render[ed] the selection of tramadol obvious[,] regardless whether or not the patent lists tramadol as a preferred embodiment." *Id.* The Federal Circuit reached the same conclusion in *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989), finding that the fact "[t]hat the '813 patent discloses a multitude of effective combinations does not render any particular formulation less obvious." And the Federal Circuit reached that conclusion even though the prior art expressed a preference for one of the alternatives, which is not present here. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).[3]

[3] *Unigene Laboratories, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1363 (Fed. Cir. 2011), cited by AstraZeneca, is not to the contrary. As this Board recognized, "in *Unigene*, the component alleged to be obvious to substitute 'ha[d] a vague role in even the closest prior art.'" *Ex Parte Eldon Q. Farnes*, Appeal 2015-002600, 2016 WL 5957931, at *4 (P.T.A.B. Oct. 11, 2016) (citation omitted). Here, each

Factually, AstraZeneca's argument fails because it is premised on an assertion that fulvestrant's properties were unknown. Contemporaneous evidence confirms that was not true. Ex. 1015 ¶¶84-101. For example, a 1994 study found that fulvestrant "***produced demonstrable antiestrogenic effects in human breast tumors in vivo***…." Ex. 1038 at 0001. AstraZeneca's expert, Dr. Robertson, then described fulvestrant as "the ***most advanced of a new class of drugs***." Ex. 1075 at 0003. And Dr. Osborne, another AstraZeneca expert, proclaimed in 1997 that fulvestrant was a "***very exciting drug***" that was "***much better than tamoxifen***." Ex. 1034 at 0001. AstraZeneca's attempt to rewrite history should be rejected, especially in light of the promising results from Howell. Ex. 1007 at 0007.

2. AstraZeneca's Efficacy Arguments Are Contrary to Law

AstraZeneca's argument that a POSA would not have considered fulvestrant because of some purported "unproven efficacy" is also at odds with Federal Circuit law. Ex. 1017 at 0018. The Federal Circuit has repeatedly made clear that "***conclusive proof of efficacy is not necessary to show obviousness***. All that is required is a ***reasonable expectation of success***." *Hoffmann-La Roche*, 748 F.3d at 1331; *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1294-95 (Fed. Cir. 2006).

And, in any event, fulvestrant's efficacy was not "unproven." It was known

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component in the formulation had a well-known purpose. Ex. 1012 ¶23.

to be "a ***potent*** and ***specific inhibitor*** of estrogen action and demonstrated ***excellen***t growth-inhibitory effects." Ex. 1031 at 0001. And its efficacy had been demonstrated in two clinical trials. *See* Ex. 1038 at 0001; Ex. 1007 at 0007. Thus, a POSA would have had a reasonable expectation of success in using fulvestrant to treat hormone-dependent breast cancer. Ex. 1015 ¶¶84-101, 190.

3. AstraZeneca's Claims of Unpredictability Are Specious

Finally, AstraZeneca has suggested that: (a) the pharmacokinetic limitations; (b) the route of administration; and (c) the claimed combination of excipients was "unexpected" and "surprising." These arguments are also flawed.

a. The Pharmacokinetic Limitations Are Expressly Disclosed in the Prior Art

Howell expressly discloses the claimed therapeutically significant blood plasma levels. Despite this teaching, AstraZeneca asserts that Howell somehow "teaches away" from these claimed blood levels based on an isolated snippet of Howell taken out of context. Ex. 1017 at 0020. Howell does not "teach away" from the '680 patent for at least four reasons.

First, AstraZeneca argues that Howell teaches away because it speaks of lowering blood levels. But Howell says nothing about lowering blood levels. Instead, Howell hypothesizes lowering the ***dose*** to achieve the ***same*** blood levels. Ex. 1007 at 0006. Howell thus provided motivation to continue to pursue its

teachings. *Id.*

Second, Howell's discussion of lower doses cannot teach away from the '680 patent because dosage is ***not*** a limitation in any challenged claim. Instead, the claims only require achieving and maintaining a plasma concentration of either 2.5 or 8.5 ng/ml, which Howell teaches. It is black letter law that nonobviousness cannot be premised on unclaimed limitations. *See, e.g., Smith & Nephew, Inc. v. Rea*, 721 F.3d 1371, 1377, 1380-81 (Fed. Cir. 2013) (error to find nonobviousness based on a feature not required by the asserted claims).

Third, AstraZeneca cannot show that Howell teaches away by pointing to one isolated snippet divorced from all context. Teaching away instead requires a showing based on the prior art ***as a whole***. *See Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 834 (Fed. Cir. 2015) (rejecting reliance on "isolated prior art disclosures" for teaching away).

Fourth, even if Howell did suggest a way to lower blood levels through lower doses, it would not teach away. Howell states only that a lower dose "***may*** be effective…although further clinical studies are required to confirm." Ex. 1007 at 0006. That does not discourage investigation into the claimed invention, and so does not teach away. *See Galderma*, 737 F.3d at 738.

Finally, AstraZeneca has argued that the claimed invention was unpredictable because a pharmacokinetic-pharmacodynamic link was "not proven"

by Howell. Ex. 1017 at 0036. But the claims do not require any particular pharmacodynamic link. They instead only require—as AstraZeneca's claim construction makes clear—specific fulvestrant blood concentrations. *See Metso Minerals, Inc. v. Powerscreen Int'l Distrib., Ltd.*, 526 F. App'x 988, 996-97 (Fed. Cir. 2013) ("Since there was no requirement of a 'stop' in the '618 patent, whether the prior art taught a 'stop' is irrelevant"), *cert. denied*, 137 S. Ct. 297 (2016).

b. It Was Well-Known That Fulvestrant Was Administered Intramuscularly

AstraZeneca has also claimed that IM administration was unpredictable. But O'Regan taught that "[***c***]***linically***, [fulvestrant] ***must be given by depot intramuscular injection*** because of low oral potency." Ex. 1009 at 0002.

Despite this express disclosure, AstraZeneca posits that a POSA would have pursued at least six routes of administration with "thousands of different excipients," and would have ultimately preferred an oral formulation. Ex. 1017 at 0043. AstraZeneca's argument again seeks to rewrite history.

"[F]ormulation science carries with it a degree of unpredictability," but "'obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art.'" *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) (citation omitted). And here, there was more than a reasonable probability of success in IM administration. The most advanced clinical trial at the

time—Howell—used that ***exact*** route of administration. Ex. 1007 at 0002. It did so, as the authors of Howell acknowledged, because fulvestrant "***was not considered to be bioavailable in an oral form***." Ex. 1041 at 0002; Ex. 1040 at 0004. AstraZeneca's argument, then, casts the already-rejected oral route as the vastly preferred technique. Instead, the far more reasonable expectation of success was with the previously successful IM route.

c. The Claimed Combination of Excipients Were Neither Unexpected Nor Surprising

AstraZeneca lastly suggested that the chosen excipients were somehow "unconventional." Ex. 1017 at 0046. This too fails.

As a threshold matter, AstraZeneca's specification confirms that these excipients were commonly used in commercialized steroidal depot formulations. Ex. 1001 at Table 1 & 2:54-66 ("In the formulations within Table 1 [commercialized steroid depot formulations] a number of different ***oils*** are used to solubilise the compound and ***additional excipients such as benzyl benzoate, benzyl alcohol and ethanol have been used***"). This admission is binding for obviousness purposes. *See PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007).

Consistent with AstraZeneca's admission, Dr. Gellert conceded that a POSA developing a fulvestrant formulation "would have selected castor oil as the oil

vehicle" and that "ethanol and/or benzyl alcohol would have been seen as the ***best co-solvent candidates*** for raising the fulvestrant solubility to the 45 mg/mL target…." Ex. 1020 ¶¶17, 21; *see* Ex. 1046 at 0158 (concluding that "adding an alcohol component to the castor oil ***would be seen as a clear choice to the skilled person***"); *see also* Ex. 1001 at Table 1.

Similarly, for benzyl benzoate, Dr. Gellert admitted that "[a] number of the commercialized formulations that would have been identified in [a] literature review (including the castor oil-based formulations) have a ***substantial benzyl benzoate component***." Ex. 1020 ¶18. Dr. Gellert's statement aligns with the contemporaneous literature, which recognized that benzyl benzoate was used to enhance solubility in steroid formulations. *See, e.g.*, Ex. 1018 at 0027 ("Benzyl benzoate may be used to enhance steroid solubility in oils"). Thus, the excipients used by AstraZeneca were conventional.

AstraZeneca tries to create unpredictability by arguing that the choice and amount of excipients can unpredictably result in side effects in the muscle. Ex. 1017 at 0049. Although the Board briefly considered this argument in the Mylan '680 IPR, Mylan had not adduced any evidence on the issue. Ex. 1011 at 0028. This Petition, in contrast, establishes at least three reasons why AstraZeneca is wrong.

First, AstraZeneca's argument again improperly relies on an unclaimed

feature. *See Aventis Pharma S.A. v. Hospira, Inc.*, 743 F. Supp. 2d 305, 343 (D. Del. 2010), *aff'd*, 675 F.3d 1324 (Fed. Cir. 2012) (finding assertions regarding the possible toxicity unavailing because the asserted claims contain no limitations regarding toxicity). Here, the challenged claims are silent on a side effect profile, and so cannot avoid obviousness on that basis.

Second, the side effects were predictable. As of the priority date of the '680 patent, castor oil, ethanol, benzyl alcohol, and benzyl benzoate had been approved by FDA for IM use in humans at or above the concentrations recited in McLeskey and the challenged claims. Ex. 1012 ¶150. This is significant because, as AstraZeneca's Dr. Gellert acknowledged, "a knowledge of which excipients have been deemed safe by the FDA or are already present in a marketed product provides increased assurance to the formulator that these excipients will probably be safe for their new drug product." Ex. 1020 ¶14. Following this logic, a POSA would reasonably expect that if the excipients were used at or below the previously approved levels, they would not produce adverse events upon IM injection. Ex. 1012 ¶150.

Third, the reference that AstraZeneca relies on—Riffkin—undermines its argument. Riffkin tested its formulations only in rabbits, which it concedes is ***not predictive of muscle damage in humans***. Ex. 1033 at 0004. The claims here are limited to humans—as AstraZeneca has stressed repeatedly—meaning that Riffkin

does not create any "uncertainty" related to muscle damage.

IX. DETAILED EXPLANATION AND SUPPORTING EVIDENCE

The challenged claims are unpatentable for the reasons set forth below.

A. Ground 1: The Challenged Claims Are Obvious Over Howell

As explained below, every limitation of the challenged claims is taught by Howell in view of the knowledge of a POSA.

1. A POSA Would Have Been Motivated to Develop a Formulation to Achieve the Results Reported in Howell

A POSA would have been motivated to develop a fulvestrant formulation that would achieve the positive results reported in Howell. *See supra* § VIII(A)(1); Ex. 1007 at 0005; Ex. 1015 ¶¶127-47. In particular, Howell taught that monthly IM injections of a castor oil-based formulation resulted in a 69% response rate and a "long median duration of remission." *See supra* § VIII(A)(1).

Thus, Howell would have been the logical starting point for any POSA interested in developing a method for treating hormone-dependent breast cancer with fulvestrant. Ex. 1012 ¶85; Ex. 1015 ¶¶127-47. The POSA would have been motivated to develop a castor oil-based formulation that, like Howell, solubilized fulvestrant at a concentration of 50 mg/ml.[4] *See In re ICON Health & Fitness*, 496

[4] It was necessary to achieve this minimum concentration because it results in the injection of 5 ml of solution—the maximum that can be injected intramuscularly.

F.3d 1374, 1380 (Fed. Cir. 2007) ("Any need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner claimed").

The way to develop that formulation was readily available to a POSA, as reflected in Dr. Gellert's declaration. *See Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013). There, Dr. Gellert opined that the skilled formulator would have tried "to formulate an intramuscular (IM) injection that would provide for the satisfactory sustained release of fulvestrant…and would have a target fulvestrant content of at least 45 mg/mL." Ex. 1020 ¶11.

To achieve that target solubility, the formulator would have performed a solubility screen and "would have selected castor oil as the oil vehicle because of the higher solubility of fulvestrant in castor oil relative to the other oils tested." *Id.* ¶17. According to Dr. Gellert, a POSA would have also recognized "ethanol and/or benzyl alcohol…as the best co-solvent candidates for raising the fulvestrant solubility to the 45 mg/mL target." *Id.* ¶21. AstraZeneca has conceded the same. *See* Ex. 1046 at 0156, 0158. Thus, the only excipient that AstraZeneca contends is novel is benzyl benzoate. Ex. 1020 ¶25.

But any such claim is undermined by the routine solubility screen described

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See Ex. 1012 ¶175; Ex. 1020 ¶11.

by Dr. Gellert. *Id.* ¶16. Such a routine screen would confirm that castor oil, benzyl alcohol, and ethanol could not solubilize fulvestrant at the target 50 mg/ml concentration. *See* Ex. 1020 at 0016. Thus, a POSA would have been motivated to add another co-solvent to the formulation.

Benzyl benzoate would have been the logical choice. As AstraZeneca's Dr. Gellert noted, "a number of the commercialized formulations…[that] would have been identified in [a] literature review…have a substantial benzyl benzoate component." Ex. 1020 ¶18. In fact, ***every castor oil-based formulation that Dr. Gellert identifies contains benzyl benzoate***. *Id.* ¶18; *see* Ex. 1012 ¶114. Thus, AstraZeneca's "surprising" discovery is again contradicted by its own admissions.

2. A POSA Would Have A Reasonable Expectation of Success in Developing a Formulation to Achieve the Howell Results.

AstraZeneca's arguments concerning reasonable expectation of success fail. As an initial matter, a POSA would recognize that co-solvents may operate synergistically, with each solvent helping to solubilize a different part of the molecule. *Id.* ¶72. Thus, a POSA would have reasonable expectation of success in combining benzyl benzoate (known for its ability to solubilize steroids in castor oil) with the other excipients that AstraZeneca concedes are obvious. *Id.* ¶163.

Moreover, the amounts of the claimed excipients are within the ranges disclosed in the art. In particular, FDA's Inactive Ingredient Guide ("IIG")

provides formulators with a list of excipients (by route of administration and concentration) approved for use in marketed formulations. As Dr. Gellert explains, this information "provides increased assurance to the formulator that these excipients will probably be safe for their new drug product." Ex. 1020 ¶14.

The IIG confirms that the recited excipient concentrations are presumptively obvious. Indeed, the IIG shows that ethanol had been used up to 11%, benzyl alcohol had been used up to 15%, and benzyl benzoate had been used up to 46% for IM injections. Ex. 1012 ¶127; Ex. 1080 at 0008, 0014-15. A POSA would be motivated to stay within those ranges because they had already been deemed safe for IM administration. Ex. 1012 ¶150. Thus, the claims are presumptively obvious. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness").

Additionally, during prosecution, the Examiner concluded that "the optimization of parameters such as the ***amount of excipients***…is obvious as being within the skill of the artisan, absent evidence to the contrary." Ex. 1046 at 0163. AstraZeneca never disputed this conclusion, which aligns with Federal Circuit law. *See In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.").

AstraZeneca's attempts to distance itself from these findings are meritless. *First*, AstraZeneca suggests that a formulation can never be obvious until it is tested *in vivo*. Ex. 1017 at 0046-49. But "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

Second, AstraZeneca and Dr. Gellert assert that a POSA would have been motivated to use ***less*** benzyl alcohol. Ex. 1020 ¶23. But benzyl alcohol was frequently used at a 10% concentration for its "anesthetic properties." Ex. 1079 at 0006. Such anesthetic properties would have been desirable here given the large 5 ml injection volume. Ex. 1012 ¶126. Thus, a POSA would have a reasonable expectation of success.

3. Howell Discloses Fulvestrant Concentrations of at Least 8.5 ng/ml at Day 28

Contrary to AstraZeneca's claims, Howell teaches that fulvestrant concentrations of at least 8.5 ng/ml are achieved four weeks after injection. In particular, Figure 2 shows mean serum[5] concentrations at different times, with bars indicating the variability of individual patient data around the mean. Ex. 1007 at

[5] A POSA would expect that plasma and serum concentrations for fulvestrant would be the same. Ex. 1013 ¶87 & n.3.

Fig. 2. While Howell does not disclose whether these lines represent the standard deviation, standard error, or range of measurements, the patient data confirms that the lines do not represent the range of measurements. Ex. 1013 ¶109.

Assuming the bars represent the standard error of the mean, day 0 of month 6 (which corresponds to day 28 of month 5) shows a mean of approximately 6.5 ng/ml with a standard error of 1 ng/ml.[6] Exhibit 1015 ¶230.

[6] Day 28 of each month will be the C_{min}, or lowest serum concentration, for each patient because the injections were given every 28 days.

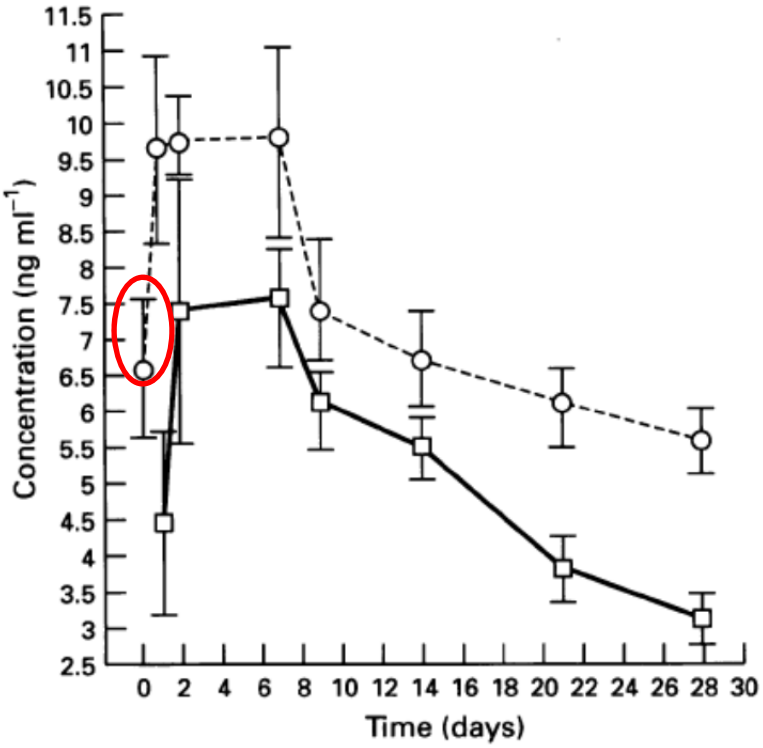

Figure 2 Mean serum concentrations of ICI 182780 during the first and sixth months of treatment. ——, Profile at entry; - - -, profile month 6.

This conservatively implies a standard deviation of 3.32. Ex. 1013 ¶114. Thus, 8.5 ng/ml falls at 0.86 standard deviation above the mean. *Id.* ¶115. Assuming the Howell sample follows a normal distribution, 19.49% of the sample, or 2.14 patients, would have maintained serum concentrations of at least 8.5 ng/ml for four weeks after the month 5 injection. *Id.* ¶¶116-17; *see Hewlett-Packard Co. v. Mustek Sys., Inc.*, 340 F.3d 1314, 1326 (Fed. Cir. 2003) (prior art that "sometimes, but not always, embodies a claimed method nonetheless teaches that aspect of the invention.").

If the POSA assumed that the bars instead represent the standard deviation,

Howell still discloses that some patients in the overall patient population will achieve serum concentrations of at least 8.5 ng/ml for at least four weeks after an injection. Assuming that the bars represent standard deviations, day 0 of month 6 (which corresponds to day 28 of month 5) shows a mean of approximately 6.5 ng/ml with a standard deviation of 1 ng/ml.[7] *Id.* ¶ 112.

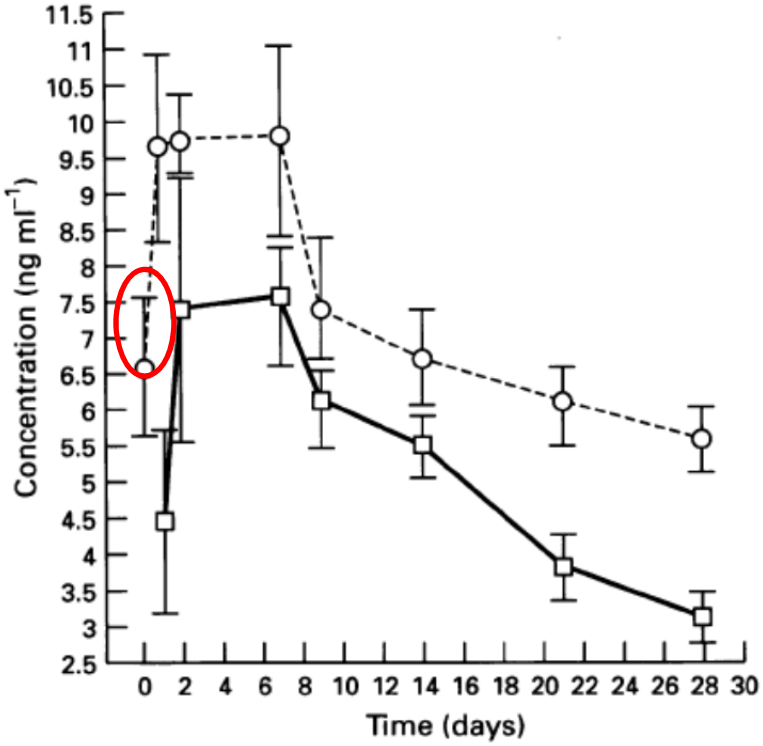

Figure 2 Mean serum concentrations of ICI 182780 during the first and sixth months of treatment. ——, Profile at entry; - - -, profile month 6.

[7] Focusing on month five alone is appropriate because the claims only require that a patient achieve and maintain the specified plasma concentration for one month—not for any given month of treatment. Ex. 1013 ¶112 n.5.

Ex. 1007 at Figure 2.

8.5 ng/ml would therefore fall within two standard deviations above the mean. Ex. 1013 ¶118.

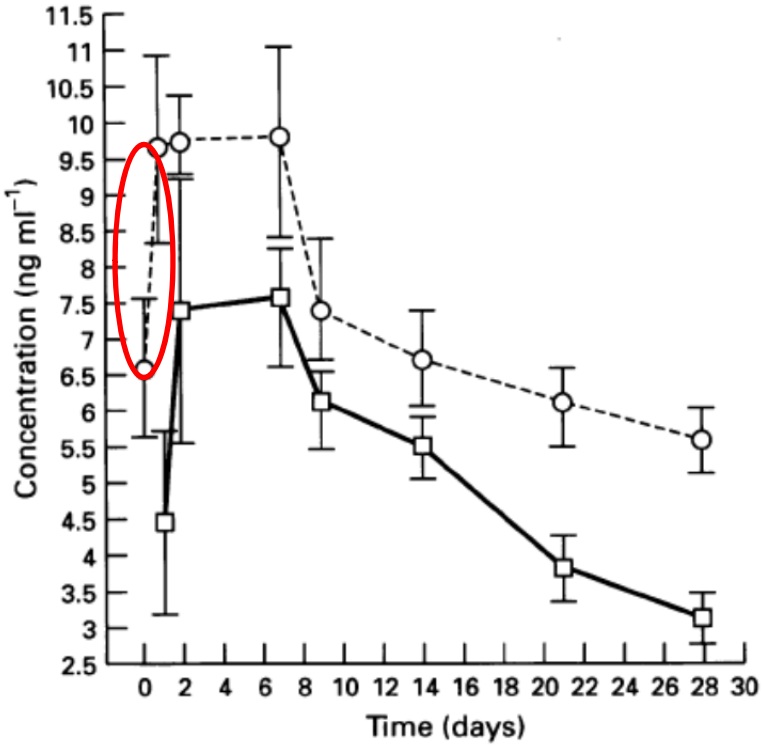

Figure 2 Mean serum concentrations of ICI 182780 during the first and sixth months of treatment. ——, Profile at entry; - - -, profile month 6.

Assuming a normal distribution,[8] at least some patients will have minimum day 28 serum (and, therefore, plasma) concentrations between 2 and 3 standard

[8] As Dr. Bergstrom explains, pharmacokinetics is assumed to follow the normal distribution, and there is nothing indicated at the time that fulvestrant followed anything other than a normal distribution. Ex. 1013 ¶118.

deviations above the mean. Ex. 1013 ¶¶117-18. Accordingly, Howell discloses that at least some (approximately 2%) patients in the overall patient population will have day 28 minimum serum concentrations above 8.5 ng/ml. The claims only require "that the concentration of fulvestrant in ***a*** patient's blood plasma is at or above the specified minimum concentration for the specified time period." Ex. 1011 at 0018. Thus, Howell discloses this limitation.

4. All Other Limitations Are Disclosed By Howell And The Knowledge of a POSA.

As described above and in the chart below, the challenged claims are rendered obvious by Howell in view of the knowledge of a POSA.

Claim 1	**Howell**
1(1) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract	Howell discloses this limitation. Ex. 1012 ¶¶79, 152-153; Ex. 1013 ¶¶84-85, 102; Ex. 1015 ¶¶105-106. Howell states: "We have assessed the pharmacokinetics, pharmacological and anti-tumour effects of [fulvestrant] in 19 patients with advanced breast cancer." Ex. 1007 at 0001, 0006-0007.
1(2) comprising administering intramuscularly to a human in need of such treatment	Howell discloses this limitation. Ex. 1007 at 0001-0002 ("ICI 182780 was administered as a long-acting formulation contained in a castor oil-based vehicle by monthly i.m. injection (5 ml) into the buttock."); Ex. 1012 ¶¶80, 82, 154-156; Ex. 1013 ¶¶86, 02; Ex. 1015 ¶¶107, 142.
1(3) a formulation comprising: about 50 $mgml^{-1}$ of fulvestrant	Howell discloses this limitation. Ex. 1012 ¶¶81, 83, 154-157; Ex. 1013 ¶86; Ex. 1015 ¶¶107, 142). Howell patients received "250 mg" of fulvestrant solubilized in a 5 mL IM injection. Ex. 1007 at 0002.
1(4) about 10% w/v	While Howell does not expressly disclose this

of ethanol; about 10% w/v of benzyl alcohol; and about 15% w/v of benzyl benzoate	formulation, a POSA would have understood that this formulation is necessary to solubilize and administer the pharmaceutical formulation. Ex. 1012 ¶¶36-42, 100-149, 163-165; Ex. 1013 ¶¶59-62; 42-44; Ex. 1015 ¶¶55-59, 147, 213-214. Dr. Gellert opined that it would have been routine experimentation for a POSA to adjust prior art formulations to achieve the claimed percentages. Thus, as the PTO found during prosecution, a POSA "***would have been motivated to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein claimed weight percent, with fulvestrant, in the dosage herein***…." Ex. 1006 at 0538; Ex. 1012 ¶26-29. A POSA would understand that solubilizing steroid hormones in oil provides the preferred slow release and that "it was necessary to add compatible and non-irritating co-solvents. Such additions consisted of benzyl benzoate, benzyl alcohol, ethyl lactate, ethyl oleate, etc." Ex. 1033 at 0002; Ex. 1018 at 0027. A POSA would also arrive at the claimed amounts of co-solvents by routine experimentation. Ex. 1012 ¶127-130; Ex. 1015 ¶214.
1(5) and a sufficient amount of castor oil vehicle	Howell discloses this limitation. Ex. 1007 at 0002; Ex. 1012 ¶¶80, 82, 154, 158; Ex. 1013 ¶¶86; Ex. 1015 ¶¶107, 142.
1(6) wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks.	Howell discloses this limitation. Ex. 1007 at 0003-0006; Ex. 1012 ¶¶82-84, 160-162; Ex. 1013 ¶¶87-89, 101-105; Ex. 1015 ¶¶144, 146.
Claim 2	**Howell**
2(1) The method of claim 1, wherein the	Howell discloses this limitation. Ex. 1007 at 0003-0004, Fig. 2; Ex. 1012 ¶¶165-168; Ex. 1013 ¶¶106-121, Ex.

therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$.	1015 ¶¶146-147 *See* Sections IX(A)(1)-IX(A)(3).
Claim 3	**Howell**
3(1) The method of claim 1, wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer.	*See* citations above regarding claim 1(1); Ex. 1012 ¶¶ 169-171
Claim 6	**Howell**
6(1) The method of claim 2, wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer.	*See* citations above regarding Claims 1(1) and 3(1); Ex. 2012 at ¶¶172-174.

B. Ground 2: The Challenged Claims Are Obvious Over Howell and McLeskey

As explained below, every limitation of the challenged claims is taught by Howell and McLeskey.

1. A POSA Would Have Been Motivated to Combine Howell and McLeskey

a. The Target Fulvestrant Concentration in Howell Would Have Led a Skilled Formulator to McLeskey.

Together, Howell and McLeskey disclose every claim limitation, and a POSA would have been motivated to combine them. This is distinct from the

argument advanced by Mylan, which used McLeskey as the lead reference, with Howell as a mere confirmatory reference. Ex. 1078 at 0062. As the Board explained, Mylan had not "adequately demonstrated that a skilled artisan had reason to ***modify the teachings of McLeskey*** in accord with a POSA's knowledge of, *e.g.*, Howell 1996, or to combine the teachings of Howell 1996 and McLeskey." Ex. 1011 at 0023. In contrast, with Howell as the lead reference—as argued here—a POSA ***did*** have reason to combine the references.

As noted above, Howell's successful use of a castor oil-based formulation would have motivated a POSA to develop a castor oil-based formulation. Ex. 1012 ¶176; Ex. 1015 ¶¶213-14; Ex. 1013 ¶166. A formulator tasked with that objective would have focused on developing a castor oil-based formulation that would solubilize fulvestrant at the same concentration as Howell, *i.e.*, 50 mg/ml. Ex. 1012 ¶176. This is undisputed. *See* Ex. 1020 ¶11 (a formulator "would have a target fulvestrant content of at least 45 mg/mL…"); *id.* ¶17.

The first step in this process would have been to conduct a literature review of known fulvestrant castor oil-based formulations. Ex. 1012 ¶177. This review would have revealed just six formulations:

(1) Dukes '814 – fulvestrant, 40% w/v benzyl alcohol, and castor oil at a concentration of 50 mg/ml. *See* Ex. 1047 at 11:9-11.

(2) Osborne – fulvestrant and castor oil. Ex. 1039 at 0002.

(3) Parczyk – fulvestrant, 80% v/v castor oil, and 20% v/v benzyl benzoate. Ex. 1048 at 0001.

(4) Chwalisz – fulvestrant, 25% benzyl benzoate v/v, 75% castor oil v/v. Ex. 1089 at 0003.

(5) Wunsche – fulvestrant, 20% benzyl benzoate v/v, 80% castor oil v/v. Ex. 1088 at 0002.

(6) McLeskey – fulvestrant, 10% ethanol, 10% benzyl alcohol, 15% benzyl benzoate, and castor oil at a concentration 50 mg/ml. Ex. 1008 at 0002.

Of these six castor oil-based formulations, only Dukes '814 and McLeskey teach fulvestrant at the target concentration of 50 mg/ml. As a result, a POSA would have focused on these two formulations. Ex. 1012 ¶182; Ex. 1015 ¶¶149-69. And, as Dr. Gellert explained, a POSA would have rejected the Dukes '814 formulation due to its high benzyl alcohol content. Ex. 1020 ¶¶21, 24; Ex. 1001 at 3:65-4:66.

That would have left the McLeskey formulation, which includes excipients that are within pharmaceutically acceptable levels and solubilizes fulvestrant at the target concentration of 50 mg/ml. Ex. 1012 ¶184. And, as the only acceptable castor oil-based formulation taught in the art to solubilize fulvestrant at the target concentration, a POSA would have been motivated to select it as the leading

candidate for formulating the drug.[9] *Id.* ¶184.

Thus, this is a classic case for obviousness: there were a "finite number of identified, predictable solutions" to a problem, and a POSA had "good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 402-03 (2007).

b. The Record Confirms the Motivation to Combine Howell and McLeskey.

The Mylan IPR left some unresolved questions about the motivation to combine Howell and McLeskey. Those questions are answered here and eliminate AstraZeneca's claim that there were "critical differences" that would have suggested that "the references should not be combined." Ex. 1017 at 0066. The record here shows that the POSA had every reason to combine these references.

As a threshold matter, McLeskey is "analogous art" for purposes of the obviousness analysis. Ex. 1015 ¶¶29, 126. Indeed, the Federal Circuit has explained that a prior art reference is analogous—and therefore readily combinable—where "the reference…is reasonably pertinent to the particular problem with which the inventor is involved." *In re Ethicon, Inc.*, 844 F.3d 1344, 1349 (Fed. Cir. 2017).

[9] Unlike Mylan, InnoPharma shows why a POSA would have selected the McLeskey formulation. *See* Ex. 1011 at 0023-24.

Here, Howell would motivate a POSA to develop a castor oil-based formulation that could solubilize fulvestrant at the target concentration. McLeskey is "reasonably pertinent to [this] particular problem," *id.*, because it specifically discloses a castor oil-based formulation with the target concentration of fulvestrant. Ex. 1012 ¶184. Moreover, a POSA would recognize that the McLeskey formulation was pharmaceutically acceptable—it used only recognized pharmaceutical excipients in concentrations that had been previously approved for IM administration by the FDA. *Id.* ¶184.

Indeed, the motivation to combine Howell and McLeskey is more pronounced than in *Ethicon*. 844 F.3d at 1347-48. There, the Board found the cardiac stent claims obvious over a combination that included a reference, Lo. *Id.* at 1348. Lo taught the copolymer weight ratio recited in the cardiac stent claims, but was "directed to coatings for harsh, industrial applications." *Id.* at 1348, 1350. The Federal Circuit rejected the patentee's argument that Lo was nonanalogous art, and upheld the Board's finding that "the skilled worker would have reasonably consulted Lo to determine the optimal concentrations for each component, ***even if Lo does not teach the use of [those components] for medical implants***." *Id.* at 1348.

Here, in contrast, McLeskey ***did*** teach that fulvestrant inhibited estrogenic activity—and so is much closer art than the invalidating Lo patent in *Ethicon*. *See*

id. at 1350. Yet the Federal Circuit agreed that a POSA would be motivated to combine Lo with references in the medical device field. If Lo was analogous, McLeskey necessarily is analogous.

Moreover, the alleged differences between McLeskey and Howell would not discourage a POSA from combining them. Each alleged difference speaks only to whether a POSA, looking at McLeskey, would consult Howell. But the question here is whether a POSA considering Howell would look to McLeskey for its pharmaceutically acceptable formulation. The POSA would not need to rely on McLeskey to teach pharmacokinetics, the route of administration, the dose, or any other topics already covered by Howell. The alleged differences are, therefore, irrelevant as explained below:

- **Monthly IM Injection v. Weekly SC Injection:** The starting point of the obviousness analysis, Howell, teaches monthly IM administration. Ex. 1007 at 0001-2. Moreover, a POSA would not discard McLeskey because it utilized fulvestrant SC in mice. Ex. 1012 ¶212; Ex. 1015 ¶154. Instead, the POSA would recognize that depot formulations are administered to mice subcutaneously because mice generally do not have adequate muscle mass for IM injections. Ex. 1012 ¶212. A POSA would appreciate these differences and would not seek to "extrapolate" the results of SC and IM administration. Ex. 1017 at 0026-27.

- **Humans v. Mice:** AstraZeneca's argument is contrary to Federal Circuit law. Indeed, in *Alcon Research, Ltd. v. Apotex Inc.*, the Court rejected an attempt to distinguish prior art on the ground that it was tested in animals because the patent was also solely based on animal testing. 687 F.3d 1362, 1369 (Fed. Cir. 2012). The same reasoning applies here. Indeed, the '680 patent discloses ***no*** human testing. Ex. 1001 at Figure 1.
- **250 mg/5 ml/Month Dose in Humans v. 5 mg/0.01ml/Week in Mice:** As Dr. Harris explains, AstraZeneca's calculation is wrong by orders of magnitude. *See* Illum Decl. ¶150. In reality, the mouse dose is approximately equivalent to 400 mg/month in humans. Ex. 1015 ¶¶198-200.
- **Hormone Independent v. Dependent Cancer:** To effectively treat breast cancer, a POSA would assess hormone-independent and hormone-dependent pathways together. Ex. 1014 ¶¶65-66. This is particularly true for second-line therapies such as fulvestrant. *Id.* ¶¶65-66. When a patient has already failed one therapy, the POSA would need to understand the mechanism of action of the cancer to appropriately treat it in a second-line setting. *Id.* ¶66; Ex. 1015 ¶84.
- **Lack of Pharmacokinetic Data in McLeskey:** As noted above, Howell—which includes fulsome pharmacokinetic data—is the starting point, not McLeskey. Moreover, AstraZeneca's assertion that a POSA would

> disregard the formulation disclosed in McLeskey because of a lack of pharmacokinetic data has been rejected. *See Duramed Pharms., Inc. v. Watson Labs., Inc.*, 413 F. App'x 289, 294 (Fed. Cir. 2011) ("[T]here is ***no requirement*** that a teaching in the prior art be ***scientifically tested***, or even guarantee success, before providing ***a reason to combine***") (internal citations omitted).

AstraZeneca, therefore, failed to identify any relevant "critical differences."

2. A POSA Would Have A Reasonable Expectation of Success in Administering the McLeskey Formulation Intramuscularly to Achieve the Results Reported in Howell

A POSA would also have had a reasonable expectation that the McLeskey formulation could be administered by IM injection, as taught in Howell, in order to achieve the successful results of Howell. Ex. 1015 ¶¶189-202. The evidence submitted here sets this Petition apart from the prior Mylan IPRs. *See* Ex. 1011 at 0028.

The goal in developing a sustained-release depot formulation, like the one used in Howell, is to maintain the desired minimum serum concentration until the next injection. Ex. 1012 ¶187. Howell shows that therapeutic levels can be maintained over 28 days by a once-monthly injection of a castor oil-based solution with a fulvestrant concentration of 50 mg/ml. *See supra* § VIII(A)(1). Thus, to achieve the results in Howell, the skilled formulator would focus on ensuring that

the day 28 serum concentration (*i.e.*, the last day before the next injection) would stay above the minimum therapeutic level.

Howell does not report any toxicity at the doses needed to reach the minimum serum concentration. *See* Ex. 1007 at 0004. As a result, a POSA would not have been concerned with maximum concentrations. Ex. 1012 ¶187; Ex. 1013 ¶¶87-89; Ex. 1015 ¶¶143-44. This is consistent with the claims, which recite only minimum plasma concentrations.

A formulator would understand that castor oil is the rate limiting factor in both the McLeskey and Howell formulations.[10] Ex. 1012 ¶189; Ex. 1076 at 0001 ("Rate-limiting step is the liberation of drug from the oil depot"); Ex. 1077 at 0001. This means that a POSA would expect the fulvestrant and castor oil in the formulation to be absorbed slowly from the depot since neither ingredient is water soluble. *See* Ex. 1012 ¶194; Ex. 1072 at 0002.

In contrast, a POSA would understand that the other excipients in the McLeskey formulation—ethanol, benzyl benzoate, benzyl alcohol—would not be expected to affect the minimum serum concentrations at day 28 because they would dissipate quickly from the injection depot. Ex. 1012 ¶196; Ex. 1013 ¶¶179,

[10] A POSA would recognize that both formulations were solutions. Ex. 1012 ¶¶199-203.

181. The '680 patent itself confirms this rapid dissipation. *See* Ex. 1001 at 9:17-21; 9:6-10; 9:14-16.

Accordingly, the fact that Howell and McLeskey disclose the same absorption rate-limiting excipient (*i.e.*, castor oil) means that a POSA would have had a reasonable expectation that the McLeskey formulation could achieve the same minimum serum concentrations achieved by Howell. Ex. 1012 ¶196.

During prosecution, AstraZeneca tried to distinguish McLeskey through the declaration of Dr. Sawchuk. But Dr. Sawchuk did not address Howell, so his analysis is missing the motivation that would have caused a POSA to look at McLeskey in the first place.

But, apart from these flaws, his testimony fails to render the challenged claims nonobvious. Unlike the Mylan IPR, which "failed to adequately address…the Sawchuk § 1.132 Declaration," Ex. 1011 at 0027, InnoPharma's experts have refuted each of Dr. Sawchuk's points:

- **Alleged "Failure" in McLeskey**: Fulvestrant worked exactly as intended in McLeskey and this would have been understood by a POSA. *See* section VIII(A)(2); Ex. 1014 ¶44-49.
- **No Preference for Castor Oil:** Dr. Sawchuk's opinion contradicts Dr. Gellert's opinion. Dr. Gellert opines that "the experienced formulator ***would have selected castor oil as the oil vehicle***…." Ex. 1020 ¶¶13, 17; Ex. 1012

¶206.

- **Preference for Arachis Oil Suspension Over McLeskey Formulation:** This contradicts Dr. Gellert's conclusion that "suspensions…were ***not*** an acceptable option for fulvestrant." Ex. 1020 ¶¶13, 17; Ex. 1012 ¶206.
- **Preference for Dukes Castor Oil Formulation Over McLeskey Formulation:** Dr. Gellert considered ***and rejected*** this formulation because the alcohol content was too high. Ex. 1020 ¶¶21, 24; Ex. 1012 ¶210.
- **No Clinical Data on Efficacy and Pharmacokinetics:** *First*, Howell provides clinical data and motivation to use the McLeskey formulation. Ex. 1012 ¶211. *Second*, a POSA would expect that McLeskey would have the same or very similar pharmacokinetics at day 28 as Howell. Ex. 1012 at § IX(D)(2). *Third*, as a matter of law, the "blood serum concentration resulting from administering a [drug] is an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012).
- **SC Route:** *First*, Howell teaches that IM injections of fulvestrant are successful. Ex. 1007 at 0001. *Second*, depot injections are generally given SC in mice because mice lack the muscle mass for IM injection. Ex. 1012

¶212; Ex. 1015 ¶154. *Third*, it was known that "clinically, [fulvestrant] must be given by depot intramuscular injection." Ex. 1009 at 0002. A POSA would not be dissuaded from that route based on the disclosure in McLeskey. *See infra* 60-61.

- **Safety Not Proven Without Clinical Trials:** This is wrong as a matter of law and fact, as explained *supra* § VIII(B)(2). *See Cubist Pharms., Inc. v. Hospira, Inc*., 805 F.3d 1112, 1124-25 (Fed. Cir. 2015) (finding reasonable expectation of success without clinical trials), *cert. denied*, 136 S. Ct. 2393 (2016).
- **Excipient Impact on Pharmacokinetics Profile:** The source cited by Dr. Sawchuk, Ex. 1037, confirms that the excipients used in a castor oil-based formulation do not affect the minimum serum concentration obtained on day 28. Ex. 1012 ¶217; Ex. 1013 ¶¶177-86.
- **W/V versus V/V Units:** *First*, the Board accepted that the McLeskey formulation matches the claimed formulation. Ex. 1011 at 0023. *Second*, formulators prefer to use w/v measurements because measuring by weight is more accurate. Ex. 1012 ¶223. *Third*, USP rules teach solids dissolved in liquids—as is the case with fulvestrant—are understood to refer to w/v measurements if no qualification is provided. *Id.* ¶224. *Fourth*, AstraZeneca's own expert, Dr. Gellert, uses percentages without units to

refer to w/v measurements. *Id.* ¶225. *Fifth*, even if McLeskey were ambiguous as to units, it was obvious to try both. *Id.* ¶226.

3. Every Limitation Is Disclosed By Howell and McLeskey

As described above and in the chart below, the challenged claims are rendered obvious by Howell and McLeskey.

Claim 1	**Howell, McLeskey**
1(1) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract	Howell discloses this limitation. *See* Ground 1, claim 1(1). Ex. 2012 at ¶230.
1(2) comprising administering intramuscularly to a human in need of such treatment	Howell discloses this limitation. *See* Ground 1, claim 1(2). Ex. 1012 ¶231.
1(3) a formulation comprising: about 50 $mgml^{-1}$ of fulvestrant	Howell discloses this limitation. *See* Ground 1, claim 1(3). Ex. 1012 ¶231. McLeskey also discloses this limitation. Ex. 1012 ¶¶ 90, 231; Ex. 1013 ¶92; Ex. 1008 at 0002; Ex. 1014 ¶43; Ex. 1015 ¶¶112, 165-66.
1(4) about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; and about 15% w/v of benzyl benzoate	Howell teaches this limitation. *See* Ground 1, claim 1(4). McLeskey discloses this limitation. Ex. 1012 ¶¶ 90-94, 235-237; Ex. 1013 ¶¶92, 179-183; Ex. 1014 ¶43; Ex. 1015 ¶¶112, 165, 169. McLeskey discloses fulvestrant formulated "in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil." Ex. 1008 at 0002.
1(5) and a sufficient	Howell discloses this limitation. *See* Ground 1, claim

amount of castor oil vehicle	1(5). Ex. 2012 at ¶¶232-233.. McLeskey also discloses this limitation. Ex. 1008 at 0002; Ex. 1012 ¶¶ 90-94, 232-233; Ex. 1013 ¶92; Ex. 1014 ¶43; Ex. 1015 ¶¶112, 165, 169).
1(6) wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks.	Howell discloses this limitation. *See* Ground 1, claim 1(6). Ex. 1012 ¶234.
Claim 2	**Howell, McLeskey**
2(1) The method of claim 1, wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$.	Howell discloses this limitation. *See* Ground 1, Claim 2(1). Ex. 2012 at ¶¶238-239.
Claim 3	**Howell, McLeskey**
3(1) The method of claim 1, wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer.	Howell discloses this limitation. *See* Ground 1, claims 1(1) and 3(1). Ex. 2012 at ¶¶240-241.
Claim 6	**Howell, McLeskey**
6(1) The method of claim 2, wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract	Howell discloses this limitation. *See* Ground 1, claims 1(1), 3(1), and 6(1). Ex. 2012 at ¶¶242-243.

is breast cancer.	

C. Ground 3: The Challenged Claims Are Obvious Over Howell, McLeskey, and O'Regan

As explained below, every limitation of the challenged claims is taught by Howell, McLeskey, and O'Regan.

1. A POSA Would Have Been Motivated to Combine Howell, McLeskey, and O'Regan

O'Regan specifically cites Howell as confirming that fulvestrant "has shown promising results clinically in Europe, with high response rates of almost 70%...." Ex. 1009 at 0002. Thus, a POSA would have been motivated by Howell to look to the follow-up study in O'Regan, especially given that O'Regan tests the same compound. Ex. 1015 ¶¶126, 170-73.

2. A POSA Would Have A Reasonable Expectation of Success in Combining Howell, McLeskey, and O'Regan

The Board faulted Mylan's IPR on the ground that it "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" because McLeskey involved SC injections to mice. Ex. 1011 at 0028. But O'Regan is strong evidence that a POSA would expect success in using the McLeskey formulation intramuscularly in humans. Ex. 1015 ¶¶189-214.

While O'Regan also reported a study of fulvestrant injected subcutaneously into mice, Ex. 1009 at 0002, it clarified that "***clinically***, [fulvestrant] must be given

by ***depot intramuscular injection*** because of low oral potency." *Id.* at 0002. The rationale for IM injection in humans is that the large injection volume (5 ml) exceeds the allowable volume for SC administration. Ex. 1012 ¶251. However, in mice, depot injections generally have to be administered subcutaneously due to a lack of sufficient muscle mass. *Id.* ¶250.

Moreover, a POSA would have known that the IM and SC routes of administration are similar. *Id.* ¶249. Because of the similarities, the same formulation may be administered either subcutaneously or intramuscularly. *Id.* ¶249; Ex. 1015 ¶¶195-200.

Therefore, a POSA following the teachings of O'Regan, Howell, and McLeskey would have a reasonable expectation of success.

3. Every Limitation Is Disclosed By Howell, McLeskey, and O'Regan

As described above and in the chart below, the challenged claims are rendered obvious by Howell, McLeskey, and O'Regan.

Claim 1	**Howell, McLeskey, O'Regan**
1(1) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract	Howell discloses this limitation. *See* Ground 1, claim 1(1). Ex. 2012 at ¶¶259-160.
1(2) comprising administering	Howell discloses this limitation. *See* Ground 1, claim 1(2). Ex. 2012 at ¶261.

intramuscularly to a human in need of such treatment	O'Regan also discloses IM administration in humans. Ex. 1009 at 0002; Ex. 1012 ¶¶98, 250-251 261; Ex. 1013 ¶¶94; Ex. 1015 ¶¶116, 170; *see supra* §§ IX(C)(1) and IX(C)(2).
1(3) a formulation comprising: about 50 $mgml^{-1}$ of fulvestrant	Howell and McLeskey disclose this limitation. *See* Grounds 1 and 2, claim 1(3). Ex. 1012 ¶261.
1(4) about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; and about 15% w/v of benzyl benzoate	Howell and McLeskey disclose this limitation . *See* Grounds 1 and 2, claim 1(4). Ex. 2012 at ¶¶264-265.
1(5) and a sufficient amount of castor oil vehicle	Howell and McLeskey disclose this limitation. *See* Grounds 1 and 2, claim 1(5). Ex. 2012 at ¶262.
1(6) wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks.	Howell discloses this limitation. *See* Ground 1, claim 1(6). Ex. 1012 ¶263.
Claim 2	**Howell, McLeskey, O'Regan**
2(1) The method of claim 1, wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$.	Howell discloses this limitation. *See* Ground 1, claim 2(1). Ex. 2012 at ¶¶266-267.
Claim 3	**Howell, McLeskey, O'Regan**
3(1) The method of claim 1, wherein the hormonal dependent	Howell discloses this limitation. *See* Ground 1, claims 1(1) and 3(1). Ex. 2012 at ¶¶268-270.

benign or malignant disease of the breast or reproductive tract is breast cancer.	
Claim 6	**Howell, McLeskey, O'Regan**
6(1) The method of claim 2, wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer.	Howell discloses this limitation. *See* Ground 1, claims 1(1), 3(1), and 6(1). Ex. 2012 at ¶¶271-273.

D. Ground 4: Claims 2 and 6 Are Obvious Over Howell, McLeskey, O'Regan, and DeFriend

As explained below, every limitation of claims 2 and 6 is taught by Howell, McLeskey, O'Regan, and DeFriend.

1. A POSA Would Have Been Motivated to Combine Howell, McLeskey, O'Regan, and DeFriend

A POSA would have been motivated to combine DeFriend, Howell, McLeskey and O'Regan, especially given that DeFriend tests the same compound for the treatment of breast cancer, and shows greater inhibition of the ER at higher doses with good tolerance. Ex. 1013 ¶¶122-32; 1015 ¶¶216-31.

First, DeFriend would have motivated a POSA to use a 500 mg/month dose. The results in Howell were undoubtedly positive and would have motivated a person skilled in the art to develop the claimed method of treatment. *See supra* § IX(A)(1). That said, there was room to improve on the results of Howell, as a

minority of patients did not respond to treatment and showed disease progression. Ex. 1007 at 0005. A companion article to Howell explained that the authors expected to observe hot flashes/sweats in the patients as a result of ER inhibition, but those effects were not observed. Ex. 1041 at 0003. Thus, a POSA would have suspected that Howell did not achieve complete inhibition of ERs. Ex. 1015 ¶179.

DeFriend teaches that the inhibition of ERs is ***dose dependent*** and that the equivalent of a 500 mg/month dose was highly effective at inhibiting ERs.[11] *See supra* § VIII(A)(4); *see* Ex. 1057 at 0007 ("[T]he lower 2-5 mg/kg dose did not fully block the trophic action of endogenous oestrogens."). Thus, DeFriend would have motivated a POSA to increase the dose from the 250 mg/month used in Howell to the 500 mg/month taught in DeFriend.

Howell's passing comment that a lower dose ***may*** be effective is based only on an evaluation of the blood levels achieved in the study, ***not*** an examination of whether the levels achieved fully inhibited the ER for all patients. Ex. 1007 at 0006 ("further clinical studies are required to confirm."). This does not discourage

[11] The fact that the DeFriend used a short-acting formulation for daily injection would not have dissuaded a POSA. A POSA would look to DeFriend for its teachings on the effect of dose on ER inhibition, ***not*** for the formulation used or the method of administration. Ex. 1015 ¶120.

investigation into the claimed invention, so it does not teach away. *See Galderma*, 737 F.3d at 738. Thus, a POSA would be motivated to use a dose of 500 mg/month to address the suspected incomplete ER inhibition in Howell.

Second, DeFriend and Howell would have motivated a POSA to use a 500 mg loading dose (two 250 mg injections) to shorten the time for a patient to reach steady state. A loading dose is useful—especially in progressive diseases—to raise patient serum concentrations to steady state levels more quickly. Ex. 1015 ¶224; Ex. 1086 at 0001 (tamoxifen loading dose achieved "rapid achievement of steady-state serum concentrations"). And Howell suggests that it may take at least six months to reach steady state. Ex. 1007 at FIG. 2, 0006. Howell also reports that, of the patients who showed disease progression, ***all showed progression in less than 8 weeks***. *Id.* at 0005. This would have motivated a POSA to use a loading dose to more quickly achieve steady state, which would have resulted in blood concentrations above 8.5 $ngml^{-1}$. Ex. 1015 ¶224; Ex. 1013 ¶¶ 148-55.

2. A POSA Would Have A Reasonable Expectation of Success in Combining Howell, McLeskey, O'Regan, and DeFriend

A POSA would have reasonably expected that increasing the dose to 500 mg/month would increase ER inhibition and improve treatment outcomes because DeFriend correlated greater ER downregulation—which was shown to be dose dependent—with superior efficacy. Ex. 1013 ¶¶136-40; 1015 ¶¶174-85. And a

POSA would not have been concerned with toxicity given that the concentrations in Howell were well tolerated. *See supra* 54.

A POSA would reasonably have predicted that, if a higher dose or loading dose were used, the concentrations of fulvestrant would be higher than that of Howell, and a greater number of patients would achieve at least 8.5 ng ml^{-1} for a 4-week period. Ex. 1013 ¶¶107-32; 1015 ¶¶220-31. For example, doubling the dose or using a loading dose would double the concentrations of fulvestrant depicted in Howell, which reports a mean concentration of 5.5 ng ml^{-1} at month 6. Ex. 1015 ¶¶222-28; *see* Ex. 1060 at 0002. Thus, a POSA would have had a reasonable expectation of success in achieving plasma concentrations of at least 8.5 ng ml^{-1} for four weeks. Ex. 1013 ¶¶122-32; Ex. 1015 ¶¶174-88.

3. Every Limitation Of Claims 2 and 6 Is Disclosed By Howell, McLeskey, DeFriend, and O'Regan

As described above and set forth in the chart below, claims 2 and 6 are rendered obvious by Howell, McLeskey, O'Regan, and DeFriend.

Claim 2	**Howell, McLeskey, O'Regan, DeFriend**
2(1) The method of claim 1, wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$.	Howell discloses this limitation. *See* Ground 1, claim 2(1). Ex. 2012 at ¶¶274-279. DeFriend discloses this limitation. Ex. 1038 at 0001, 0004; Ex. 1012 ¶¶99, 274-279; Ex. 1013 ¶¶96-98, 122-155; Ex. 1015 ¶¶119-120, 173-87, 214-27; *see supra* §§ IX(D)(1) and IX(D)(2) above.
Claim 6	**Howell, McLeskey, O'Regan, DeFriend**

6(1) The method of claim 2, wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer.	Howell discloses this limitation. *See* Ground 1, claims 1(1), 3(1), and 6(1). Ex. 2012 at ¶¶280-282. DeFriend discloses this limitation. Ex. 1038 at 0001; Ex. 2012 at ¶¶99, 280-282.

X. SECONDARY CONSIDERATIONS FAIL TO OVERCOME THE EVIDENCE OF OBVIOUSNESS

In the Mylan '680 IPR, AstraZeneca asserted long-felt need and unexpected results. Ex. 1017 at 0075-77. AstraZeneca's alleged evidence fails because there is no nexus and, even if there is, AstraZeneca's purported evidence is insufficient.

A. There Is No Nexus to the Claimed Invention

AstraZeneca's purported secondary considerations are attributable to the unclaimed fulvestrant ***compound***, not the claimed treatment method.[12] *See* Ex. 1016; Ex. 1015 ¶¶234-38. Thus, there is no nexus. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

First, industry development of fulvestrant was blocked by AstraZeneca's compound patent, which expired in 2007, long after the priority date of the '680 patent. *See* Ex. 1016; *cf. Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005). Moreover, Dr. Robertson claimed that fulvestrant met the "need to improve on the current standard of care," but that is attributable to the

[12] Dr. Illum seems to concede as much. Illum Decl. ¶¶123-125.

fulvestrant compound, not to the challenged claims. Robertson Decl. ¶198.

Second, Dr. Robertson's purported evidence of unexpected safety and efficacy—for example, the lack of bone loss—is also attributable to the compound. Ex. 1015 ¶237.

Third, Dr. Robertson cannot create a nexus based on clinical trials that utilize a 500 mg dose, which is unclaimed. Robertson Decl. ¶215. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) ("evidence of non-obviousness ***must be commensurate in scope with the claims***") (citation omitted).

Fourth, Dr. Robertson's citation to FDA's approval of Faslodex® cannot confer nexus, *see AstraZeneca LP v. Breath Ltd.*, 603 F. App'x 999, 1003 (Fed. Cir. 2015). *Fifth*, Dr. Illum's analysis ignores Howell and McLeskey. She thus failed to compare the claims to the closest prior art as required. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1370 (Fed. Cir. 2007).

B. AstraZeneca's Secondary Considerations Arguments Fail

Regardless of nexus, AstraZeneca's arguments fail for multiple reasons.

1. AstraZeneca Cannot Show Long-Felt Need

According to Dr. Robertson, fulvestrant filled a "need to improve on the current standard of care." Robertson Decl. ¶198. This argument fails because: (i) there is no nexus to the claims; and (ii) because long-felt need is assessed as of the filing date of patent. *See* Ex. 1015 ¶¶233-43; *Perfect Web Techs., Inc. v. InfoUSA,*

Inc., 587 F.3d 1324, 1332–33 (Fed. Cir. 2009). And all of the evidence Dr. Robertson cites post-dates the '680 patent. Robertson Decl. ¶199.

2. The Results Were Not Unexpected

AstraZeneca also cannot show unexpected results because every result was expected as of the priority date. *See Pfizer*, 480 F.3d at 1370-71.

a. Dr. Robertson's Arguments Are Contradicted By His Own Work.

Dr. Robertson's attempts to re-cast fulvestrant as an "unproven" therapy are meritless. *First*, fulvestrant was long known to be effective in treating hormone-dependent cancer. *See supra* § VIII(B)(1).

Second, Dr. Robertson's published work confirms that fulvestrant was known to have a favorable safety profile. *See* Ex. 1007 at 0004. It was known that fulvestrant did not affect bone density in animals, so it is not surprising that the same held true in humans. *See* Ex. 1031 at 0007.

Third, Dr. Robertson's claim that it was surprising that "the injections…are ***well tolerated locally***" is again contradicted by Dr. Robertson's papers. Using that phraseology, Howell confirmed that fulvestrant "appeared ***well tolerated locally***…." Ex. 1007 at 0004; *see* Ex. 1032 at 0012. Thus, these results were expected.

b. The Release Profile and Effect of Benzyl Benzoate Were Expected

The effect of benzyl benzoate and the release profile would have been expected. As explained above, a POSA would have expected the addition of benzyl benzoate to improve the solubility of fulvestrant in castor oil. *See supra* § IX(A)(1); Ex. 1012 ¶116. Additionally, the release profile would have been expected based on the known properties of castor oil. *See supra* § IX(B)(2); Ex. 1012 ¶289; Ex. 1033 at 0005.

Dr. Illum's arguments are not persuasive. She argues that the release profile was "surprising" because aqueous suspensions had a poor release profile. Illum Decl. ¶217. Aqueous suspensions, however, are not an appropriate comparison because "suspensions…were ***not*** an acceptable option for fulvestrant." Ex. 1020 ¶¶13, 17. Additionally, it was known that castor oil-based vehicles did not produce extensive local tissue irritation. Ex. 1007 at 0004. AstraZeneca's argument fails.

XI. CONCLUSION

For the foregoing reasons, *inter partes* review is requested.

Respectfully submitted,

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CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(c) and (d), Petitioner certifies that the word count of InnoPharma Licensing, LLC's Petition for *Inter Partes* Review (exclusive of any table of contents, table of authorities, mandatory notices under § 42.8, certificate of service or word count, or appendix of exhibits or claim listing) as measured by Microsoft Word is 13,927 words.

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CERTIFICATE OF SERVICE ON PATENT OWNER
UNDER 37 C.F.R. § 42.105(A)

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(b), the undersigned certifies that, on the 17th day of February 2017, a complete and entire copy of this Petition for *Inter Partes* Review, together with all supporting exhibits, was provided to the Patent Owner by delivering a copy via same-day courier service and by mailing another copy of the same via FedEx® Priority Overnight with Saturday delivery to the following attorneys of record for the Patent Owner:

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