Filed October 6, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC.
Petitioner

v.

ASTRAZENECA AB
Patent Owner.

Case IPR2016-01325
U.S. Patent No. 8,329,680

PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,329,680

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I. INTRODUCTION

The '680 Patent claims are method of treatment claims—methods to treat hormonal dependent breast cancer with the active ingredient (fulvestrant) administered intramuscularly with a combination of ingredients that interact with the muscle, to provide and maintain specific blood levels over extended periods of time. At the time the patent application was filed, the skilled artisan reviewing the prior art would never have expected it to be a successful treatment—it combined an active ingredient with then-unproven efficacy administered through the unpredictable intramuscular route using ingredients that interact with the muscle in a still-unknown manner to achieve blood plasma levels that differed from then-conventional wisdom and were maintained for 2-4 weeks.

The Petition uses the patent claims to filter out unknowns, failures, and critical differences, and guide an argument of obviousness over two references: (1) McLeskey (Ex. 1005), about a study of basic biology using a mouse model and various actives, which identifies fulvestrant formulations as "treatment failures," and (2) Howell 1996 (Ex. 1006), about an early stage clinical trial, which advocates seeking blood plasma levels in the opposite direction from the claims. Both were thoughtfully considered during patent prosecution. Three requirements of the claims highlight the faults in the Petition's arguments.

First, the claims are to a method of ***treatment***. The lynchpin of Petitioner's

obviousness arguments is that McLeskey discloses the "complete formulation details" claimed and that they were a ***successful*** treatment. Petition at 34 ("McLeskey—disclosed a ***successful*** castor oil formulation, including the complete formulation details." (emphasis added)). But, the explicit language of McLeskey repeatedly states the opposite, i.e., that the fulvestrant formulations used in that study were a "***treatment failure***." What's more, McLeskey includes nothing to recommend its fulvestrant formulation, no physical characteristics (solubility), no blood plasma levels (if any fulvestrant even reached the blood), and no *in vivo* activity (failure). Yet, Petitioner argues that "[t]he POSA would have used this formulation as a starting point." *Id.* A skilled artisan would not use a self-described "treatment failure" as a starting point for a method of treatment.

Second, the claims require administration by intramuscular injection. The claims require intramuscular injection of a unique combination of ingredients that interact with the muscle tissue so fulvestrant is released into the blood slowly and steadily over a month. How this interaction works remains a mystery—in fact, as the patent application explains, even slightly varying the ingredients causes the fulvestrant to crystallize in the muscle causing necrosis (death) of the muscle tissue and loss of the desired levels of drug in the blood. So, while the Petitioner-dubbed "complete formulation details" of the claims require intramuscular administration, McLeskey explicitly requires an entirely different route of administration,

subcutaneous. And, four references cited during prosecution (yet unaddressed by Petitioner here) proved that "switching" from subcutaneous to intramuscular administration was entirely unpredictable.

Third, the claims include specific therapeutic levels of fulvestrant (an endocrine agent) to deliver to a patient's blood to treat the cancer. Meanwhile, the other reference relied on by Petitioner, Howell 1996, teaches away from these levels. Howell 1996 published results of exploratory work in a small group of patients that explicitly taught to decrease the dose and avoid the high levels in the blood claimed in the patent. That was bolstered by almost universal experience with other endocrine agents for cancer treatment where higher tolerated levels were not found to add any clinical benefits and the lowest possible plasma levels were used. Or put differently, fulvestrant surprisingly worked differently than *all* other known endocrine agents.

And, compounding the errors, evaluating the totality of Petitioner's arguments reveals them to be composed via hindsight. For Ground One (McLeskey alone), to shoehorn it into the claims, McLeskey would need to be modified to administer fulvestrant and excipients through an entirely different route (intramuscular v. subcutaneous), for a different indication (hormonal dependent v. hormonal independent), in different volumes and doses (milligrams v. grams), to different species (human v. mice), over a different schedule (once every

4 weeks v. once a week) and expect specific therapeutic blood plasma limits (although McLeskey itself provides none). Not one of the eleven references Petitioner cites as "common knowledge" gives a reason to make these many modifications or believe they would be successful.

Similarly, for Ground Two (McLeskey plus Howell 1996), Petitioner tries to shore up McLeskey by combining it with an unrelated publication reporting on an early stage human trial with fulvestrant (Howell 1996). But far from matching up, Howell 1996 and McLeskey discuss different aims (use of fulvestrant v. eschewing fulvestrant in favor of growth factors), different administration (intramuscular v. subcutaneous), to different subjects (humans v. genetically engineered mice), and give different results (not cross resistant v. cross resistant). Just as with McLeskey alone, Petitioner provides no reason for a skilled artisan to make a single one of the many modifications that would be necessary to combine the two. As described in detail in the declarations attached[1] and below, each modification matters and

[1] Dr. Robertson, a leading breast cancer clinician and author of Howell 1995/1996, explains in his declaration (Ex. 2002) that the Howell studies raised more questions than were answered.

Dr. Illum, an expert formulator, illustrates in her declaration (Ex. 2001) how under standard formulation principles an ordinary researcher would not expect the

carries with it no reason to expect success. Indeed, nothing in Howell 1996 suggests the many modifications would convert the "treatment failure" of McLeskey into a success. Institution should be denied.

II. THE '680 PATENT

A. Specification

The invention relates to "a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound [fulvestrant], more particularly to a formulation adapted for administration by injection containing the compound [fulvestrant] in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle." Ex. 1001 at Abstract.

Amongst other things, the inventors of the '680 Patent "surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 $mgml^{-1}$." *Id.* at 6:9-13. This was surprising because

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very (and many) modifications to McLeskey to succeed or combine McLeskey with Howell 1996.

Dr. Sawchuk, a pharmacokinetics expert, explains in his declaration (Ex. 2003) the criticality of the blood plasma level limitations to the claimed method of treatment.

"[t]he solubility of fulvestrant in non-aqueous ester solvents . . . is significantly lower than the solubility of fulvestrant in an alcohol" and "in castor oil." *Id.* at 6:14-19. In addition, the inventors noted that "[s]imply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site." *Id.* at 9:42-44.

The inventors further discovered that the claimed inventions "provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time." *Id.* at 8:58-60. The specification of the '680 Patent states that "[b]y use of the term 'therapeutically significant levels' we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient." *Id.* at 9:24-27. Further, the specification describes "extended release" as "at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved." *Id.* at 9:29-31. In addition, the inventors discovered that "the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site." *Id.* at 10:49-51.

B. Claims

All of the claims of the '680 Patent are directed to methods of treatment. The methods of treatment include a choice of: active ingredient, method of administration (i.e., a combination of excipients and active ingredient injected

intramuscularly), and amount of active ingredient to be delivered to the blood over a delineated amount of time in a sustained release fashion to treat hormonal dependent disease of the breast or reproductive tract.

Independent claims 1 and 9 of the '680 Patent are provided below.

> A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment a formulation comprising [consisting essentially of]:
>
> about 50 $mgml^{-1}$ of fulvestrant;
>
> about 10% w/v of ethanol;
>
> about 10% w/v of benzyl alcohol;
>
> about 15% w/v of benzyl benzoate; and
>
> [a sufficient amount of castor oil vehicle;]
>
> wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks.

Dependent claims limit claims 1 and 9 to a method: wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$ (claims 2, 10); wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer (claims 3, 6, 11, 14); wherein the method

comprises administering intramuscularly to a human in need of such treatment 5 mL of the formulation (claims 4, 7, 12, 15); wherein the method further comprises once monthly administration of the formulation (claims 5, 8, 13, 16); wherein the formulation is administered in a divided dose (claims 17-20).

C. Prosecution history

Petitioner's proposed grounds rely on Howell 1996 and McLeskey, but both were thoughtfully considered by the Patent Office prior to issuance. Howell 1996 was identified at the outset of patent prosecution (Ex. 1002 at 124), and the Examiner found all claims patentable over it. *Id.* at 270-272, 717-719. After learning of McLeskey during litigation in 2009, AstraZeneca disclosed it and explained to the Examiner the very argument that Petitioner trumpets now in Ground Two—"obviousness" based on McLeskey and Howell 1996. *Id.* at 295-300. The Examiner rejected the notion those references could be combined and further found that McLeskey alone fails to teach "hormonal dependent disease[]," the "dosing regimen to be once a month," "intramuscular administration," "volume administered," and "serum concentration[s] of fulvestrant." *Id.* at 313. A declaration by Dr. Ronald J. Sawchuk submitted with applicant's response, confirmed the importance of the differences noted by the Examiner and added other independent reasons for non-obviousness over McLeskey. *Id.* at 334-383.

First, as Dr. Sawchuk's declaration during patent prosecution explained—

and Petitioner tellingly does not challenge here—(1) "*McLeskey* did not disclose plasma or blood levels of fulvestrant in mice after subcutaneous administration of either the peanut oil or the castor oil [fulvestrant] compositions," and (2) the authors "concluded that treatment with fulvestrant (ICI 182,780), using either of the disclosed compositions ***was not effective*** in that it 'did not slow estrogen-independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice." *Id.* at 367-368 (emphasis added). Thus, Dr. Sawchuk logically concluded "because of the lack of fulvestrant efficacy and the absence of pharmacokinetic data in *McLeskey*, one of ordinary skill in the art would have been unable to conclude whether either of the two fulvestrant *McLeskey* compositions (peanut oil or castor oil) was able to deliver a dose of fulvestrant that had an antitumour therapeutic effect in the mice when administered subcutaneously, nor any insight about fulvestrant absorption characteristics (rate and extent) when administered via the *intramuscular route* in any species, including humans." *Id.* at 369. He further noted, "judging solely on the basis of efficacy, the *McLeskey* castor oil composition would have been among the least favored compositions to select for further development [] because the *McLeskey* experiments were ***ineffective***[.]" *Id.* at 371 (emphasis added).

Second, Dr. Sawchuk describes—and again Petitioner does not challenge—how "[t]he mode of administration of a drug (e.g., oral, intramuscular,

subcutaneous, etc.) and the dose administered affects the release profile of the drug" and "[o]ne of ordinary skill in the art would have understood that results from subcutaneous administration in general, and including those reported in *McLeskey*, cannot be extrapolated to intramuscular administration." *Id.* Specifically, Dr. Sawchuk discusses the "abundant evidence in the scientific literature that the intramuscular and subcutaneous administration of a drug to the same animal or human may produce very different plasma level curves, and therefore very different pharmacologic effects" including, e.g., "desired effects (efficacy) and those that are not desired (adverse events, or side effects)." *Id.* at 371-372. He cites to numerous references which show that "subcutaneous administration result[s] in faster absorption compared to intramuscular injection" and others which show the opposite. *Id.* at 372-375, 482-496, 549-556. Thus, Dr. Sawchuk concluded "one of ordinary skill in the art having the very limited experimental subcutaneous data from *McLeskey* would not have had an expectation that the intramuscular administration of fulvestrant using the *McLeskey* castor oil composition would have been effective following intramuscular administration, such as in the method described in the claims." *Id.* at 376.

Third, Dr. Sawchuk's declaration stated "because all of the components of the vehicle disclosed in *McLeskey* are liquids, one of ordinary skill in the art would have concluded that the composition was described in terms of volume/volume

percent units (% v/v)." *Id.* at 363. This principal had been applied in publications and patents known in the art as of the priority date (e.g., "*Neema* lists liquid solvents, co-solvents, and solubilizing agents, and identifies commercial products in which the content of such liquid agents is described on a % v/v basis."). *Id.* at 363, 543-548. Moreover, a component measured in % w/v will have a different concentration value when measured in % v/v. *Id.* at 364-367.

Without citing any one argument as dispositive, the Examiner allowed the claims to issue. *Id.* at 648-656, 717-719.

Petitioner is aware of all of these arguments and references. Petition at 13-14. But, it is only able to muster a response to ***one*** argument: given the absence of units in the McLeskey reference, would the formulation have been understood to be % w/v or % v/v. *Id.* at 37-38.

III. PERSON OF ORDINARY SKILL IN THE ART

The priority date of the '680 Patent is January 10, 2000. The skilled artisan with respect to the '680 Patent at that time would have been a person having a bachelor's or advanced degree in a discipline such as pharmacy, pharmaceutical sciences, endocrinology, medicine or related disciplines, and having at least two years of practical experience in drug development and/or drug delivery, or the clinical treatment of hormone dependent diseases of the breast and reproductive tract. Because the drug discovery and development process is complicated and

multidisciplinary, it would require a team of individuals including, at least, medical doctors, pharmacokineticists, and formulators. Regardless of which definition is adopted, the readings of the references remain the same, and the experts' opinions do not change (Exs. 2001-2003) and institution should be denied.

IV. CLAIM CONSTRUCTION

A. Malignant diseases of the breast

Petitioner alleges no grounds of invalidity dependent on the construction of this term. Accordingly, should the Board institute *inter partes* review, it is not necessary for the Board to construe this term.

B. Sufficient amount of castor oil vehicle

Petitioner alleges no grounds of invalidity dependent on the construction of this term. Accordingly, should the Board institute *inter partes* review, it is not necessary for the Board to construe this term.

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

Petitioner asserts that "[t]he concluding clause of claims 1 and 9 is a 'wherein' clause stating the intended result of the administration of the claimed formulation, namely, a certain blood plasma concentration" and is therefore "non-limiting." Petition at 16. This assertion is wrong. The "wherein" clauses are essential to practicing the claimed methods (e.g., because they identify the dosage and the dosing schedule), and are material to patentability. *Hoffer v. Microsoft*

Corp., 405 F.3d 1326, 1329 (Fed. Cir. 2005) (A wherein, or whereby, clause that "states a condition that is material to patentability . . . cannot be ignored."). Specifically, the wherein clauses set forth the requirement for certain blood plasma concentrations (at least 2.5 $ngml^{-1}$ or at least 8.5 $ngml^{-1}$) to be achieved and maintained for prolonged periods of time (namely, at least four weeks).

First, the '680 Patent expressly identifies the invention as "relat[ing] to a sustained release pharmaceutical formulation." Ex. 1001 at Abstract. Ignoring the wherein clauses removes from the claims this essential characteristic of the formulations delineated. That is wholly improper. A *sustained release formulation* is a drug delivery system that slowly releases the drug over an extended period of time to achieve and maintain a prolonged therapeutic effect (also often described as an extended release system). Ex. 2003 at ¶¶30-33, 36; Ex. 1001 at Abstract; Ex. 2080 at 6; Ex. 2134 at 5. This contrasts with conventional or *immediate release formulations*, which produce relatively rapid increases in blood plasma drug levels—to a high peak—followed by a relatively rapid decrease in those levels. Ex. 2003 at ¶¶28-29, 36.

That the sustained release characteristics of the formulations delineated in the claimed methods are critical cannot be questioned. The specification explains that the inventors "surprisingly found that the [] formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over

an *extended period of time*." Ex. 1001 at 8:58-60 (emphasis added). Further, the formulation is taught to achieve a "*particularly even release profile*," (*id.* at 10:49-50 (emphasis added)), which as explained above is decidedly not what is achieved using an immediate release formulation. Ex. 2003 at ¶¶28-33, 36; Ex. 2080 at 6; Ex. 2134 at 5.

Moreover, like the specification, the prosecution history is replete with references to the invention involving sustained release formulations. For example, the inventors explained to the Patent Office that "[t]he *invention* is focused in particular on the discovery of a novel and unobvious formulation for this extremely difficult to formulate molecule, which formulation is suitable for intramuscular injection to a human patient and is capable of dissolving the therapeutic target amount of fulvestrant in a small enough volume for IM administration, and which formulation provides for the satisfactory *sustained release* of fulvestrant *over an extended period of time as specified in the present claims*." Ex. 2133 at 14 (emphasis added).

Given the identification throughout the specification and prosecution history of the invention as relating to the use of sustained-release formulations, it would be inappropriate to ignore the limitations set forth in the wherein clauses. Those clauses characterize the formulations claimed as sustained release formulations.

The Board has rejected similar assertions to those made by Petitioner. In

BioDelivery Scis. Int'l, Inc. v. RB Pharms. Ltd., Claim 15 recited "an orally dissolving film formation, 'wherein said formulation provides' specific pharmacokinetic profiles." IPR2014-00325, 2015 WL 4045328, at *3 (P.T.A.B. June 30, 2015). There the Board agreed with Patent Owner "that the pharmacokinetic ranges recited in the wherein clause 'give crucial meaning to, and provide defining characteristics provided by the film formulation at issue.'" *Id.* at *3-4. The Board found that in order to meet the requirements of the claim, a formulation "must be capable of producing the pharmacokinetic profile recited in the wherein clause of the claim." *Id.* (citing *Griffin v. Bertina*, 285 F.3d 1029, 1033-34 (Fed. Cir. 2002)). As Dr. Illum explains, it is simply not true that ***any*** formulation would be capable of producing the fulvestrant time-concentration profile recited in the wherein clause of the claims. Ex. 2001 at ¶¶38-42, 166-168.

Second, the fact that the blood plasma fulvestrant concentrations differ amongst the claims (i.e., at least 2.5 $ngml^{-1}$ or at least 8.5 $ngml^{-1}$), means that the wherein clauses provide defining characteristics. Ex. 2003 at ¶60. These limitations, in fact, are pivotal as they dictate the dose and dosing frequency that must be utilized. Ex. 2002 at ¶38; Ex. 2001 at ¶¶33-37; Ex. 2014 at 13. Moreover, clinical studies demonstrated the therapeutic importance of the different blood plasma level limitations of the claims. Ex. 2002 at ¶39 (citing Exs. 2028-2031, 2004-2007). Logically the wherein clauses are meant to impart features that must

be practiced and are not simply an intended result.

D. Therapeutically significant

The term "therapeutically significant" would have been understood by the skilled artisan to be the specified blood plasma fulvestrant concentrations set forth in the respective claims. Ex. 2003 at ¶68. This is clear from the specification, which states: "[b]y use of the term 'therapeutically significant levels' we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient." Ex. 1001 at 9:24-27.

E. Achieves

A skilled artisan would have understood the term "achieves" to mean that the plasma fulvestrant concentration is "achieved for [a period of time]." That is, after injection the minimum specified blood plasma level is achieved and then maintained for the stated period of time.[2] Ex. 2003 at ¶70; Ex. 2001 at ¶34. Petitioner's construction—"achieved an average concentration [C_{avg}] in a patient over the specified time period" (Petition at 18)—is wrong. To begin, the term C_{avg} is *not* mentioned in the claims, specification or prosecution history. Ex. 2003 at ¶70. Second, importing C_{avg} into the claims eviscerates another *explicitly used*

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[2] This is precisely how the term was construed by the district court in the related litigation involving the '680 Patent. Ex. 1011 at 3-4.

claim term: "at least." The claims require blood plasma concentrations of "at least" 2.5 or 8.5 $ngml^{-1}$, but use of an average would make nonsense of the "at least" term as blood plasma levels below those values would be acceptable under Petitioner's construction so long as they are off-set by other higher values. Ex. 2003 at ¶70.

V. STATE OF THE ART

A. McLeskey [Ex. 1005] and Howell 1996 [Ex. 1006]

Petitioner's proposed grounds are based on two references: McLeskey and Howell 1996. Alone and (improperly) in combination these references do not disclose the limitations of the challenged claims.

McLeskey reports on basic biology research studies evaluating an artificial hormone independent / FGF-mediated mouse tumor model. Ex. 2002 at ¶89. These studies were not designed to assess the treatment of any disease with fulvestrant; instead, four different actives, tamoxifen, 4-OHA, letrozole, and ICI 182,780 (fulvestrant) were used as research tools to assess the genetically engineered mouse model. *Id.* at ¶92. And, a skilled artisan would understand that the formulations used for these four actives were specifically designed for small animal (rodent) research (for example, tamoxifen was administered as specially made mouse subcutaneous pellets while humans take oral pills). *Id.* at ¶¶153-159, 168; Ex. 2001 at ¶¶57, 157, 178, 184; Ex. 1005 at 2.

McLeskey does not disclose data related to the safe or effective treatment of humans (or even animals) with fulvestrant or any of the other actives used. Ex. 2002 at ¶93. In fact, McLeskey repeatedly indicated that the formulations were "***treatment failures***," i.e., they did ***not*** inhibit tumor growth. *Id.* at ¶161; Ex. 1005 at 4-6, 10. Indeed, McLeskey points to Howell 1996, and the poor response with fulvestrant disclosed, as a rationale for studying an alternative (i.e., hormone independent) FGF mediated model of tumor growth. Ex. 1005 at 1-2; Ex. 2002 at ¶¶162, 191-192. There is also no disclosure in McLeskey of pharmacokinetic data or solubility of fulvestrant in any formulation. Ex. 2002 at ¶¶94, 165; Ex. 2001 at ¶¶59, 66-72.

Howell 1996 discloses a small preliminary clinical study designed to investigate whether fulvestrant itself could have an effect on progression of metastatic cancer. Ex. 2002 at ¶170. Participation was risky—fulvestrant was from an unproven class—so the 19 patients were "highly selected" for the best chance of response. *Id.*; Ex. 1006 at 7. Fulvestrant was administered as a monthly intramuscular injection in a castor oil-based vehicle (with no other formulation details provided). Ex. 1006 at 2.

With respect to response rate, Howell 1996 points to a number of confounding factors, including the "highly selected" nature of the patients and the well-known phenomena of tamoxifen resistance (that a positive response may be

an artifact of stopping tamoxifen treatment). Ex. 1006 at 7. Accordingly, the paper concluded that further studies were needed to confirm the observed response rate. *Id.* In particular, the tumors in seven patients showed a positive response (shrinking), but as explained in Howell 1996, tamoxifen resistance could account for ***one third*** of those. *Id.* Taking that into account, only five patients showed a positive response to fulvestrant. Ex. 2002 at ¶¶74, 106, 171. And, in any event, researchers at the time warned that Howell 1996 data "should be interpreted with care." *Id.* at ¶¶74, 106, 174; Ex. 2038 at 1.

Howell 1996 also reported that the study could not determine the appropriate therapeutically significant blood plasma fulvestrant level because "a direct pharmacokinetic-pharmacodynamic link [was] not proven with the few patients studied to date." Ex. 1006 at 6. However, because drug accumulation was observed, the authors advised ***lowering*** the dose from that used in the study. Ex. 1006 at 6-7; Ex. 2002 at ¶¶103-105, 176-178.

With few questions answered and but a few patients responding, the Howell 1996 authors concluded that fulvestrant only "warrant[ed] further evaluation." Ex. 1006 at 1. That left fulvestrant as only a "maybe." Ex. 2002 at ¶¶100-106, 169-186.

B. Active: A skilled artisan had no reason to start with fulvestrant

Breast cancer is divided into hormonal dependent and hormonal independent

subtypes. This classification dictates the appropriate treatment paradigm. Ex. 2002 at ¶40. In "hormonal dependent" cancers, estrogen binds to the estrogen receptor and causes growth of the cancer cells. Thus, an approved "endocrine therapy" that acts on this hormonal pathway may be effective. *Id.*

AstraZeneca developed the first endocrine therapy for breast cancer, tamoxifen. Tamoxifen became the "most important" endocrine agent for breast cancer, in part, because it balanced anti-estrogenic ("antagonist") properties with beneficial estrogenic ("agonist") properties. Ex. 2002 at ¶¶42-43; Ex. 2010 at 4; Ex. 2022 at 1; Ex. 2023 at 1-2. Tamoxifen blocks estrogen from fueling breast cancer tumors in breast tissue. Ex. 2010 at 4. But in other tissues, like bone and the heart, it acts like estrogen, providing beneficial protection. Ex. 1018 at 5. Unfortunately, patients treated with tamoxifen eventually develop resistance and resumed tumor growth. Ex. 2010 at 4; Ex. 2013 at 1. Thus, prior to 2000, there was a need for (1) improved treatments for hormone dependent breast cancer, and (2) improved treatment options for patients following tamoxifen failure. Ex. 2002 at ¶¶44-45; Exs. 2013-2021. Any treatment would have to be either more effective, or at least as effective but safer than, tamoxifen. Ex. 2002 at ¶46. Also, it was believed that treating physicians and patients would be highly reluctant to try any treatment other than a once a day pill. *Id.*; Ex. 2020 at 4.

1. Petitioner ignores the many other treatment options available to the skilled artisan

In 2000, when the '680 Patent foreign priority application was filed, researchers were looking at a host of potential targets for treating breast cancer—and for each target, a number of different "active ingredients." Ex. 2002 at ¶¶47-48.

A "better" tamoxifen seemed promising—at least six other chemicals in the same class as tamoxifen, selective estrogen receptor modulators ("SERMs"), were being considered. *Id.* at ¶¶49-52; Ex. 2022 at 2; Ex. 2023 at 11-12. The excitement surrounding SERMs led to an "explosion of research" and "race to develop [] 'designer estrogens' or [SERMs] as pharmaceutical products." Ex. 2023 at 2. Another leading class were aromatase inhibitors ("AIs"). Ex. 2002 at ¶¶53-56. AIs inhibit the production of estrogen by targeting the aromatase enzyme and this mechanism of action had been proven to be effective against hormone dependent breast cancer in thousands of patients. *Id.* Because this mechanism of action differs from that for tamoxifen, it was understood AIs were likely to be effective in patients who had developed resistance to tamoxifen. *Id.*; Ex. 2025 at 2. In fact, Arimidex® (whose active ingredient is an AI, anastrozole) was becoming the gold standard for endocrine therapy. Ex. 2002 at ¶¶54, 207. Three AIs were approved by the priority date here, and four new AIs were in development. *Id.* at ¶¶54-55. All of these AIs, like the SERMs, were convenient once daily pills. Ex.

2022 at 4; Ex. 2025 at 4; Ex. 2026 at 5, 9. Other endocrine classes also had been approved and marketed (that is, had proven mechanisms of action) and researchers were investigating new agents with promise in those classes, including estrogens, progestins and androgens. Ex. 2002 at ¶64; Ex. 2037 at 1; Ex. 2035 at 2-3; Ex. 2016 at 7; Ex. 2036.

In contrast to these proven classes, fulvestrant was the first in a new class of compounds known as "pure antiestrogens." Ex. 2002 at ¶¶57, 68. As of the priority date of the '680 Patent there was no established link between pure anti-estrogens and successful treatment of breast cancer in patients—the most any reference cited by Petitioner concluded was that further testing was warranted. *Id.* at ¶¶57-63, 66-75.

Moreover, this new and unproven class was tainted by fears about "cross-resistance," and potentially detrimental bone, cardiovascular and other off-target effects. *Id.* at ¶¶58, 70; Ex. 1028 at 7 ("One predicted undesirable action of pure antiestrogens in therapeutic use may be a tendency to reduce bone density and hence to precipitate or exacerbate osteoporosis."); Ex. 1018 at 5 ("On the basis of our data, we would predict that most patients with ICI 182,780-resistant tumors, would not respond well to subsequent treatment with tamoxifen. . . . The effect of [fulvestrant] on [bone and blood lipids] is not yet known, but it might be deleterious given its lack of estrogenic qualities.").

All told, there were at least 15 other more promising candidates for endocrine treatment for hormonal dependent breast cancer as of the priority date. Ex. 2002 at ¶68.

2. Fulvestrant had not been established to be an effective treatment

As of the priority date, fulvestrant was far from a "known [] effective treatment" as Petitioner alleges. Petition at 11.

Petitioner's "known" efficacy assertion hinges on results in but a very few patients. As described above, Howell 1996 reports that seven patients had tumors shrink, but as the authors noted, the withdrawal of tamoxifen could account for about 1/3 of those responses, leaving only five patients. Ex. 1006 at 7; Ex. 2002 at ¶¶74, 106, 171. Indeed, researchers at the time instructed that the results of Howell 1996 "should be interpreted with care" because of tamoxifen withdrawal and issues with study design, including the "highly selective" nature of the patients. Ex. 2002 at ¶¶74, 98, 170, 174; Ex. 2038 at 1. McLeskey itself points to Howell 1996 as an example of the poor response rate achieved through fulvestrant therapy. Ex. 1005 at 2 ("***[O]nly about*** 30-40% of such patients have a positive response to subsequent [fulvestrant]." (emphasis added)).

While Petitioner also relies on Wakeling 1993 and Osborne 1995 (both non-clinical animal studies on basic biological activity), neither says or suggests efficacy was "***known***." Both note potential areas of serious concern. Ex. 2002 at

¶¶59, 127, 142, 172; Ex. 1028 at 7; Ex. 1018 at 5. Petitioner's cited state-of-the-art proves fulvestrant was far from a "known [] effective treatment."

C. Critical questions remained about the amount of fulvestrant to deliver and how

1. Amount: Therapeutically effective blood plasma levels

Virtually all previous endocrine drugs for treating breast cancer at the time had struggled with determining the right blood plasma level for effective, safe treatment of breast cancer and all eventually went to lower doses than those originally predicted in animal studies and used in initial clinical trials. Ex. 2002 at ¶¶179-182. Studies with endocrine breast cancer treatments (e.g., tamoxifen, toremifene, fadrozole, aminoglutethemide, and anastrozole) proved that although higher doses could be tolerated, they showed ***no*** corresponding increase in clinical benefit and could increase off target effects. *Id.*; Ex. 2010 at 4 ("Several randomized studies demonstrated that tamoxifen doses higher than 20 mg/d do not confer further advantages. . . . Toremifene doses higher than 60 mg/d did not offer any advantages over lower doses."); Ex. 2022 at 3 ("The group using 10 mg/day [anastrozole] showed no advantage in response rate or survival over the group using 1 mg/day [anastrozole].").[3]

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[3] In a previous litigation, the clinical expert testifying for the patent challengers admitted that this concept was well known. Ex. 2002 at ¶182; Ex.

Howell 1996 reports that "a direct pharmacokinetic-pharmacodynamic link is not proven with the few patients studied to date" and instructs that—consistent with the experience with other endocrine treatments—"lower doses of the drug may be effective in maintaining therapeutic serum drug levels." Ex. 1006 at 6; *see also id.* at 7 ("At the dose used, there was accumulation of the drug over time and thus lower doses than those administered in this study may be as effective in maintaining therapeutic serum drug levels, although further clinical studies are required to confirm this hypothesis."); Ex. 2002 at ¶¶103-105, 176-182.

The patent claims go in the opposite direction from the conventional wisdom discussed above, they teach ***increasing*** blood plasma fulvestrant levels.

2. Administration: Route, excipients, and result intertwined

Petitioner asserts "a POSA would have known that steroid drug products like fulvestrant would be formulated in an oily vehicle," and thus "oily vehicles should be used to deliver the drug." Petition at 28. But Petitioner completely ignores—in an example of improper hindsight—that commercial formulations of other steroids utilized virtually every route of administration, including oral, transdermal, intravenous, intramuscular, nasal and suppositories, using thousands of different

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2049 at 216:4-7 ("Q. Dr. Mehta, you are familiar with the experience with endocrine therapies that greater doses even without toxicity did not lead to increased efficacy, right? A. I'm familiar with that.").

excipients. Ex. 2001 at ¶¶45, 51, 139-143; Ex. 2082 at 5-9; Ex. 2083 at 24-32; Ex. 2084 at 5. And, each route of administration, in turn, presented a multitude of potential dosage forms (Ex. 2001 at ¶47; Ex. 2083 at 25; Ex. 2087 at 20; Ex. 2086 at 11) and hundreds of possible excipients (in countless potential combinations). Ex. 2001 at ¶¶49, 132; Ex. 2088 at 1; Ex. 1043. In fact, the vast majority of steroids were formulated as oral dosage forms, not intramuscular injections in oily vehicles. Ex. 2001 at ¶¶130-131; Ex. 2101; Ex. 2102 at 9, 17-18; Ex. 2127 at 4. And, no prior art steroid was formulated in an injection as large as 5 ml (as claimed) or in an injection with ***all four*** of the excipients found in the formulations of the challenged claims (let alone in the claimed ratios). Ex. 2001 at ¶¶143, 175, 185-187; Ex. 2054 at 1; Ex. 2002 at ¶186.

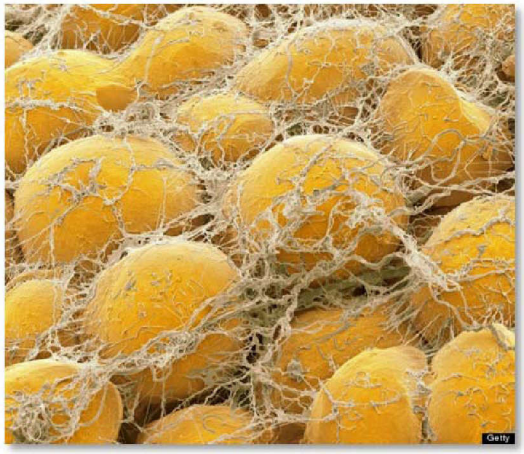
Each potential route of administration is different from the others, and would result in different absorption profiles of the drug after administration. Ex. 2001 at ¶46; Ex. 2082 at 7; Ex. 2083 at 24; Ex. 2085 at 7; Ex. 2086 at 16. For example, as may be intuitive, absorption profiles for oral and transdermal administration differ.

So it is with intramuscular and subcutaneous administration—all "injections" are not the same. In particular it was (and is) well understood that the local environment the formulation encounters following an *intramuscular* injection is very different from the environment the same formulation would encounter, following a *subcutaneous* injection. Ex. 2001 at ¶¶167, 191-199; Ex. 2108 at 8

("Intramuscular injections are made deep into the skeletal muscles."); Ex. 2106 at 9 (Subcutaneous injection is usually made in the loose interstitial tissues beneath the surface of the skin.); Ex. 2083 at 30. Electron micrographs illustrate these differences:

Intramuscular

Subcutaneous



Studies that compared the administration of the *same* formulation via intramuscular versus subcutaneous injection found that the results were entirely unpredictable—sometimes drastically faster releases with intramuscular injection and sometimes with subcutaneous injection and sometimes more tolerable in intramuscular injection than subcutaneous injection or vice versa while for some the change in environment meant no release at all. Ex. 2001 at ¶¶191-199; *Cf.*, e.g., Ex. 2121 at 1 ("The s.c. route appears to be superior to the i.m. route in terms of local tolerance and serum drug level[.]") *with* Ex. 2119 at 2 ("Absorption of drugs which are given subcutaneously is generally slower than after intramuscular

administration because of less efficient regional circulation.").

The three early stage human experiments with fulvestrant that were reported in the prior art (Howell 1996 (Ex. 1006), DeFriend 1994 (Ex. 2027), and Thomas (Ex. 2039)) demonstrated that for fulvestrant the method of administration for clinical use was far from having been determined and the preferred route was oral. Ex. 2001 at ¶¶122-135; Ex. 2002 at ¶¶76-86. Preliminary studies like these often used prototype formulations to answer basic questions, with full formulation work to follow later. Ex. 2001 at ¶135; Ex. 2051 at 14 (such trials "are frequently conducted with experimental formulations which will not be marketed"). What these three early trials did establish was that once a day (DeFriend 1994 (Ex. 1027) and Thomas (Ex. 2039)) and long-term administration (Howell 1996 (Ex. 1006)) were being considered. Potential once-a-day formulations included oral, subcutaneous, nasal and pulmonary. Ex. 2001 at ¶¶45, 51. Once-monthly options for formulation included transdermal, subcutaneous depot, and intramuscular injection. *Id.*

Of these, a once-a-day oral formulation of fulvestrant was unquestionably favored: "[c]ompared with alternate routes, the oral route is considered the most natural, uncomplicated, convenient, and safe means of administering drugs." Ex. 2083 at 26. The leading breast cancer treatments, tamoxifen and Arimidex®, were daily oral tablets and physicians thought that patients would be reluctant to

consider any treatment but a once a day pill. Ex. 2020 at 4 ("An orally active agent should be an ***essential*** component of any strategy to introduce a new antiestrogen. Oral tamoxifen is so well tolerated that patients would be reluctant to consider injections or sustained-release implants as an alternative." (emphasis added)). There was no reason to believe that a suitable replacement for a once-daily pill would be an unconventionally large 5 ml oily injection.

3. Claimed combination of excipients was unconventional

Petitioner asserts that the excipients used in the claims were "conventional excipients" used under "standard formulation principles." Petition at 28. But, Petitioner does not—and cannot—cite to any prior art disclosing the combination of castor oil, benzyl benzoate, benzyl alcohol and ethanol for intramuscular administration. The logical conclusion for this conspicuous absence is that the combination was unconventional. Ex. 2001 at ¶¶143, 185-187.

In fact, for intramuscular injections, the unpredictable and poorly understood impact of physical, chemical, and biological properties meant absorption was understood to be "very erratic and variable." *Id.* at ¶¶162, 165-169. Absorption of the drug is influenced by the physical shape of the formulation as it spreads within the muscle, absorption and metabolism of the vehicle itself and biological factors like lymphatic transport and inflammation caused by the formulation changes at the injection site. Ex. 2116 at 4; Ex. 2115 at 2; Ex. 2114 at 13-14. The physical

shape of the formulation as it spreads within the muscle may influence absorption. Ex. 2115 at 2. Changes in composition of the formulation in the muscle over time may change physicochemical properties, such as the solubility of the active, possibly leading to precipitation of solid particles in the muscle. Ex. 2082 at 11. This, in turn, can damage tissue and results in unpredictable or incomplete absorption into the blood plasma. Ex. 2108 at 4. Intramuscular injection is not, as Petitioner suggests, always long-acting and slow release (Petition at 24)—it can be short-acting instantaneous release (like that in DeFriend 1994 (Ex. 1027)). Release rates from intramuscular injection can be fast, slow, erratic, or nonexistent—leading to a multitude of different blood plasma profiles (or no blood plasma levels). Ex. 2001 at ¶¶40-41, 191-199. Success of an intramuscular injection cannot be predicted through modelling or *in vitro* testing, but rather, only through *in vivo* testing in live subjects. *Id.* at ¶¶169, 216.

In short, the results of intramuscular administration of the formulations set forth in the challenged claims would have been considered surprising and unpredictable by a skilled artisan as of the priority date. Ex. 2001 at ¶¶19, 36, 42, 66, 200-217. The irritation of muscle that had plagued prior art formulations of other steroids was nonexistent. *Id.* at ¶¶66, 72, 103-105, 137, 163-165, 201, 217; Ex. 1022 at 3-4. And, also surprisingly, although the claimed excipients dissipate from the muscle in days, fulvestrant slowly enters the blood stream for over a

month. Ex. 1001 at 9:6-23. It is still a mystery—and Petitioner provides no cogent explanation—as to how the claimed intramuscular injection provides consistent release over a month without precipitation.

Nothing in the prior art would have led a skilled artisan to believe that the patented method of treatment, including the administration of an unconventional combination of excipients would succeed. Petitioner notes that a skilled artisan "would have also understood basic principles of pharmaceutical formulation well-known in the art." Petition at 31. One of the most basic of these is that the active and excipients in a formulation interact with each other and the tissue into which they are administered. Ex. 2001 at ¶¶43-49, 160-169; Ex. 2114 at 1-2, 7, 14; Ex. 2082 at 5; Ex. 2085 at 7; Ex. 2107 at 12, 31-32.

The very reference relied upon by Petitioner for its theory that because other steroids had been delivered in castor oil formulations with benzyl benzoate, fulvestrant could be, actually proves the opposite. Petition at 30. Riffkin discloses that different active ingredients, with the same excipients, showed markedly different properties in the muscle. Ex. 2001 at ¶¶103-105, 163-164; Ex. 1022 at 3-4. As to excipients, Riffkin similarly demonstrated that small changes in excipients—even just small changes in the amounts—resulted in very different effects in the muscle. *Id.* For example, comparing formulation SHY-47-7 in Table IV of Riffkin to SHY-14-15 shows that adding 2% benzyl alcohol caused a 40%

increase in lesion size—disproving Petitioner's unsupported argument that all formulations with "conventional" excipients are the same. *Id.*; Petition at 28-30. As another example, comparing formulation SHY-47-7 to SHY-47-4 in Table IV shows that adding 35% benzyl benzoate increased the lesion from "too small to measure" to 262 mm^3. Ex. 1022 at 3. Further, in Table V of Riffkin, a formulation with 58% castor oil, 40% benzyl benzoate, and 2% benzyl benzoate had double the lesion size of a formulation of just 54% castor oil and 46% benzyl alcohol. *Id.*

VI. THE '680 PATENT IS VALID AND NOT OBVIOUS

A. Law of Obviousness

Petitioner must prove that the claims of the '680 Patent are obvious by preponderance of the evidence. A claimed invention is obvious when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Obviousness is based on four factual determinations: (1) scope and content of the prior art; (2) differences between the prior art and the claimed invention; (3) level of skill in the art; and (4) any objective evidence of non-obviousness. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1566-67, 1569 (Fed. Cir. 1987). This inquiry considers whether "a skilled artisan would have had reason to combine the teaching of the prior art

references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012) (citation omitted).

Ignoring the entirety of the art, and thus clearly using hindsight—Petitioner picks one small early (inclusive) clinical trial, Howell 1996, and anoints it the crown jewel of the extensive research directed to hormonal dependent breast cancer (it was not) and combines it with McLeskey, a paper concerning (1) basic biological research in animals; (2) a different type of cancer (hormone independent); and (3) advocating treatment with a different class of active ingredient (growth factor inhibitors). Petitioner ignores the required threshold showing of a reason to ***select*** the prior art elements in the first place. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011) ("[O]bviousness requires [] showing that a person of ordinary skill at the time of the invention would have selected and combined th[e] prior art elements in the normal course of research and development to yield the claimed invention."). Reasoning of the type employed by Petitioner, which "simply retrace[s] the path of the inventor with hindsight, discount[s] the number and complexity of the alternatives, and conclude[s] that the invention [is] obvious . . . is always inappropriate for an obviousness test." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

Moreover, only after justifying the initial selection of prior art does the obviousness analysis progress to asking whether the skilled artisan would have combined the references as Petitioner suggests. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 424-25 (2007). To protect against the "distortion caused by hindsight bias," there must be "a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does." *Id.* at 418, 421. And, a finding that it would have been obvious to combine multiple prior art references also requires a showing that "the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*, 676 F.3d at 1069. Petitioner fails to provide this reason to combine or the expectation of success—either failing fatal to its Petition.

B. Ground One: McLeskey

The McLeskey reference does not disclose critical claim limitations, and would in fact have directed a skilled artisan away from those limitations.

All of the '680 Patent claims are to methods of treatment and include the route of administration (intramuscular), specific blood plasma levels and duration, the particular condition (hormone dependent disease) and patients (humans) to be treated, as well as the components and amounts of the formulation administered. Petitioner ignores most of the claim elements and looks only at the ingredients in the formulation of the claims and compares those to McLeskey. But, as the chart

below illustrates, every other element of the claimed methods of treatment is missing from (or contradicted by) McLeskey. Ex. 2001 at ¶¶150-152; Ex. 2002 at ¶¶147-148.

'680 Patent Claim Limitations	**McLeskey**
A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising	NOT hormonal dependent . . . "hormone independent" NOT treatment . . . "treatment failure" NOT malignant disease of the breast . . . genetically engineered model
administering intramuscularly	NOT intramuscular . . . "subcutaneous"
to a human in need of such treatment a formulation comprising	NOT human . . . "mice"
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.	NO blood plasma levels NOT therapeutically significant . . . "treatment failure" NOT once every four weeks . . . "once weekly"

First, McLeskey does not teach a "method of treating" breast cancer—the authors found the tested formulations to be "treatment failure[s]." Ex. 1005 at 10.

Second, McLeskey involved a model of estrogen-independent growth, and not the claimed hormonal dependent breast cancer. Ex. 1005 at 2 ("We therefore sought to determine the sensitivity of the estrogen-independent tumor growth of FGF-transfected MCF-7 cells to [fulvestrant]."). ***Third***, McLeskey administered the castor oil-based formulation to mice, not humans, as in the claimed methods. Ex. 1005 at 2-3. ***Fourth***, the formulations were administered subcutaneously, not by the claimed intramuscular route. Ex. 1005 at 2 ("ICI 182,780 . . . was administered s.c."). ***Fifth***, as to the claimed blood plasma levels, no data concerning blood plasma levels are disclosed in McLeskey. And, ***sixth***, the claims required that the therapeutic blood plasma levels be maintained for four weeks and McLeskey required weekly administration. Ex. 1005 at 2 ("ICI, 182,780 . . . was administered . . . every week."); Ex. 2001 at ¶¶159, 190.

That the McLeskey reference does not disclose these critical claim limitations was also acknowledged by the Examiner during prosecution of the '680 Patent. Ex. 1002 at 313 ("Mc[L]eskey et al. teaches a studies employing subcutaneous injection of fulvestrant to nude mice. . . . [it] does not expressly teach the use of fulvestrant in treating hormonal dependent diseases of the breast. It does not expressly teach the dosing regimen to be once a month, intramuscular administration, or the volume administered. Mc[L]eskey et al. does not expressly teach the herein claimed serum concentration of fulvestrant."). And, Dr.

Sawchuk's Declaration explained the importance of these missing limitations, as well and why a skilled artisan would have been directed away from the limitations of the claims. *See supra* at 8-11.

Petitioner attempts to "fill in" the missing limitations by reference to ***eleven*** other references: Wakeling 1991, Wakeling 1992, Osborne 1995, Wakeling 1993, Dukes 1992, Dukes 1993, Howell 1995, Howell 1996, DeFriend 1994, O'Regan 1998, Dukes 1989. Petition at 21 (citing Ex. 1003 at ¶¶63-92, 163-174; Ex. 1004 at ¶¶62-109). To the extent Petitioner is arguing that a skilled artisan would have combined these eleven references with McLeskey to render the claims obvious, Petitioner has not even attempted to argue a motivation to combine or reasonable expectation of success as is required under the law.[4] It is axiomatic that "[o]bviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. Rather, obviousness requires the additional showing that a skilled artisan as of the priority date would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention."

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[4] For this reason, Petitioner's Petition fails to comply with 37 C.F.R. § 42.104(b)(2) "which requires Petitioner to identify 'the patents or printed publications relied upon for each ground.'" *Boehringer Ingelheim Int'l GmbH v. Biogen Inc.*, IPR2015-00418, 2015 WL 4467391, at *9 (P.T.A.B. July 13, 2015).

Unigene, 655 F.3d at 1360.

The sheer number of references and modifications here indicates the nonobviousness nature of the claims in view of McLeskey. This Board has denied institution when "the Petition lacks adequate reasoning, with rational underpinning, to show sufficiently that a person of ordinary skill would . . . simultaneously make all of the many particular proposed changes and implementation choices" and "given the extent of the proposed modifications as well as the thin reasoning proffered for each modification," has concluded "that the Petition improperly 'reli[es] upon *ex post* reasoning' and impermissible hindsight reconstruction to piece together the [patent claims]." *Apple, Inc. v. Contentguard Holdings, Inc.*, IPR2015-00449, 2015 WL 4760572, at *11 (P.T.A.B. July 15, 2015).

In any event, the McLeskey reference by its very text demonstrates there would be no motivation to combine and no expectation of success in doing so. The authors describe the fulvestrant formulations as a "treatment failure" and expressly use administration by a different route, to different subjects, and over a different schedule. Ex. 1005 at 2, 10.

1. McLeskey describes the fulvestrant formulations as a "treatment failure"

Petitioner's entire argument hangs on the assertion that "McLeskey—disclosed a *successful* castor oil formulation, including the complete formulation details." Petition at 34 (emphasis added). But, the very text of

McLeskey refutes this. McLeskey characterizes the fulvestrant animal formulations used as "***treatment failure[s]***." Ex. 1005 at 10 (emphasis added). In fact, McLeskey repeatedly emphasizes the failure of these fulvestrant (ICI 182,780) animal formulations to arrest the cancer:

- "Treatment with ICI 182,780 ***did not inhibit*** tumor growth" (*Id.* at 4 (emphasis added));
- "***[F]ailure of ICI 182,780 to inhibit*** the estrogen-independent growth exhibited by this cell line" (*Id.* (emphasis added));
- "Fig. 1 Growth of FGF-transfected MCF-7 cells in ovariectomized nude mice is ***not inhibited by treatment with ICI 182,780***" (*Id.* at 5(emphasis added));
- "ICI 182,780 ***did not decrease tumor growth***" (*Id.* (emphasis added));
- "ICI 182,780 ***did not inhibit*** estrogen-independent tumor growth" (*Id.* (emphasis added));
- "Administration of ICI 182,780 to animals . . . ***produced no effect***" (*Id.* (emphasis added));
- "[T]he continued ***progressive in vivo growth***" (*Id.* (emphasis added));
- "Table 1 Metastasis of FGF-transfected MCF-7 cells is ***not inhibited by treatment with ICI 182,780*** or aromatase inhibitors" (*Id.* at 6 (emphasis added));

- "Metastatic Frequency of Tumors Produced by FGF-transfected MCF-7 Cells in Mice Treated with ICI 182,780 or Aromatase Inhibitors Is ***Not Affected by Treatment***" (*Id.* (emphasis added));
- "FGF-transfected MCF-7 cells is ***not affected by ICI 182,780*** or by either of two aromatase inhibitors . . . treatment failure" (*Id.* at 10 (emphasis added)).

Further, the McLeskey reference provides absolutely no physical characterization of the compositions. While Petitioner argues that McLeskey shows the solubility of fulvestrant in the components of the formulation (Petition at 42-44), no solubility information is disclosed nor is it stated that the composition is a solution. Ex. 2001 at ¶¶54-55, 66-72, 172, 176. More importantly, no pharmacokinetic data—no blood levels of fulvestrant—is disclosed. *Id.* at ¶¶144, 159, 170; Ex. 2002 at ¶¶94, 159, 165. Given the authors' conclusion that fulvestrant was a treatment failure and the absence of pharmacokinetic data, the skilled artisan could not conclude whether the formulation delivered a dose of fulvestrant that had any potential antitumour therapeutic effect in the mice when administered subcutaneously. *Id.*

Despite the fact that Dr. Sawchuk's Declaration, submitted during prosecution, pointed out this very issue, Petitioner's Petition ignores it. Petitioner only waves at what it terms "common knowledge" that fulvestrant (the compound)

worked in other assays in other (or unknown) formulations administered in different ways. But, that cannot convert what the McLeskey reference itself describes as a "treatment failure" into the opposite, a "successful treatment."[5]

2. McLeskey utilizes a different route of administration (subcutaneous) with vastly different subjects (genetically engineered mice)

Petitioner relegates a critical distinction between the challenged claims (intramuscular injection) and the McLeskey reference (subcutaneous administration) to a footnote. Petition at n.14. Admitting that "the McLeskey experiments used subcutaneous administration," Petitioner gives ***no*** reason

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[5] The Board has agreed with this logic previously. In *Lupin Ltd. v. Pozen Inc.*, the Board denied institution, when petitioner did not sufficiently explain why a skilled artisan would reach "'enteric-coated naproxen and immediate-release esomeprazole' with a reasonable expectation that it would 'be therapeutically effective'" when the cited reference, explicitly taught a preference otherwise (i.e., esomeprazole "protected from contact with the acidic gastric juice" in an enteric coated layer and NSAID "transferred in intact form" to the gastrointestinal tract). The Board refused to accept reliance "on selective portions of Chen, without adequate considerations of the surrounding context" and "conclusory statements . . . without citing additional evidence in support." IPR2015-01774, 2016 WL 1081583, at 3, 5-6 (P.T.A.B. Mar. 1, 2016).

whatsoever to modify this route, or expect success, except to note that other castor oil formulations ***can*** be used intramuscularly. That, of course, ignores that the formulation used in McLeskey *was not* administered intramuscularly, but rather subcutaneously.

The art is clear that changing from subcutaneous to intramuscular administration would be expected to markedly change absorption rates and resulting blood plasma levels and durations. Ex. 2001 at ¶¶158, 166-170, 191-199; Ex. 2002 at ¶¶166, 193. On one hand, some substances and formulations administered by subcutaneous injection are more quickly absorbed, and quicker to act, as compared to administration by intramuscular injection. Ex. 2001 at ¶194; Ex. 2086 at 15; Ex. 2120 at 6; Ex. 2121 at 1. Other references taught that substances administered by intramuscular injection were more quickly absorbed, and quicker to act, as compared to subcutaneous injection. Ex. 2001 at ¶195; Ex. 2107 at 12, 17; Ex. 2119 at 2; Ex. 2113 at 50.

This proof that the outcome of Petitioner's proposed change in route of administration was entirely unpredictable was cited during patent prosecution. Ex. 1002 at 372-375, 482-496, 549-556. Nevertheless, Petitioner fails to address this issue and those references—tantamount to an admission that it cannot.

Moreover, the text of the McLeskey reference provides no support for such a modification, and gives no reason to believe that such a modification would be

successful. In fact, a skilled artisan would have understood that the formulations used in McLeskey were ***all*** designed for the constraints of small animal research and ***unsuitable*** for other routes of administration. Ex. 2001 at ¶¶57, 157, 178, 184; Ex. 2002 at ¶¶152-159, 168. For example, for humans, tamoxifen was administered in oral tablets, while in McLeskey, the tamoxifen was administered using preformulated subcutaneous mouse pellets purchased from Innovative Research of America, a company that manufactured only specialty animal research formulations. Ex. 1005 at 2; Ex. 2044 at 9; Ex. 2045 at 4. Similarly, in McLeskey, letrozole was administered in a liquid vehicle of 0.3% hydroxypropyl cellulose via gavage—for humans, letrozole was approved and sold as oral tablets. Ex. 1005 at 2; Ex. 2046 at 12. 4-OHA, also known as formestane, was administered in an aqueous vehicle of 0.3% hydroxypropyl cellulose by subcutaneous injection once daily, six days a week in McLeskey—for humans, that active was only approved in Europe and was administered intramuscularly every two weeks using as a completely different formulation. Ex. 1005 at 2; Ex. 2047 at 8. Dr. McLeskey herself stated that "[t]he paper is clear that the formulations of these drugs were for research purposes for subcutaneous administration to mice—not treatment of humans." Ex. 2043 at 2; Ex. 2002 at ¶153. Indeed, the conclusion is inescapable: a skilled artisan would have believed all the formulations used in McLeskey—including the fulvestrant formulations—were for use in animal

research, not for human therapy.

Petitioner asserts that "McLeskey's mice were administered fulvestrant s.c. due to their small muscle volume." Petition at 40. And, it is true that for basic biological research in animals, subcutaneous administration is more convenient—that is why materials specially pre-formulated for subcutaneous administration (like the tamoxifen pellets) are often used in such research. And, Petitioner's expert Dr. Oleksowicz provides opinions that support this. Ex. 1004 at ¶169. However, different formulations are used for different routes of administration—as is clear from the comparison of the formulations used in McLeskey for the various actives to the human formulations utilizing different routes (*supra* at 43). In fact, the skilled artisan would have known that small animals such as rats and mice ***can*** receive intramuscular injections, to test intramuscular formulations. Ex. 2002 at ¶83; Ex 2001 at ¶158; Exs. 1007, 2128-2131. Petitioner's argument that a preformulated subcutaneous animal research formulation (like a tamoxifen pellet) would be seen as interchangeable with an intramuscular human formulation (Petition at 40) is inconsistent with the art and contradicted by the basis of its own expert's testimony.

Petitioner's reliance on other references to argue that "[i]ntramuscular monthly doses of fulvestrant were repeatedly disclosed in the art" (Ex. 1004 at ¶138) does not cure the fact McLeskey teaches subcutaneous administration—if

anything those references highlight how different the McLeskey reference really is. Moreover, Petitioner provides no details supporting a motivation for modifying the McLeskey disclosure from subcutaneous to intramuscular injection and no explanation as to why there would have been an expectation of success in doing so.[6] Petition at 40 (citing Ex. 1003 at ¶¶56-62, 98; Ex. 1004 at ¶¶138-144). *See Universal Remote Control, Inc. v. Uei Cayman, Inc.*, IPR2014-01111, 2014 WL 6737921, at *6 (P.T.A.B. Nov. 24, 2014) (denying institution where petitioner failed "to make any persuasive evidentiary presentation" that a skilled artisan "would have had either the ability or the motivation to modify").

These types of "conclusory" assertions which "lack[] an articulated or apparent reason supported by 'some rational underpinning' to modify/combine the purportedly known elements into the fashion claimed" by the patent but instead "leave[] it to the Board to ascertain what gaps to fill" are insufficient to sustain institution. *Apple, Inc. v. Contentguard Holdings, Inc.*, IPR2015-00357, 2015 WL 9899009, at *5 (P.T.A.B. June 29, 2015); *see also General Plastic Indus. Co. v. Canon Inc.*, IPR2015-01954, 2016 WL 1084221, at *9-10 (P.T.A.B. Mar. 9, 2016)

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[6] In fact, one of the references cited by Petitioner in supposed support of its assertion, Dukes 1989, discloses the ***intramuscular*** administration of a different fulvestrant formulation to rats, confirming that formulations are route specific. Ex. 2001 at ¶¶180-181.

(denying institution where "[p]etitioner proffers only conclusory obviousness assertions" which do "not sufficiently persuade[] that a skilled artisan would have had a reason to modify . . . and that the proposed modification . . . would arrive at the claimed subject matter").

3. McLeskey provides no pharmacokinetic data nor any suggestion of the specific blood plasma levels and durations claimed

Specific therapeutically significant blood plasma levels are required by the claims. But, McLeskey lacks any blood plasma level information and states nothing to point to a specific level as therapeutically significant. Ex. 2002 at ¶¶94, 165; Ex. 2001 at ¶¶59, 66-72.

Given this unmistakable deficiency in McLeskey, Petitioner tries to argue that the therapeutically significant blood plasma levels should be ignored as supposedly not a claim limitation. Petition at 16-17. Petitioner's claim construction argument is wrong (*see supra* at 12-16). While it is clear that the blood plasma levels are a claim limitation and not simply a recitation of a result, even if simply a "result," Petitioner never shows that McLeskey reached it.

Petitioner's sole argument is that other references showed that "fulvestrant formulations like that disclosed in McLeskey . . . would achieve a blood plasma fulvestrant concentration level of 2.5 $ngml^{-1}$ for a period of two weeks." Petition at 41. Of course, a formulation "like that disclosed in McLeskey" provides no

information about the McLeskey formulation. And, to the extent Petitioner means Howell 1996, its characterization of "like" is only one common excipient, castor oil, and an entirely different administration route. But, more fundamentally, even if a formulation "like that" could achieve these blood plasma levels, obviousness requires a reason to do so. McLeskey provides no reason to do so and Howell 1996 says not to—Howell 1996 says to go down in dose. Ex. 1006 at 6-7. This teaching in Howell 1996 was consistent with the teachings for all of the other endocrine therapies. Ex. 2002 at ¶¶179-182. All found no increased efficacy from higher tolerated doses and the possibility of serious off-target effects. *Id.* There was no teaching of the therapeutically significant amounts of the patent claims in McLeskey or otherwise.

As to duration of the blood plasma levels, the claims require over four weeks. The skilled artisan would have believed that because the formulations in McLeskey had to be administered on a weekly basis, those formulations could provide only one week of fulvestrant release. Ex. 2001 at ¶¶159, 190; Ex. 1005 at 2. The patent claims of a duration of at least a month of blood plasma levels are quadruple the duration of the McLeskey formulation based on McLeskey's disclosure.

4. McLeskey does not disclose the "exact" formulation

Petitioner incorrectly claims that McLeskey discloses the "exact formulation

recited in [the claims]." Petition at 37. But, formulations are inextricably linked to their route of administration. Ex. 2001 at ¶¶160-165, 190-198; Ex. 2002 at ¶¶76-86; Ex. 2084 at 5 ("The nature of the product will determine the particular route of administration that may be employed. Conversely, the desired route of administration will place requirements on the formulation."). And, even Petitioner admits there is no disclosure in McLeskey of the units employed: the reference only states that "50 mg/mL preformulated drug [] in a vehicle of **10%** ethanol, **15%** benzyl benzoate, **10%** benzyl alcohol, brought to volume with castor oil, was supplied by B.M. Vose (Zeneca Pharmaceuticals)." Petition at 37 (citing Ex. 1005 at 2 (emphasis added)). It says nothing about whether the percentages are in weight per volume or volume per volume.[7] The difference between % v/v and % w/v results in different amounts of each component in the formulation. Ex. 1002 at

[7] Petitioner asserts that should AstraZeneca argue the McLeskey or Howell 1996 formulations are different than what is recited in the challenged claims, AstraZeneca "should provide the details of those formulations, consistent with its duty of candor to the Board." Petition at n.4. Needless to say, AstraZeneca's internal, confidential documents are not prior art and, hence, are irrelevant. They could not be accessed by a skilled artisan and cannot be used to support a challenge before this Board, as any such challenges are limited to "patents or printed publications." 37 C.F.R. § 42.104(b)(2).

363-367; Ex. 2001 at ¶¶60-65. A skilled artisan would not know if the differences in percentages of each component would affect the activity of fulvestrant in mice (let alone humans); these results could not be reasonably predicted. *Id.* Dr. McLeskey herself stated that she "assumed that the percentages were in v/v units, because the components of the formulation were liquids." Ex. 2043 at 3; Ex. 2001 at ¶60.

C. Ground Two: McLeskey In Combination With Howell 1996

In Ground Two, Petitioner reasons a skilled artisan would start with Howell 1996, try to match its "castor oil depot" formulation by looking to the art "to determine an appropriate formulation" and "immediately f[i]nd McLeskey." Petition at 51. Nothing in the prior art supports Petitioner's reasoning and the text of the two references would actually have discouraged such a combination.

1. No reason to combine McLeskey with Howell 1996

Petitioner provides no "reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does" which is required to protect against the "distortion caused by hindsight bias." *KSR*, 550 U.S. at 418, 421.

In fact, critical differences between Howell 1996 and McLeskey would have suggested to a skilled artisan that the references should ***not*** be combined and, if they were, that such a combination would not succeed.

Howell 1996	McLeskey
Intramuscular administration	Subcutaneous administration
To humans	To mice
Once monthly	Once weekly
250 mg/month dose in woman	5 mg/week/mouse (0.025 kg) (5 mg/0.025 kg * 60 kg = **12,000 mg/week dose in woman**)
5 ml/month volume in woman	0.01 ml/week/mouse (0.1 ml/0.025 kg * 60 kg = **240 ml/week volume in woman)**
Aim = no cross resistance	Result = cross resistance

A skilled artisan searching to find a formulation that "matches" that disclosed in Howell 1996 would have tossed McLeskey aside, seeing the following differences:

- The castor oil-based formulation used in McLeskey was administered weekly by subcutaneous injection, while the formulation in Howell 1996 was administered monthly by intramuscular injection. Ex. 2001 at ¶179; Ex. 2002 at ¶¶189-190.
- All of the formulations used in McLeskey were specially made for use

with laboratory animals and unsuitable for humans. Ex. 2001 at ¶¶57, 157, 178, 184; Ex. 2002 at ¶¶152-159, 168.

- When normalized, the doses and volumes used in McLeskey are exponentially higher than those in Howell 1996. Ex. 2001 at ¶¶150, 179; Ex. 2002 at ¶¶86, 156, 168, 189-190.

The two references differ on almost every important parameter. And, Petitioner's "piecemeal analysis" is precisely the kind of impermissible hindsight the law forbids. *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" (citation omitted)).

Again, the disclosure in McLeskey that the fulvestrant formulations were "treatment failure[s]" (i.e., cross-resistant) would have discouraged a researcher from pursuing the combination Petitioner now proposes. Ex. 2001 at ¶¶144-149, 155, 172, 180; Ex. 2002 at ¶¶155, 160-168, 189-197; Ex. 1005 at 1, 4-6, 10 (*see supra* at 38-40).

While the results presented in Howell 1996 are inconclusive and limited to a few patients (*see supra* at 18-19, 23-24), it is clear the goal was to discover a treatment ***without*** cross resistance and ***with*** antitumor effect (Ex. 1006 at 1), neither of which are achieved by the fulvestrant formulations disclosed in

McLeskey. Ex. 2002 at ¶¶149, 161-162, 189-197.

Setting aside that the formulation and route of administration used in early phase clinical trials, like that disclosed in Howell 1996, often are not acceptable for clinical development—Ex. 2051 at 14; Ex. 2052 at 9 ("'Heroic' approaches describe efforts to solubilize drugs for early clinical studies [] using additives that probably are not acceptable for commercial formulations.")—a skilled artisan could not have used the scant information in Howell 1996 to further development. Indeed a skilled artisan would have understood injections of this magnitude (5 ml), of oil-based material into the muscle, were virtually unprecedented. Ex. 2001 at ¶175; Ex. 2002 at ¶186.

Regardless, Petitioner fails to explain or provide any specific evidence to establish how the combination of McLeskey and Howell 1996 would work "such that [a skilled artisan] would have recognized the results of the combination to be [] desirable." *Bumble Bee Foods, LLC v. Kowalski*, IPR2014-00224, 2014 WL 2584188, at *12 (P.T.A.B. June 5, 2014) (reasoning that it would have been "eas[]y" or "simple" to modify the art "does not explain *why* one of ordinary skill would have [done so] in the first place"). Rather, Petitioner simply glosses over the differences in administration route, schedule and subjects. The Board has found such unsupported obviousness assertions unpersuasive and insufficient to sustain institution. *Id.*

The sole connection between the two references that Petitioner can muster is a cite in McLeskey to Howell 1996. Petition at 51. But in this citation, the authors of the McLeskey article disparage the results in Howell 1996 noting the low response rate as a reason ***not*** to use fulvestrant, or other endocrine treatments. Ex. 1005 at 2 ("[O]nly about 30-40% of such patients have a positive response to subsequent [fulvestrant]."). And, McLeskey instead encourages that "agents directed against the autocrine or paracrine effects of FGFs" should be tried as they "might result in beneficial effects." Ex. 1005 at 12-13. This is the opposite of a motivation to combine. Ex. 2001 at ¶¶147, 156, 174; Ex. 2002 at ¶¶191-192.

With no motivation to combine, Ground Two should be rejected.

2. No reasonable expectation of success

A finding that it would have been obvious to combine multiple prior art references also requires a showing that "the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*, 676 F.3d at 1069; *see also Lupin*, 2016 WL 1081583, at 5-6.

Petitioner provides not even an argument as to an expectation of success in combining Howell 1996 with McLeskey. And, in fact, a skilled artisan would not have expected that using the castor oil formulation disclosed in McLeskey with the method disclosed in Howell 1996 would successfully treat postmenopausal women with hormone dependent breast cancer. Ex. 2001 at ¶¶182-199; Ex. 2002 at ¶¶192-

197.

First, and most simply, the fulvestrant formulations in McLeskey are reported to be a "treatment failure." Petitioner neither explains nor provides evidentiary support as to why a POSA searching for a *successful* treatment for hormonal dependent breast cancer would look to McLeskey and expect success given it discloses just the *opposite*. The Board has denied institution in such circumstances. *Lupin*, 2016 WL 1081583, at 5-6; *see also Boehringer*, 2015 WL 4467391, at *16 ("We are not persuaded that an improvement characterized as 'nonsignificant' would have suggested to an ordinary artisan that rituximab should be employed as maintenance therapy in patients who responded to chemotherapy.").

Second, McLeskey administered a castor-oil based fulvestrant formulation weekly, while Howell 1996 administered a fulvestrant formulation monthly. Petitioner raises not a shred of evidence that the once-a-week McLeskey animal formulation would have been expected to sustain fulvestrant blood plasma levels for ***four*** times as long in human patients. Ex. 2001 at ¶¶159, 190. Indeed logic dictates that the very fact the fulvestrant formulations are administered once weekly would have led a skilled artisan to believe once weekly administration was required. *Id.*

Third, the skilled artisan could not have reasonably predicted how a

formulation designed to be administered subcutaneously would work when administered intramuscularly. Numerous treatises recite this fundamental formulation principle. Ex. 2001 at ¶¶191-198; Ex. 2083 at 30; Ex. 2119 at 1-5; Ex. 2122 at 8, 10. In fact, as described above, prior art experiments comparing these two different routes demonstrated that entirely different blood plasma profiles, including shape and duration, were obtained even when formulation was controlled. *See supra* at 25-29. Furthermore, Petitioner has provided "no discernible reason" for a skilled artisan to start with McLeskey only to "disregard one of [its] distinguishing characteristics" (i.e., subcutaneous administration) when combining it with Howell 1996. *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1358 (Fed. Cir. 2008); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1356 (Fed. Cir. 2010).

Fourth, a skilled artisan could not have reasonably predicted that the combination of McLeskey and Howell 1996 would result in the claimed therapeutically significant blood plasma levels. No blood plasma data is disclosed in McLeskey. And, Howell 1996 concluded that the appropriate therapeutically significant blood levels were not known—"a direct pharmacokinetic-pharmacodynamic link is not proven with the few patients studied to date." Ex. 1006 at 6. The authors go on to state "at the dose used, there was accumulation of the drug over time and thus ***lower*** doses than those administered in this study may

be as effective," but noted that "further clinical studies are required to confirm this hypothesis." *Id.*; *see also id.* at 7. Howell 1996 ***did not*** set a minimum blood plasma concentration of at least 2.5 $ngml^{-1}$—in fact it did not set a minimum blood plasma level at all. And, as to the "at least 8.5 $ngml^{-1}$" limitation, given that the data reported in Howell 1996 did not report blood levels of at least 8.5 $ngml^{-1}$ during the dosing period and because Howell 1996 said to go down in dose, Howell 1996 taught squarely away from the "at least 8.5 $ngml^{-1}$" limitation.[8] Ex. 2002 at ¶¶176-183, 192-197; Ex. 1006 at 6-7. Petitioner has not, and cannot, cite a single prior art reference that teaches this limitation.

The teaching in Howell 1996 to explore lower doses was consistent with the knowledge of other endocrine drugs at the time. Ex. 2002 at ¶¶179-182. For example, tamoxifen was studied clinically at doses of 40 and 20 mg, but it was determined that the 40 mg dose did not confer any significant advantages over the

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[8] The phase III clinical trials of fulvestrant post-Howell 1996 followed the direction in Howell 1996 to lower the dose and included a lower dose of 125 mg, confirming that the skilled artisan not only would have pursued lower blood plasma fulvestrant levels, but did. Ex. 2002 at ¶183. After the priority date, however, it was found that this lower 125 mg dose was ineffective. Ex. 2028; Ex. 2029. The currently accepted therapeutic dose in AstraZeneca's label is 500 mg, *double* the dose in Howell 1996.

lower 20 mg dose. Ex. 2010 at 4. Similarly, toremifene was investigated at doses of 200 and 60 mg and it was concluded that 200 mg provided no benefit over 60 mg and, in fact, may be associated with increased toxicity. *Id.* Anastrozole was also studied clinically at two doses, 10 mg and 1 mg, and researchers concluded that there was no difference between the doses. *Id.*; Ex. 2022 at 3. All three are approved and used at the lower doses.

Simply put, Petitioner does not—and cannot—explain why a skilled artisan would possibly have expected the McLeskey fulvestrant formulations, which failed in animal experiments, would achieve success in humans when combined with the teachings of Howell 1996. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (The evidence must show that "the skilled artisan would have had that reasonable expectation of success that [the invention] ***would work*** for its intended purpose." (emphasis added)). As described above, the McLeskey reference taught nothing about the critical characteristics that would be needed to "reasonably expect success" in using the formulation in patients. That reference contains no data on blood plasma levels. And, in fact, the only reported results are that the fulvestrant formulations ***failed***: "[they] did not slow estrogen-independent growth or prevent metastasis of tumors." Ex. 1005 at 1. Meanwhile, Howell 1996 does

not disclose the specifics of the formulation used.[9] Indeed, only with the benefit of hindsight can Petitioner make its conclusion that the inactive, subcutaneous, once-weekly formulation of McLeskey could be substituted for the unknown formulation of Howell 1996, which needed to work intramuscularly and once-monthly.

VII. OBJECTIVE INDICIA DEMONSTRATE THE NONOBVIOUS NATURE OF THE CLAIMED METHOD OF TREATMENT

In the specification, the inventors described a number of advantages associated with the claimed treatment methods, none of which could have been reasonably predicted. Importantly, it was "surprisingly found . . . after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time." Ex. 1001 at 8:58-60. This was surprising because other fulvestrant

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[9] To the extent Petitioner is alleging that the castor oil-based formulation recited in Howell 1996 is the same as that used in McLeskey, this argument was raised in a related litigation with the patent challengers' clinical expert testifying—under questioning by the Court—that a skilled artisan at the time of the invention would have no idea what formulation was used in Howell 1996, that any guess as to what formulation was used in that study would be "speculating," and that "[t]here is nothing in the literature to confirm [this] speculation." Ex. 2049 at 213:10-17; Ex. 2002 at ¶175.

formulations administered intramuscularly caused "extensive local tissue irritation" and were associated with "a poor release profile." *Id.* at 8:64-65. As the inventors explained, there was no way to predict the long duration of release from the identity of the excipients, which would be expected to dissipate quickly from the muscle. Ex. 1001 at 9:6-10 (benzyl alcohol); *see also* Ex. 1022 at 3 (castor oil leaving in 3 days). This particular release pattern and blood plasma levels have been tied to a surprising survival benefit for patients. Ex. 2002 at ¶¶213-222.

Petitioner tries to argue that the only basis for allowance was "improved solubility" of fulvestrant in the ingredients of the claimed formulation. Petition at 42. Neither the Examiner nor the specification is that restrictive. In fact the specification says otherwise: "[s]imply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site." Ex. 1001 at 9:42-44.

Moreover, the unique combination of fulvestrant, the claimed formulation and the specific blood plasma levels and profile achieved upon administration of the claimed treatment methods, surprisingly and unexpectedly showed improved clinical outcomes compared to AIs, i.e., provides better disease control, overall survival, and progression-free survival than the current gold standard anastrozole (Exs. 2055-2058, 2079); and has an improved side effect profile compared to other hormone therapies (e.g., antiestrogens, progestins), i.e., has a surprisingly lower

incidence of bone loss compared to aromatase inhibitors (Exs. 2075-2077). Ex. 2002 at ¶¶206-212.

Researchers attributed these results to the invention: "[when administered t]he formulation offers the assurance of stable drug exposure, with plasma fulvestrant concentrations maintained within a narrow range throughout the administration interval." Ex. 2060 at 10; Ex. 2002 at ¶¶213-222. The challenged claims are not obvious.

VIII. CONCLUSION

For the foregoing reasons, institution of Petitioner's Petition for *Inter Partes* Review of the '680 Patent should be denied.

Dated: October 6, 2016

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

This Preliminary Patent Owner Response complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1) because this Preliminary Patent Owner Response contains 13,920 words, as determined by the word-count function of Microsoft Word, excluding parts of the Preliminary Patent Owner Response exempted by the Rule (i.e., a table of contents, a table of authorities, a certificate of service or word count, or appendix of exhibits or claim listing).

Dated: October 6, 2016

/s/ Filko Prugo
Filko Prugo

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served a true and correct copy of the foregoing: PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,329,680 and supporting exhibits 2001-2135 by electronic mail on this day on the Petitioner's counsel of record as follows:

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