PATENT
Attorney Docket No. 11285.0056-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
John R. Evans et al.	) Group Art Unit: 1628
Application No.: 12/285,887	) Examiner: HUI, San Ming R.
Filed: October 15, 2008	) Confirmation No.: 1199
For: FORMULATION	) **VIA EFS-WEB**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132 OF RONALD J. SAWCHUK

I, **Ronald J. Sawchuk**, declare as follows:

Qualifications

1. My academic background and work experience are summarized in my curriculum vitae, which is attached as **Exhibit 1**.

2. Currently, I am a Professor of Pharmaceutics, Emeritus, and Morse Alumni Distinguished Teaching Professor. I am also the Director of the Bioanalytic and Pharmacokinetic Services Laboratory at the University of Minnesota.

3. I obtained a Bachelor of Science Degree in Pharmacy in 1963 from the University of Toronto. I also received a Masters of Science Degree in Pharmaceutics from the University of Toronto in 1966 and completed a Doctoral Degree (Ph. D.) in Pharmaceutical Chemistry (pharmacokinetics emphasis) at the University of California, San Francisco in 1972.

4. I joined the University of Minnesota in 1971 as an Instructor in Pharmaceutics, and served from 1972 to 1977 as an Assistant Professor of Pharmaceutics, from 1977 to 1983 as an Associate Professor of Pharmaceutics, and as a full Professor of Pharmaceutics from 1983 until my retirement in July of 2010.

5. At the University of Minnesota, I served as a member of the graduate programs in Pharmaceutics, Neurosciences, and Experimental and Clinical Pharmacology. From 1983 to 1989 and 1991 to 1994 I was the Director of Graduate Studies in Pharmaceutics at the University. From 1998 to 1999 I served as the Head of the Department of Pharmaceutics at the University of Minnesota.

6. Also, from 1982 to 1995, I served as Director of the Clinical Pharmacokinetics Laboratory at the College of Pharmacy at the University of Minnesota.

7. During my career, I received several honors, scholarships and awards, including the Weaver Medal of Honor in 2001, the Meritorious Manuscript Award from the American Association of Pharmaceutical Scientists in 1999 and the Hallie Bruce Memorial Lecture Award in 1996. In 2007, I received the American Pharmacists Association (APhA) Research Achievement Award in the Basic Pharmaceutical Sciences.

8. I am a member of numerous scientific and clinical societies. I am a Fellow of the American Association of Pharmaceutical Scientists and of the American Association for the Advancement of Science. I have been a member of the International Society of Anti-infective Pharmacology and the International Society for the Study of

Xenobiotics (ISSX). I recently served as a member-at-large on the American Association of Pharmaceutical Scientists (AAPS) Executive Council.

9. I have served on the editorial boards of scientific journals such as the Journal of Pharmaceutical Sciences and the Saudi Pharmaceutical Journal. I am currently on the Editorial Board of the AAPS Journal, and on the ISSX Journal, Xenobiotica. I have also served on numerous advisory committees and review panels.

10. I have participated in multiple research projects focused in the areas of preclinical and clinical pharmacokinetics, both publicly and privately funded. I am a named author on over 100 refereed scientific publications, in addition to several book chapters, a book that I co-edited on drug bioavailability, and over 170 abstracts which have been presented at scientific meetings. I have also given hundreds of invited lectures.

11. I have significant experience in the areas of pharmaceutical research, pharmacokinetics, and drug development. Therefore, I believe that I am qualified to render the opinions set forth in this declaration.

12. I have read the Office Action dated September 16, 2011 ("Office Action"), which is attached as **Exhibit 2**. Among other rejections, I understand that the Office Action rejects the claims pending in the captioned application as unpatentable over the following references:

a. McLeskey et al., "Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant in vivo to the antiestrogen ICI 182,780 and

two aromatase inhibitors", *Clinical Cancel Research* 4:697-711 (1998) ("*McLeskey*", attached hereto as **Exhibit 3**);

b. European Patent Specification No. EP 0 346 014, which names Michael Dukes as inventor ("*Dukes*", attached hereto as **Exhibit 4**);

c. Osborne et al., "Comparison of the effects of a pure steroidal antiestrogen with those of tamoxifen in a model of human breast cancer", *J. National Cancer Institute*, 87(20):746-750 (1995) ("*Osborne*", attached hereto as **Exhibit 5**); and

d. the abstract of Wakeling et al., "ICI 182,780, a new antioestrogen with clinical potential", *J. Steroid Biochemistry & Molecular Biology*, 43(1-3):173-177 (1992) ("*Wakeling*", attached hereto as **Exhibit 6**);

13. I have read the instant application ("the '887 application"), which I believe corresponds to U.S. Application Publication No. US 2010/0152149 (attached hereto as **Exhibit 7**.)

14. I attach hereto **Exhibit 8**, which I believe is a copy of the pending claims in the '887 application with proposed amendments. I understand the claims in **Exhibit 8** will be filed in the Patent and Trademark Office as part of the response to the Office Action.

15. I understand that the earliest priority date for the '887 application is January 10, 2000. In the paragraphs below, I will refer to the state of the art in the areas of pharmaceutical research, pharmacokinetics, and drug development prior to January 10, 2000. I will also explain how a person of ordinary skill in that art at that time

would have understood the references cited in the Office Action and how such a person would have interpreted certain experimental results related to various fulvestrant formulations.

Disclosure in *McLeskey* regarding the castor oil fulvestrant composition

16. *McLeskey* discloses two fulvestrant compositions. One composition was prepared by dissolving powdered drug in 100% ethanol and then spiking it into warmed peanut oil to give a final concentration of 50 mg/ml ("the *McLeskey* peanut oil composition"). *McLeskey* at 698, col. 2, under "Drugs". The second composition is a 50 mg/ml fulvestrant composition "in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil" ("the *McLeskey* castor oil composition"). *Id*. *McLeskey* does not specify whether the percentages in the castor oil composition are in weight/volume units (% w/v, as recited in the claims of the '887 application) or in volume/volume units (% v/v).

17. In a liquid composition, when a solute or cosolvent is a liquid, it is often convenient to express its concentration as a volume percent, i.e., % v/v. For the reasons that follow, I believe one of ordinary skill in the art would have concluded the *McLeskey* castor oil composition was described in volume/volume units (% v/v).

18. For example, U.S. Patent No. 3,164,520 ("the '520 patent", attached as **Exhibit 9**) entitled "Injectable Steroid Compositions Containing at least 75% Benzyl Benzoate" discloses the preparation of parenteral injections of steroid drugs in formulations containing benzyl benzoate, and often also containing castor oil or sesame oil. *See*, *e.g.*, the working examples. The '520 patent states: "The amount of benzyl

benzoate which may be employed in the compositions of this invention while still yielding satisfactory results has been found to range from about 75% to 100% by volume of the pharmaceutical vehicle employed." The '520 patent at col. 2, ll. 10-14. In addition, each of the four claims of the '520 patent refers to a parenteral steroid formulation in a pharmaceutical vehicle or pharmaceutical carrier wherein at least 75% by volume of said vehicle is benzyl benzoate.

19. Raymond Huber, the named inventor of the '520 patent, is a co-author of a similar publication in which parenteral formulations of steroid hormones in castor oil are described. Riffkin, C., Huber, R., and Keysser, C.H., "Castor oil as a vehicle for parenteral administration of steroid hormones", *J Pharm Sci*, 53(8): 891-95 (1964) ("*Riffkin*", attached as **Exhibit 10**). *Riffkin* lists the compositions of various vehicles prepared in Tables IV to VI, which reference liquid components and their proportions in the overall composition in terms of percentage units ("%"). Although *Riffkin* does not specifically state that those compositions are % v/v, one would understand them to be % v/v because *Riffkin* refers to the concentrations of the solid solutes (the steroids) in terms of w/v, (e.g., mg./ml.), whereas the concentrations of the liquid components are simply reported in terms of "%" units. *See, e.g.*, Tables V and VI. One would reasonably assume that, had *Riffkin* intended the concentration of the liquid components to be in terms of % w/v units, *Riffkin* would have explicitly indicated that fact, as it did for the solid components. Footnote 4 is another example of the use of the above nomenclature. Footnote 4 refers to the concentration of estradiol valerate in the injectable formulations, in terms of "mg./ml.", but refers to a "%" value for the liquids—

castor oil, benzyl benzoate, and benzyl alcohol. Therefore, one would conclude that the composition of the solvents in *Riffkin's* vehicles is expressed as % v/v.

20. Other publications also describe the composition of injectable formulations comprising liquid solvents or co-solvents on a "by volume" basis. For example, a published review tabulates various excipients included in the formulation of injectable products marketed in the Unites States. Neema, S, Washkuhn, R.J., and Brendel, R.J., "Excipients and their use in injectable products", *PDA J Pharm Sci Tech*, 51(4):166-171 (1997)("*Neema*", attached as **Exhibit 11**). *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 (e.g., benzyl benzoate, 20% v/v; PEG 40 castor oil, 11.5% v/v; sorbitol, 50% v/v). *See, e.g.*, Tables I and II.

21. Considering the above examples, and 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).

22. Therefore, one of ordinary skill in the art would have concluded that the *McLeskey* castor oil composition on page 698 was reported in % v/v units and referred to a composition containing 10% **v**/v ethanol, 15% **v**/v benzyl benzoate, and 10% **v**/v benzyl alcohol in a castor oil vehicle. This composition *is different* from a composition containing 10% **w**/v ethanol, 15% **w**/v benzyl benzoate, and 10% **w**/v benzyl alcohol in a castor oil vehicle.

23. It is possible to convert % v/v values for a given component in a liquid composition into % w/v values by calculating the weight of the corresponding volume of that component in the composition. As a first approximation, the weight of the component can be calculated by multiplying the volume of the component by its density.

24. In order to facilitate this calculation, I assumed the preparation of 100 ml of the *McLeskey* castor oil composition and reported the associated volume and weight values in Table 1 below, using densities reported or calculated at 25°C. The resulting % w/v values are independent of the choice of a particular volume of the *McLeskey* castor oil composition for this calculation. However, a volume of 100 ml of the castor oil composition was selected for simplicity to show the corresponding volumes and weights. The differences between % v/v and % w/v compositions for each of the three components can be seen by comparing the values in Columns A and E. It should be noted that although these compositions are identical, they are described differently; in Column A, the composition is described on a percentage "by volume" (% v/v) basis, and in Column E, the composition is described on a percentage "by weight" (% w/v) basis.

Table 1. Information for 100 ml of the fulvestrant *McLeskey* castor oil composition[1]

	A	B	C	D	E
Component	**% v/v**	**Volume (ml)**	**Density (mg/ml)**	**Weight (g)**	**% w/v**
Ethanol	10	10	0.808	8.08	8.1
Benzyl Benzoate	15	15	1.118	16.77	16.8
Benzyl Alcohol	10	10	1.04156	10.42	10.4

25. In Table 1, Column A represents the concentration of each component in the *McLeskey* castor oil composition in % **v**/v units (i.e., as one of ordinary skill in the art in would have understood the *McLeskey* disclosure). Column B represents the volume in milliliters (ml) of each component necessary to prepare 100 ml of the *McLeskey* castor oil composition.

26. Column C represents the density of each component in g/ml at 25°C, reported or calculated from published relative density data from the Merck Index, **Exhibit 12**. The Merck Index reports specific gravity values for liquid substances as the ratio of the density of the substance at a given temperature relative to the density of water at a reference temperature. **Exhibit 12** at p. xiv (entry for "d"). Regarding the benzyl benzoate and benzyl alcohol values, their densities were reported at 25°C and

[1] *McLeskey* does not indicate whether the ethanol used in its castor oil fulvestrant composition is dehydrated ethanol or the binary azeotropic ethanol composition containing about 96% ethanol by volume (see entry no. 3806 for ethanol in the Merck Index, 12th Ed., Merck & Co., Inc. (1996) at pp. 641-642 ("the Merck Index", relevant copies attached as **Exhibit 8**)). The value in Table 1 for the density of ethanol corresponds to the density of the azeotropic ethanol composition. The density of dehydrated ethanol is 0.789 mg/ml at 20°C (**Exhibit 8**), which would produce an even lower w/v% value for ethanol than that reported in Table 1.

the density of water was reported at 4ºC (**Exhibit 12** at entries no. 1159, 1162; pp. 189-190). Because the density of water at 3.98ºC is 1.0000 g/ml (**Exhibit 12** at entry 10175; p. 1715), the values reported in the Merck Index for benzyl benzoate and benzyl alcohol were used in Table 1 as the corresponding densities in mg/ml (considering that 3.98ºC is 4ºC for purposes of this calculation). For ethanol, the Merck Index reports a specific gravity of 0.810 at 25ºC with respect to the density of water at 25ºC (**Exhibit 12** at entry no. 3806; p. 642). Thus, to obtain the density of ethanol (the binary azeotrope) at 25ºC, I multiplied the density of water at 25ºC, 0.997 mg/ml (**Exhibit 12** at entry no. 10175; p. 1715), by the specific gravity reported in the Merck Index (0.810) to produce a value of 0.808 mg/ml for the density of ethanol at 25ºC.

27. Column D represents the weight of each component, obtained by multiplying the volume of each component (Column B) by its density (Column C). Column E represents the concentration of each component in the *McLeskey* castor oil composition in w/v% units, which is the weight of each component (Column D) in 100 ml of solution (the total volume of the composition) after rounding the value to a single decimal place.

28. Accordingly, based on the values in Table 1, a composition containing 10% v/v ethanol, 15% v/v benzyl benzoate, and 10% v/v benzyl alcohol translates into a composition containing about 8.1% w/v ethanol, about 16.8 % w/v benzyl benzoate, and about 10.4% w/v benzyl alcohol.

29. Thus, one of ordinary skill in the art reading *McLeskey* would have concluded that *McLeskey* described a composition containing about 8.1% w/v ethanol,

about 16.8 % w/v benzyl benzoate, and about 10.4% w/v benzyl alcohol in a castor oil vehicle.

30. Neither *McLeskey* nor any of the references cited in the Office Action contain any disclosure that would have suggested to one of ordinary skill in the art the modification of a composition containing about 8.1% w/v ethanol, about 16.8 % w/v benzyl benzoate, and about 10.4% w/v benzyl alcohol (i.e., the *McLeskey* castor oil composition) in an attempt to produce a composition as recited in the claims containing about 10% w/v ethanol, about 15% w/v benzyl benzoate, and about 10% w/v benzyl alcohol.

Disclosure in *McLeskey* regarding administration of fulvestrant compositions

31. As mentioned above, *McLeskey* disclosed two different fulvestrant compositions, the peanut oil composition and the castor oil composition. *McLeskey* at 698. *McLeskey*, however, did not provide any experimental data that would have allowed one of ordinary skill in the art to compare any aspect of the performance of the two fulvestrant compositions for the treatment of cancerous tumors. Therefore, *McLeskey* provided no information that would have suggested to one of ordinary skill in the art the desirability of either of its fulvestrant compositions over other known fulvestrant formulations.

32. *McLeskey* did not disclose plasma or blood levels of fulvestrant in mice after subcutaneous administration of either the peanut oil or the castor oil compositions. Thus, no information regarding the rate and/or extent of absorption of fulvestrant from

the subcutaneous injection site is available to one of ordinary skill in the art for either composition.

33. *McLeskey* concluded that treatment with fulvestrant (ICI 182,780), using either of the disclosed compositions was not effective in that it "did not slow estrogen-independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice." *McLeskey* at Abstract. Thus, one of ordinary skill in the art would not have been informed about the usefulness of either fulvestrant formulation when administered subcutaneously to a mouse for the treatment of cancerous tumors.

34. *McLeskey* also reports that fulvestrant "retained activity" based on the results from injecting fulvestrant into "reproductively intact female mice for two weeks . . . at the same doses used in the above experiment" and the uteri subsequently harvested from those mice "weighed less than those from control mice and exhibited a complete lack of endometrial glandular structures (data not shown)." *Id.* at ¶ bridging 701-702. Unfortunately, *McLeskey* does not specify which of the two fulvestrant formulations, if any, (the peanut oil composition or the castor oil composition), was used in these experiments. *McLeskey* does not disclose the route of administration (subcutaneous, intramuscular, intraperitoneal, etc.) for the injection of fulvestrant into those "reproductively intact female mice." Thus, one of ordinary skill in the art reading *McLeskey* cannot draw any conclusions regarding the extent to which fulvestrant administered subcutaneously became absorbed, if at all, when using the peanut oil or the castor oil compositions.

35. Indeed, 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 antitumor 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.

36. Thus, *McLeskey* provides no information that would have led one of ordinary skill in the art to have a preference for either the peanut oil or the castor oil fulvestrant compositions over the other one, or even a preference for one of the two *McLeskey* fulvestrant compositions over other fulvestrant compositions known in the art prior to January 10, 2000.

37. While I have not performed a search for fulvestrant compositions known in the art prior to January 10, 2000, I note that some of the references cited by the Examiner in the Office Action do disclose other fulvestrant compositions. For example, *Osborne* discloses experiments in which a composition of fulvestrant "in castor oil" was injected subcutaneously to female nude mice. *Osborne* (**Exhibit 5**) at 747, col. 1. Based on the positive results of those experiments, *Osborne* concludes that fulvestrant "is a more effective estrogen antagonist than tamoxifen in the MCF-7 tumor cell/nude mouse model system." *Osborne* at Abstract.

38. The fulvestrant composition in *Wakeling* is described as having fulvestrant "in oil suspension" for parenteral administration to mice. *Wakeling* (**Exhibit 6**) at

Abstract. *Wakeling* reports that, "over a 1 month period, a single injection of [fulvestrant] in oil suspension achieved effects comparable with those of daily tamoxifen treatment." *Id.*

39. *Dukes* discloses two different fulvestrant compositions for intramuscular injection, one containing fulvestrant dissolved "in a mixture of propylene glycol: ethanol: water: poloxamer 407" administered daily by intramuscular injection to rats. *Dukes* (**Exhibit 4**) at Example 2, p. 8. The second composition contained 50 mg of fulvestrant, "400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml." *Id.* at Example 3, p. 9. For each composition, *Dukes* reports that "at all doses tested the compound [fulvestrant] selectively inhibits the action of the animals' endogenous oestrogen on their uteri." *Id.* at Examples 2 & 3, pp. 8-9.

40. Thus, it is clear that one of ordinary skill in the art had other choices besides the *McLeskey* castor oil composition with respect to potential fulvestrant formulations that could have been further investigated for the development of a method of treating humans with intramuscular fulvestrant. However, none of the references cited in the Office Action provides any information that would have guided one of ordinary skill in the art to select the *McLeskey* castor oil composition, over any of the other fulvestrant compositions mentioned above, for the potential development of such a method of treatment.

41. Moreover, none of the references cited by the Examiner provides any guidance as to the relevant factors to consider when selecting a formulation for the potential development of a method of treatment as recited in the instant claims.

However, 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 from the fulvestrant compositions discussed above because the *McLeskey* experiments were ineffective and one of ordinary skill in the art would not have been able to conclude from the information in *McLeskey* whether fulvestrant, using that composition, was sufficiently bioavailable to have an antitumor effect. In this regard, and considering only efficacy, the fulvestrant oil suspension from *Wakeling* would have been among the most favored formulations to select for further development from among those discussed above because at least that formulation, when given as a single injection, showed a therapeutic antitumor effect in mice for over a one-month period.

Lack of disclosure in *McLeskey* regarding intramuscular efficacy of either fulvestrant composition disclosed therein

42. The mode of administration of a drug (e.g., oral, intramuscular, subcutaneous, etc.) and the dose administered affects the release profile of the drug. One 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. As a result, one of ordinary skill in the art would not have had an expectation as to whether the *McLeskey* castor oil composition would have had a therapeutic effect when administered intramuscularly before actually performing suitable *in vivo* experiments.

43. There is abundant evidence in the scientific literature that the intramuscular and subcutaneous administration of a drug to the same animal or human

may produce very different plasma level curves, and therefore very different pharmacologic effects. These effects include the desired effects (efficacy) and those that are not desired (adverse events, or side effects). If a drug is poorly absorbed from the injected site, (e.g., too slowly, or to only a modest extent) the drug may show no effects whatsoever.

44. For example, a study in sheep using probenecid, a drug which may be used to prolong the half-life of some antibiotics in animals, demonstrates significant differences in the absorption of intramuscular and subcutaneous injections of probenecid. Guerrini V.H., Filippich L.J., English P.B., Schneider J., Cao G.R. and Bourne D.W.A., "Pharmacokinetics of probenecid in sheep", *J Vet Pharmacol Ther.* 8(2):128-35 (1985) ("*Guerrini*", attached as **Exhibit 13**).

45. Those investigators administered probenecid to ewes in doses of 1 gram by both intramuscular and subcutaneous injection. *Guerrini* at 129. The study shows that the absorption of probenecid is more rapid and complete following intramuscular injection, compared to subcutaneous injection. *Id.* at Abstract. *Guerrini* reports that the bioavailability of the intramuscular dose was 135% of that of the subcutaneous dose (corresponding to an average bioavailability of 46% for intramuscular injection compared with an average bioavailability of 34% for subcutaneous injection). *Id.* The subcutaneous dose was also absorbed more slowly, with average plasma levels of the drug peaking at 1.5 hr, compared to 0.67 hr for the intramuscular dose. *Id.* at 131. Because of this slower absorption following subcutaneous dosing, probenecid plasma concentrations remained higher after 2 hours when the drug was administered

subcutaneously than when it was administered intramuscularly. *Id.* at 135. Consistent with these observations, the rate constant for absorption for the intramuscular dose was 41% greater than for the subcutaneous dose (5.45 vs. 3.87 hr^{-1}). *Id.* at 133.

46. In this case, despite the overall higher bioavailability of intramuscular probenecid, the "higher and more prolonged plasma probenecid concentration" following subcutaneous administration resulted in "similar plasma concentrations to those found in man after oral administration." *Id.* at 135. *Guerrini* concludes that "[t]he s.c. [subcutaneous] administration of probenecid in animals is preferred [to intramuscular administration] because muscle damage is avoided and it provided useful plasma concentrations." *Id.* Thus, this is an example where subcutaneous administration achieves a certain desired result but where intramuscular administration does not accomplish the same result.

47. Another study shows that, contrary to the pharmacokinetic profiles observed in *Guerrini*, subcutaneous administration resulted in faster absorption compared to intramuscular injection. Lavy E, Ziv G, Shem-Tov M, Glickman A, Dey A., "Pharmacokinetics of clindamycin HCl administered intravenously, intramuscularly and subcutaneously to dogs", *J Vet Pharmacol Ther.* 22(4):261-5 (1999) ("*Lavy*", attached as **Exhibit 14**).

48. *Lavy* reports that when a 10 mg/kg dose of clindamycin HCl, an antibioitic, was given subcutaneously to dogs, the average maximum blood serum concentration (Cmax) of clindamycin was 20.8 µg/ml, and the time when this maximum occurred (Tmax) averaged 46.7 min. *Lavy* at Table 3. When the same dose was given

intramuscularly to the same animals, the corresponding values for Cmax and Tmax were 4.4 µg/ml and 73 min, exhibiting a very much slower rate of absorption. *Id.* In addition, the exposure of the dogs to clindamycin, assessed through an analysis of the plasma serum area under the curve (AUC) was 2.9 times greater for the subcutaneous dose than for the intramuscular dose. *Id.* This means that the bioavailability of the subcutaneous dose of this drug is 2.9 times that of the intramuscular dose.

49. Based on the differences in pharmacokinetic profiles for subcutaneous and intramuscular administration, *Lavy* concludes that "it appears from the present study that the s.c. [subcutaneous] route is superior to the i.m. [intramuscular] in practical terms by permitting a longer treatment interval." *Id.* at 265. This is another example in which subcutaneous administration is able to fulfill certain design criteria (maintain a therapeutic plasma concentration for a longer period of time) better than intramuscular administration. Therefore, under these circumstances, one of ordinary skill in the art would not have been able to rely on data from subcutaneous administration to predict results of intramuscular administration because intramuscular administration would not have produced the same level of long-term efficacy achieved by subcutaneous administration.

50. There are other reports in the literature that show that, in contrast to the results from *Lavy*, the absorption of a drug is more rapid and complete following intramuscular dosing than after subcutaneous injection. For example, when the fluoroquinolone antimicrobial agent difloxacin was given by these routes to the same calves in a crossover study, the rates of absorption differed greatly, with intramuscular

injection showing higher and earlier peak plasma concentrations, confirming much more rapid absorption. Ismail M., "Disposition kinetics of difloxacin after intravenous, intramuscular and subcutaneous administration in calves", *Vet Res Commun.*, 31(4):467-76 (2007) ("*Ismail*", attached as **Exhibit 15**).

51. After intramuscular and subcutaneous dosing, maximum plasma concentrations (Cmax) of 3.38 and 2.18 µg/ml were observed after (Tmax) 1.22 and 3.7 hr, respectively. *Ismail* at Abstract. The time for half of the dose to be absorbed when given by intramuscular injection was only 0.38 hr, whereas the corresponding time for absorption of the subcutaneously injected dose was 2.1 hr, over 5 times as long. *Id.* at 473.

52. Under the conditions of its study, *Ismail* concludes that "the doses of difloxacin used in this study are likely to involve better pharmacodynamic characteristics that are associated with greater clinical efficacy following i.m. [intramuscular] administration than following s.c. [subcutaneous] administration." *Id.* at Abstract. In this case, contrary to the two examples above, the intramuscular administration was considered to be associated with greater clinical efficacy.

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

54. Moreover, the examples above underscore the fact that efficacy of a given drug administered by a given route of dosing (e.g., intramuscular) cannot be known until appropriate comparative studies are performed in a suitable animal model. For some drugs, the desired effect might be achieved following a particular route of dosing, but for other drugs it might not. The rate and extent of drug absorption, and the associated pharmacodynamics (e.g., the achievement of a desired drug effect) may differ greatly depending on the properties of the drug, the choice of an animal model, and the site of drug administration.

55. Consequently, 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. This is especially true because *McLeskey* did not disclose plasma or blood levels of fulvestrant in mice after subcutaneous administration of the formulation, nor any information regarding the rate and/or extent of absorption of fulvestrant from the subcutaneous injection site. Additionally, the claims recite achieving a given therapeutic plasma concentration for at least four weeks, and there is no information in any of the references cited in the Office Action that would have suggested that such long-term efficacy associated with a single dose would be exhibited using the *McLeskey* castor oil composition by any route of administration.

56. Thus, one of ordinary skill in the art would not have had an expectation that the castor oil composition disclosed in *McLeskey*, which was administered

subcutaneously to mice, would have been therapeutically effective upon intramuscular administration of fulvestrant, for example, by following the method described in the claims.

The composition of a formulation can have a significant effect on the efficacy observed when the formulation is administered

57. Where a dosage form of a drug is being developed for intramuscular administration in humans, one of ordinary skill in the art typically relies upon the results of intramuscular dosing studies in suitable animal models where pharmacokinetic data are collected to characterize the absorption of the drug from its dosage form.

58. Typically, during the development of an intramuscular dosage form for administration of a drug in humans, one would have carried out, among other tasks, formulation studies to determine suitable compositions in which the drug of interest is dissolved, as well as initial intramuscular dosing experiments in animals (e.g., mice, rabbits, and/or dogs) under various conditions (e.g., different compositions, different solvents, varying the proportion of the components of the composition, different drug concentrations, etc.) in order to gain an understanding of the pharmacokinetics of fulvestrant before attempting human administration. The very existence of this generalized approach highlights the lack of expectation of success with respect to the extrapolation of the *McLeskey* disclosure of subcutaneous administration to mice, lacking any pharmacokinetic information, to human intramuscular administration.

59. With respect to the importance of formulation studies, I have read the Declaration Under 35 U.S.C §1.132 of Dr. Paul Gellert filed on August 2008 ("the Gellert

Declaration", cited as "Gellert Decl." and enclosed here as **Exhibit 16**). I understand that the Gellert Declaration was submitted to the U.S. Patent and Trademark Office in Application No. 10/872,784 (as indicated by the caption on the first page of the declaration).

60. As part of the discussion of the development of methods of treatment involving the administration of fulvestrant, the Gellert Declaration states that "the experienced formulator would want to minimize the amount of co-solvents and excipients in any injectable formulation." Gellert Decl. at ¶ 22.

61. Thus, even if the *McLeskey* castor oil composition had been considered as a potentially useful formulation in the development of a method of treatment for humans, one of ordinary skill in the art would have performed additional formulation studies to obtain a composition with suitable characteristics for the desired route of administration. The Gellert Declaration explains one of the rationales to perform those additional studies:

> Ideally, it is best to select and use solvents that would maximize the solubility of the compound. Maximizing the solubility of a compound in a particular cosolvent system would result in lower total levels of the non-aqueous solvent(s) being administered to the patient, thereby lowering the chance for potential side effects.

Gellert Decl. at ¶ 22 (quoting directly from P.K. Gupta and G.A. Brazeau (eds), "Injectable Drug Development: Techniques to Reduce Pain and Irritation" Chapter 11, p. 217, Interpharm Press, Denver, Colorado (1999)).

62. Regardless of how high or low the cosolvent concentrations are in a given formulation, the preparation of formulations in which a drug such as fulvestrant can be

solubilized is not sufficient to ensure the desired therapeutic effect when such formulation is administered to patients. As explained in the '887 application "[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." **Exhibit 7** at ¶ [0054]. Thus, suitable experiments are needed to determine the pharmacokinetic performance of any candidate formulation(s).

63. In that regard, it is understood that an animal model for drug dosage form performance may provide some discrimination among candidate dosage forms in development. Thus, the plasma concentration profile should reflect changes in the release characteristics of the drug from the formulation. That type of pharmacokinetic data could be used to characterize important variables in the development of a suitable method of treatment. For drugs that are difficult to formulate, such as fulvestrant (**Exhibit 7**, at ¶ [0014]), the pharmacokinetic data could be useful to investigate the most promising formulation for the desired route of administration.

64. For example, for fulvestrant, PCT Application Publication No. WO 03/006064 ("WO 03/006064", attached here as **Exhibit 17**) shows pharmacokinetic results of intramuscular administration of fulvestrant to rabbits. Figure 1 shows differences in results when seven different formulations of fulvestrant, each containing 100 mg/ml of the drug, but having different co-solvent compositions, were dosed intramuscularly in rabbits. The table related to Example 4 on page 30 of WO 03/006064 reports the composition of each formulation, labeled F1 to F7. As can be seen, all of these fulvestrant formulations contained ethanol, benzyl alcohol, and benzyl benzoate in

a castor oil vehicle; these are the same components of the fulvestrant composition recited in the claims, but with different proportions for each component.[2]

65. WO 03/006064 reports that "[p]lasma levels were more variable than Control over the first 30 days" following intramuscular administration of fulvestrant. WO 03/006064 at 30, l. 23. WO 03/006064 explains that "some differences in profiles were noted over the first 30 days such that they were divided into 2 groups (with Formulation F7 showing intermediate behaviour)." *Id.* at 30, ll. 29-30. According to WO 03/006064, Group A demonstrates "rapid release early time points", corresponding to formulations containing high benzyl benzoate and low castor oil concentrations, while Group B shows a "lower release, flatter profile" corresponding to formulations containing lower benzyl benzoate and higher castor oil concentrations. *Id.* at 30, ll. 31-34. WO 03/006064 replotted the data from Figure 1 corresponding to those formulations in Group A as part of Figure 2A and the data corresponding to those formulations in Group B as part of Figure 2B.

66. Therefore, based on WO 03/006064's own characterization of the differences in the pharmacokinetic profile of different fulvestrant formulations, higher benzyl benzoate concentrations in the formulation resulted in a more rapid initial release of fulvestrant, whereas lower benzyl benzoate concentrations resulted in a lower initial release, and a flatter plasma level profile. Depending on the overall objective of the administration of fulvestrant, some of the fulvestrant formulations tested in

[2] The right-hand column in this table appears to indicate the % w/v composition of castor oil. All the entries in this column should more properly be "to 100%", as they are in the Tables provided in the preceding Examples 2 and 3.

WO 03/006064's study would be more desirable than others for that given purpose and, based on the relevant pharmacokinetic profiles, one of ordinary skill in the art would be able to select one of those fulvestrant formulations for further development and/or testing.

67. However, one of ordinary skill in the art would not have been able to determine whether a given fulvestrant formulation injected intramuscularly as in WO 03/006064 would have had the desired pharmacokinetic profile until such *in vivo* pharmacokinetic studies were carried out. The testing of various formulations having different compositions, as portrayed in Figures 1, 2A and 2B, would typically be undertaken during the development of a dosage form in order to ensure an optimal method of treatment using a drug that is difficult to formulate. Such studies would be expected to demonstrate differences in the blood plasma concentrations of a test drug, and would allow the investigators to identify factors that would enhance the performance of the formulation.

68. Therefore, when considering the differences in pharmacokinetic profiles demonstrated in the example from WO 03/006064, it becomes clear that one of ordinary skill in the art knowing only the composition of a given formulation administered subcutaneously, but having no pharmacokinetic data following its intramuscular administration, would have had no expectation, one way or another, that the formulation would be effective when administered intramuscularly in a given method of treatment.

69. In particular, one of ordinary skill in the art would not have had a reasonable expectation that the *McLeskey* castor oil composition would have been

effective when given as an intramuscular injection, such as in the method of treatment recited in the claims.

70. I hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

January 13, 2012
Date:

Ronald J. Sawchuk
Ronald J. Sawchuk