UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.

Petitioner,

v.

ASTRAZENECA AB

Patent Owner.

Patent No. 8,329,680

DECLARATION OF LAIRD FORREST, Ph.D. IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW

TABLE OF CONTENTS

I. QUALIFICATIONS AND BACKGROUND

A. Education and Experience; Prior Testimony

1. My name is M. Laird Forrest, Ph.D. I have been retained by counsel for Mylan Pharmaceuticals Inc. ("Mylan"). I understand that Mylan intends to petition for *inter partes* review of U.S. Patent No. 8,329,680 ("the '680 patent") [Ex. 1001], which is assigned to AstraZeneca AB. I also understand that Mylan will request that the United States Patent and Trademark Office cancel certain claims of the '680 patent as unpatentable in that petition. I submit this expert declaration in support of Mylan's petition.

2. I am currently an Associate Professor in the Department of Pharmaceutical Chemistry at the University of Kansas in Lawrence, Kansas, a position I have held since 2013. I am also an Associate Professor in the Bioengineering Center, a position I have held since 2011, and an Associate Professor in the Department of Chemistry, a position I have held since 2011, both also at the University of Kansas.

3. I received a Bachelor of Science in Chemical Engineering from Auburn University in 1998, a Master of Science in Chemical Engineering from the University of Illinois in 2001, and a Ph.D. in Chemical and Biomolecular Engineering from the University of Illinois in 2003. I was a Postdoctoral Fellow in the Division of Pharmaceutical Sciences at the University of Wisconsin, Madison

from 2004 to 2006. In 2006, I became an Adjunct Assistant Professor in the Department of Pharmaceutical Sciences at Washington State University, a position I held until 2011. In 2007, I accepted a position as Assistant Professor in the Department of Pharmaceutical Chemistry at the University of Kansas. I was promoted to Associate Professor at the University of Kansas in 2013.

4. Since 2009, I have been a Member of the Scientific and Medical Advisory Board of Exogenesis Corporation, which develops nanoscale surface modifications for implantable medical devices. I am the co-founder of Nanopharm LLC (d/b/a HylaPharm), founded in 2011, which specializes in formulation of anti-cancer chemotherapeutics. My research toward anti-cancer drug formulation has been competitively funded by multiple awards from the National Institutes of Health and the National Cancer Institute, the Food and Drug Administration ("FDA"), the American Cancer Society, the Department of Defense, Susan G. Komen Race for the Cure, and the Pharmaceutical Research and Manufacturers of America Foundation ("PhRMA"), among others.

5. I have received numerous awards and honors, including the University of Kansas Leading Light award (2014); the Japan Society for Promotion of Science Visiting Scholar Fellow (2010); the American Cancer Society Research Scholar (2008 to 2012); the American Association of Colleges of Pharmacy, New

Investigators Award (2007); and the PhRMA Foundation Postdoctoral Fellow (2006); among others.

6. I am currently or have been in the past a member of various professional societies, including the American Association for Cancer Research, the American Association of Pharmaceutical Scientists, and the American Institute of Chemical Engineers. I serve or have served on numerous scientific review panels for the National Institutes of Health's National Cancer Institute, the American Cancer Society, and the Association for International Cancer Research (United Kingdom). I am a standing member of the American Cancer Society review panel on Cancer Drug Development.

7. I have authored more than 70 peer-reviewed journal articles and 5 book chapters. I have also edited 2 special journal issues on drug delivery and a book on drug delivery and formulation. A list of all publications that I have authored is included in my *curriculum vitae*, attached as Exhibit A to this Declaration.

8. I have taught drug formulation, including all aspects of drug excipient choice and the effects of excipient modification on drug chemical stability, solution solubility, dissolution, and pharmacokinetics, to clinical pharmacy students and graduate students studying pharmaceutical formulation since 2007.

9. I have experience in all aspects of parenteral and oral drug formulation through my research and teaching. Additionally, as part of my work with Nanopharm and Exogenesis, I have worked on pharmaceutical formulations for intramuscular, subcutaneous, intravenous, topical, and oral formulation.

10. In the past six years, I have testified in the following litigations:

a. *Merck Sharp & Dohme Corp. v. Savior Lifetec Corp.*, No. 5:15-cv-00415-TWB (E.D.N.C.)

b. *Medac Pharma, Inc. et. al. v. Antares Pharma Inc. et al.*, No. 1:14-cv-01498-JBS-KMW (D.N.J.), and

c. *Par Pharmaceutical, Inc. et al. vs. Breckenridge Pharmaceutical, Inc. et al.*, No. 1:15-cv-00486-SLR (D. Del.).

11. I am being compensated for my time at my standard consulting rate of $595/hour. Neither the amount of my compensation nor the fact that I am being compensated has altered the opinions that I have given in this Declaration. My compensation is in no way dependent on the outcome of this proceeding.

B. Bases for Opinions and Materials Considered

12. In addition to the materials cited herein, I have considered the materials identified in Exhibit B, in addition to my experience, education, and training, in providing the opinions contained herein.

13. I have also reviewed the expert declaration of Dr. Leslie Oleksowicz, M.D., and agree with her analysis as to the treatment aspects of the '680 patent.

II. SUMMARY OF OPINIONS

14. It is my opinion that claims 1–20 of the '680 patent were obvious over McLeskey [Ex. 1005]. Independent claims 1 and 9 of the '680 patent relate to the administration of a certain fulvestrant formulation in an intramuscular ("i.m.") injection to humans to treat benign and malignant diseases of the breast or reproductive tract, such as breast cancer. A formulation falling squarely within the claimed excipient percentage ranges was expressly disclosed in McLeskey. Furthermore, fulvestrant was already long known in the art to be useful to treat breast cancer. Still further, fulvestrant was known to be administered as an intramuscular injection.

15. It is also my opinion that claims 1–20 of the '680 patent would have been obvious over Howell 1996 [Ex. 1006] in view of McLeskey [Ex. 1005]. Howell 1996 disclosed fulvestrant formulations in a castor oil-based depot injection to treat malignant breast cancer in women. Howell 1996 also disclosed that fulvestrant formulations in castor oil achieve long-acting effects. With Howell 1996's disclosure that fulvestrant administered in castor oil-based depots was efficacious in the treatment of breast cancer, a person of ordinary skill in the art ("POSA") would investigate prior art formulations of fulvestrant. This investigation would quickly uncover McLeskey, a reference that would reveal to

the POSA a formulated fulvestrant product exactly as recited in the claims of the '680 patent.

III. LEGAL STANDARDS

16. In preparing and forming my opinions set forth in this declaration, I have been informed of the relevant legal principles. I have used my understanding of these principles in forming my opinions. My understanding of these principles is summarized below.

17. I have been told that Mylan bears the burden of proving unpatentability by a preponderance of the evidence. I am informed that this preponderance of the evidence standard means that Mylan must show that unpatentability is more probable than not. I have taken these principles into account when forming my opinions in this case.

18. I have also been told that claims should be given their broadest reasonable interpretation in light of the specification from the perspective of a POSA.

19. I am told that the concept of obviousness involves four factual inquiries: (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) secondary considerations of non-obviousness.

20. I am also informed that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable, and known solutions, a POSA has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the expected success, it is likely not the product of innovation but of ordinary skill and common sense. In such a circumstance, when a patent simply arranges old elements with each performing its known function and yields no more than what one would expect from such an arrangement, the combination would have been obvious.

21. I also understand that a whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited. If the language in the whereby clause does not inform how the method is carried out, the whereby clause is generally not given patentable weight.

IV. PERSON OF ORDINARY SKILL IN THE ART ("POSA")

22. I understand that the obviousness analysis is to be conducted from the perspective of a POSA at the time of the invention. I have applied that standard in the analysis in this declaration. When I discuss the teachings of the prior art, I discuss those teachings from the perspective of how the POSA would understand the prior art.

23. I also understand that in defining a POSA, the following factors may be considered: (1) the educational level of the inventor, (2) the type of problems

encountered in the art, (3) prior art solutions to those problems, (4) rapidity with which innovations are made, and (5) sophistication of the technology and educational level of active workers in the field.

24. As of the earliest possible priority date of the '680 patent,[1] a POSA would have had a pharmacy degree or graduate degree in either pharmacy, pharmaceutics, chemistry, or a related discipline, or equivalent experience in drug development and formulation, and would also have familiarity with and knowledge of designing and formulating drug dosage forms. The POSA would have at least 2 years of practical experience in pharmaceutical formulations and pharmacokinetics. A POSA would collaborate with others having expertise in, for example, methods of treating disease and administering medicines.

25. A POSA would have a general understanding and knowledge of the basic principles of formulation development. In addition to experimental knowledge in formulation development, the POSA would have knowledge in theoretical aspects of formulation science and physical chemistry. The POSA would be familiar with general drug formulation strategies; procedures and tools of pharmaceutical formulation; and theoretic and experimental methodologies of

[1] I understand that the earliest application giving rise to the '680 patent was filed on January 10, 2000. Thus, I understand that the '680 patent is to be evaluated from the viewpoint of a person of ordinary skill in the art as of January 10, 2000.

pharmaceutical formulation, including pre-formulation studies, formulation screening, optimization, and experimental design. The POSA would have also been generally familiar with commonly used textbooks and reference manuals in the field of formulation development and would have general knowledge of printed publications and relevant references in the field of pharmaceutical formulation.

26. A POSA would also have both the tools and the ability to research prior art literature to find information on fulvestrant, its prior art formulations, and its prior art utility.

V. U.S. PATENT NO. 8,329,680 [Ex. 1001]

27. I have read and understood the '680 patent, entitled "Formulation." The '680 patent was filed on October 15, 2008, and claims priority to two foreign patent applications: GB Patent Application No. 0000313, filed January 10, 2000; and GB Patent Application No. 0008837, filed April 12, 2000. Ex. 1001. The '680 patent also disclosed that it was a continuation of No. 10/872,784, filed on June 22, 2004, which was now U.S. Patent No. 7,456,160. The '680 patent issued on November 25, 2008, and names John R. Evans and Rosalind U. Grundy as inventors.

28. The following table organizes each recitation in the claims by the claim(s) in which the recitation appears:

Table 1. Claims of the '680 Patent	
Fulvestrant Component	**As Claimed in the '680 Patent**
Indications for Fulvestrant	**Claims 1, 9**: hormonal dependent benign or malignant diseases of the human breast or reproductive tract
	Claim 3, 6, 11, 14: breast cancer
Route of Administration	**Claims 1, 4, 7, 9, 12, 15:** IM[2] injection
Frequency of Administration	**Claims 5, 8, 13, 16:** once monthly
Fulvestrant Dose	**Claims 17–20:** divided dose
Volume of Formulated Fulvestrant Administered	**Claims 4, 7, 12, 15**: 5 ml
Fulvestrant Concentration	**Claims 1, 9**: about 50 mg/ml
Final Formulation of Fulvestrant	**Claim 1:** "comprising" about 50 $mgml^{-1}$ of fulvestrant about 10% w/v ethanol about 10% w/v benzyl alcohol about 15% w/v benzyl benzoate sufficient amount of a castor oil vehicle
	Claim 9: "consisting essentially of" about 50 $mgml^{-1}$ of fulvestrant about 10% w/v ethanol about 10% w/v benzyl alcohol about 15% w/v benzyl benzoate
Blood Plasma Fulvestrant Concentration Levels and Their Durations	**Claims 1, 9:** at least 2.5 ng/ml for at least 4 weeks
	Claim 2, 10: at least 8.5 ng/ml for at least 4 weeks

29. I understand that Mylan is challenging claims 1–20. The '680 patent includes 2 independent claims: claims 1 and 9.

[2] Intramuscular, also denoted "i.m."

30. Independent claim 1 recites:

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: 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 a 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.

31. Independent claim 9 recites:

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 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 a 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.

32. In comparing claims 1 and 9, the primary difference between them is that claim 1 recites that the formulation is "comprising" the listed elements, whereas claim 9 recites that the formulation is "consisting essentially of" the listed elements. Claim 1 also requires a "a sufficient amount of castor oil vehicle,"

whereas claim 9 omits this requirement. The disclosed method is otherwise identical between claims 1 and 9.

33. Dependent claims 2–8 and 17–18 depend directly or indirectly from independent claim 1. Dependent claims 10–16 and 19–20 depend directly or indirectly from independent claim 9.

34. Dependent claims 2 and 10 depend from claims 1 or 2, respectively, and alter the blood serum concentration level to at least 8.5 $ngml^{-1}$ for at least four weeks.

35. Dependent claims 3 and 11 depend from claims 1 or 2, respectively, and recite that the disease being treated is breast cancer. Dependent claims 6 and 14 depend indirectly from claims 1 or 2, respectively, and recite that the disease being treated is breast cancer.

36. Dependent claims 4 and 12 depend from claims 1 or 2, respectively, and recite that 5 ml of the fulvestrant formulation is administered intramuscularly to a human. Dependent claims 7 and 15 depend indirectly from claims 1 or 2, respectively, and recite that 5 ml of the fulvestrant formulation is administered intramuscularly to a human.

37. Dependent claims 5 and 13 depend from claims 1 or 2, respectively, and recite that the fulvestrant formulation is administered once monthly.

Dependent claims 8 and 16 depend indirectly from claims 1 or 2, respectively, and recite that the fulvestrant formulation is administered once monthly.

38. Claims 17–18 depend directly or indirectly, respectively, from claim 1, and 19–20 depend directly or indirectly, respectively, from claim 9, and recite that the fulvestrant formulation is administered in a divided dose.

VI. CLAIM CONSTRUCTION

39. The term "sufficient amount of a castor oil vehicle" is understood, based on the specification, to mean that for a given volume of formulation, after the addition of fulvestrant, ethanol, benzyl alcohol, benzyl benzoate, and any further optional excipients, the remaining volume of the formulation would be castor oil. *See* Ex. 1001 at col. 11, ll. 6–10.

40. The term "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks," Ex. 1001 at col. 12 ll. 51–53, col. 13 ll. 14–16, merely expresses an intended result of the administration of the fulvestrant formulation recited in the claims of the '680 patent. Likewise, the term "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration [of] at least 8.5 $ngml^{-1}$," Ex. 1001 at col. 12 ll. 54–56, col. 13 ll. 17–19, merely expresses the intended result of the administration of the fulvestrant formulation recited in the claims of the '680 patent. None of this language informs how the method of

administering the fulvestrant formulation to a human patient is carried out. Therefore, it is my understanding that this phrase is not to be given any patentable weight.

41. To the extent the Board believes that any of the "wherein" terms recited in paragraph 40 are entitled to any patentable weight, the term "therapeutically significant" is understood, based on the specification, to mean any blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ (claims 1, 9) or 8.5 $ngml^{-1}$ (claims 2, 10) that is attained for 4 weeks after injection. Ex. 1001 at col. 9, ll. 24–28.

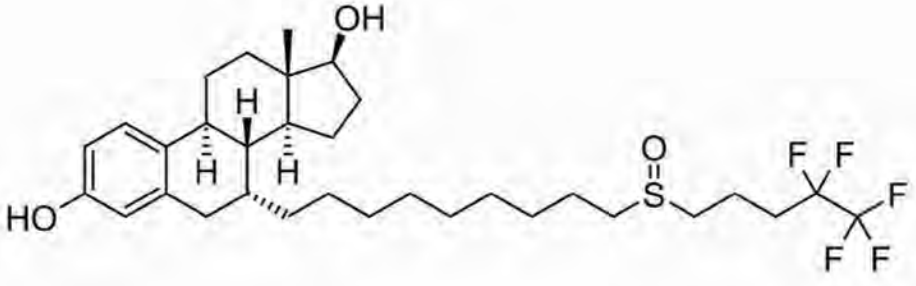
42. To the extent the Board believes that any of the "wherein" terms recited in paragraph 40 are entitled to any patentable weight, the term "attained" is understood under the broadest reasonable interpretation of the term to mean "achieved an average concentration (C_{avg}) in a patient over the specified time period." The term "attained" is never defined in the specification, and the patent does not include any instructions on how the POSA would have maintained the specified concentrations over the entire specified time periods (or why it would even be necessary to do so). Absent these instructions, under a broadest reasonable construction, the POSA would understand attained to mean the patient has a blood plasma concentration that is, on average, at least 2.5 $ngml^{-1}$ (claims 1, 9) or at least 8.5 $ngml^{-1}$ (claims 2, 10) for 4 weeks after injection. I understand a district court

has construed attained as "achieved and maintained." *See* Ex. 1011 at 2–3. My opinions are unchanged even if the Board were to adopt this construction.

VII. SCOPE AND CONTENT OF THE PRIOR ART

A. Fulvestrant Was Well Known in the Prior Art as a Pure Antiestrogen

43. Fulvestrant, the compound that is the subject of the claims of the '680 patent, is known chemically as 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl] oestra-1,3,5(10)-triene-3,17β-diol. It is also known by its code name ICI 182,780. Fulvestrant has the following chemical structure:



44. Fulvestrant was known in the prior art to be a pure antiestrogen that has high binding affinity for the estrogen receptor and no residual estrogen stimulating activity. *See*, *e.g.*, Ex. 1008 at 5. Because of their mechanism of action, antiestrogens are known to be effective in the treatment of breast cancer.

B. The Prior Art Disclosed Fulvestrant Formulations

45. The prior art disclosed a number of fulvestrant formulations. *See*, *e.g.*, Exs. 1005 (McLeskey); 1006 (Howell 1996); 1007 (Dukes 1989); 1008 (Wakeling 1991); 1009 (Wakeling 1992); 1012 (Howell 1995); 1013 (O'Regan

1998); 1014 (Lu 1998); 1018 (Osborne 1995); 1025 (Dukes 1992); 1026 (Dukes 1993); 1027 (Defriend 1994); 1028 (Wakeling 1993); 1030 (Lu 1999). These formulations used conventional excipients, e.g., castor oil, benzyl alcohol, benzyl benzoate, and ethanol, for their known purposes to achieve a formulated product. McLeskey, as one example, disclosed a fulvestrant formulation with 10% ethanol, 10% benzyl alcohol, 15% benzyl benzoate and a sufficient amount of a castor oil vehicle. Ex. 1005 at 2.

46. The excipients used in prior art fulvestrant formulations are conventional excipients often used in injectable depots. The POSA would understand that a fulvestrant formulation containing excipients as disclosed in McLeskey and other prior art references were suitable and appropriate for intramuscular injection in humans.

(a) ***Castor Oil***

47. Many prior art publications disclosed fulvestrant formulated in castor oil. *See, e.g.*, Exs. 1006 (Howell 1996) at 2; 1005 (McLeskey) at 2; 1007 (Dukes 1989) at 7, 9; 1025 (Dukes 1992) at 3, 6; 1026 (Dukes 1993) at 2; 1018 (Osborne 1995) at 2; 1030 (Lu 1999) at 7.

48. Castor oil has long been known as a conventional pharmaceutical carrier for steroid hormones. *See, e.g.*, Exs. 1019 (Lehmann) at col. 1, ll. 21–26; 1007 (Dukes 1989) at 5; 1020 (GB '286) at 1; 1022 (Riffkin) at 2–4; 1040

(Schülze) at col. 7, ll. 42–43. It was known in the art to formulate both steroidal and non-steroidal antiestrogens in castor oil. *See, e.g.*, Ex. 1041 (Neumann) at col. 9, ll. 22–29 (discussing the formulation of both non-steroidal and steroidal antiestrogens in castor oil suitable for i.m. injection).

49. Castor oil differs from corn, peanut, and most other vegetable oils in that castor oil has significant quantities of ricinoleic acid. Ex. 1022 (Riffkin) at 3. Ricinoleic acid has a hydroxyl functional group that increases the oil's hydrogen bonding and polarity character compared to other vegetable oils. *See id.* This in turn increases the solvent power of the oil. *Id.* In other words, castor oil is a particularly good solvent for pharmaceutical applications.

50. Castor oil is frequently used to create long-acting pharmaceutical formulations. This is because castor oil persists longer in the tissue than some other pharmaceutically acceptable oils. *See, e.g., id.* at 1.

(b) ***Ethanol***

51. Ethanol was a common conventional excipient used in prior art oil-based fulvestrant formulations. *See, e.g.*, Exs. 1005 (McLeskey) at 2; 1008 (Wakeling 1991) at 2. Ethanol was and is one of the most common solvents used in pharmaceutical formulations. *See, e.g.*, Ex. 1021 (Remington's) at 7. It is typically included in formulations as an antimicrobial agent, *id.*, but it can also be used as a solvent. The POSA would understand that a product for i.m.

administration can contain 5–50% alcohol. *See* Ex. 1010 (Spiegel & Noseworthy) at 8 (referring to the United States Pharmacopeia standard and giving examples of drug formulations containing 50% ethanol or less and administered intramuscularly or intravenously).

(c) ***Benzyl Alcohol***

52. Benzyl alcohol was also included in prior art formulations of fulvestrant. *See, e.g.*, Exs. 1005 (McLeskey) at 2; 1007 (Dukes 1989) at 7, 9; 1016 (Poyser) at 2. The prior art disclosed that solvents such as benzyl alcohol can be used to increase the solvent power of oils. Exs. 1022 (Riffkin) at 2; 1041 (Neumann) at col. 9, ll. 27–29 ("To increase solubility [of the non-steroidal or steroidal antiestrogen in an oily solution, such as a solution in castor oil], it is also possible to add solubilizers, for example, benzyl benzoate or benzyl alcohol."); *see also* Ex. 1040 (Schülze) at col. 7, ll. 43–45.

53. Benzyl alcohol has other beneficial properties that often warrant its inclusion in pharmaceutical formulations. For example, benzyl alcohol is known to reduce the viscosity of oil-based formulations and to act as a local anesthetic for injectables. *See, e.g.*, Ex. 1022 (Riffkin) at 4 (noting that the addition of benzyl alcohol and benzyl benzoate to castor oil resulted in a more favorable viscosity, which made the formulation easier to inject, and benzyl alcohol was an effective preservative and local anesthetic).

(d) ***Benzyl Benzoate***

54. Benzyl benzoate is a conventional synthetic solvent often used for steroid hormones. *See* Exs. 1005 (McLeskey) at 2; 1019 (Lehmann) at col. 1, ll. 14–36; 1020 (GB '286) at 1; *see also* Ex. 1040 (Schülze) at col. 7, ll. 43–45, 52–53.

55. Benzyl benzoate is commonly used as a solubilizing agent and non-aqueous solvent in intramuscular injections. Ex. 1023 (Handbook of Pharmaceutical Excipients) at 9; *see also* Ex. 1010 (Spiegel & Noseworthy) at 2–3. Benzyl benzoate is typically used at concentrations between 0.01–46.0% v/v. Ex. 1023 (Handbook of Pharmaceutical Excipients) at 9. Benzyl benzoate may be used to enhance steroid solubility in oils. *See, e.g.*, Exs. 1024 (Pharmaceutical Dosage Forms) at 5; 1037 (Modern Pharmaceutics) at 10; 1041 (Neumann) at col. 9, ll. 27–29 ("To increase solubility [of the non-steroidal or steroidal antiestrogen in an oily solution, such as a solution in castor oil], it is also possible to add solubilizers, for example, benzyl benzoate or benzyl alcohol."); *see also* Ex. 1040 (Schülze) at col. 7, ll. 43–45.

C. Intramuscular Injection of Fulvestrant Was Known as the Superior Route of Administration in the Prior Art

56. At least as early as 1991, fulvestrant was known to have an oral potency that was an order of magnitude lower than fulvestrant's potency in parenteral (i.e., other than the digestive tract) routes of administration. Ex. 1008

(Wakeling 1991) at 3, 6; *see also* Ex. 1009 (Wakeling 1992) at 2. The prior art noted that this lower oral potency likely meant that the oral bioavailability of fulvestrant was relatively low. Exs. 1008 (Wakeling 1991) at 6; 1009 (Wakeling 1992) at 2 ("A comparison of the oral and parenteral antiuterotrophic potency of ICI 182,780 indicated that the oral bioavailability of the compound is relatively poor[.]"); *see also* Ex. 1028 (Wakeling 1993) at 10. "A common means of circumventing the practical constraints consequent on the poor [oral] bioavailability of steroids is to use parenteral depot formulations with an extended duration of action." Ex. 1008 (Wakeling 1991) at 6; *see also* Ex. 1009 (Wakeling 1992) at 2.

57. Howell 1996 disclosed the intramuscular injection of castor-oil based fulvestrant formulations in human patients suffering from breast cancer. Ex. 1006. Howell 1996 demonstrated efficacy when fulvestrant was administered intramuscularly in castor oil depot injections. *Id.*

58. Accordingly, the POSA would understand that fulvestrant should be administered in a castor oil-based intramuscular injection.

D. Oil-Based Intramuscular Depot Injection Was Conventional in the Prior Art

59. Depot injections are slow-release injections whereby the active ingredient is slowly released into the body over a number of weeks. Depot injections work by depositing the drug into a localized area, i.e., a depot. Depot

injections are most commonly either oil-based or solid suspensions. Oily depot injections most commonly use the intramuscular route of administration.[3]

60. Oily depot injections are especially useful in situations in which a compound has low oral bioavailability. *See*, *e.g.*, Exs. 1008 (Wakeling 1991) at 6; 1009 (Wakeling 1992) at 2. As early as 1991, oil-based parenteral administration of a compound (such as a steroid hormone) with low oral bioavailability was an established procedure. *Id.* This technique was necessary because, as the prior art recognized, many steroids have a sustained duration of action when administered parenterally in oil. *See*, *e.g.*, Ex. 1008 (Wakeling 1991) at 3. It was understood in the prior art that fulvestrant must be given by an intramuscular depot injection because of low oral bioavailability. Ex. 1013 (O'Regan 1998) at 2 ("Clinically, [fulvestrant] must be given by depot intramuscular injection because of low oral potency.").

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[3] Although the intramuscular route of administration is common for administering drugs in humans, it is less common in animal research. The subcutaneous (under the skin) route of administration is typically used in these situations, due to the decreased size of the muscles of many small animals (e.g., mice). *See*, *e.g.*, Ex. 1051 (Waynforth 1998) at 3 ("Intramuscular injection in small laboratory species can be difficult because of the lack of big muscles. It is a route which is not recommended unless there are good scientific reasons for using it.").

61. Oily solutions, especially castor oil and sesame oil solutions, are particularly suitable for intramuscular depot injections. Ex. 1041 (Neumann) at col. 9, ll. 22–24; *see also* Ex. 1040 (Schülze) at col. 7, ll. 42–43 (discussing that castor oil and sesame oil are preferred oily solvents for formulation of steroid hormones in an i.m. depot injection). Indeed, castor oil was known in the prior art to provide a long-acting release of fulvestrant. *See* Exs. 1012 (Howell 1995) at 1; 1006 (Howell 1996) at 2; 1007 (Dukes 1989) at 7, 9; 1025 (Dukes 1992) at 3; 1026 (Dukes 1993) at 2; 1027 (DeFriend 1994) at 5 ("[F]uture studies which are planned with a different, long-acting, formulation of ICI 182780 contained in a castor oil-based vehicle"). In contrast, propylene glycol-based fulvestrant formulations were known to provide a short-acting release of fulvestrant. Exs. 1006 (Howell 1996) at 1; 1027 (DeFriend 1994) at 2; 1026 (Dukes 1993) at 2.

62. Therefore, the POSA would have expected that fulvestrant could be formulated in an oil—such as castor oil—to achieve a sustained duration of action when administered parenterally.

E. McLeskey [Ex. 1005]

63. McLeskey, titled "Tamoxifen-resistant Fibroblast Growth Factor-transfected MCF-7 Cells are Cross-Resistant *in Vivo* to the Antiestrogen ICI 182,780 and Two Aromatase Inhibitors," was published in March 1998. I

understand that because McLeskey was published more than one year before the earliest priority date of the '680 patent, it qualifies as prior art.

64. McLeskey would have been highly relevant to the POSA in formulating fulvestrant. McLeskey is the type of publication the ordinarily skilled formulator would look to in order to effectively solubilize a drug. Relevant publications are at least those that administer drug formulations to a living organism. In researching formulations of a drug product, the POSA would consider studies in which a drug formulation is administered to an animal, especially an animal that is a common preclinical model (e.g., rodents, primates, and dogs). Each of these animals is routinely used in pharmacokinetic and toxicity studies to collect data to support approval of a drug with the FDA. Therefore, it is my opinion that the POSA would find publications reporting formulations used in any of these animals to be highly relevant to the formulation of that drug in a human in the clinical setting.

65. McLeskey examined the effect of fulvestrant on murine xenograft models of an estrogen-insensitive breast cancer. These breast cancer models were transformed to express high levels of FGF (fibroblast growth factor), a factor expressed by many clinical breast cancer patient specimens. McLeskey was intended to determine if patients who had initially presented with or acquired

resistance to the existing antiestrogen tamoxifen may benefit from fulvestrant treatment.[4] Ex. 1005 (McLeskey) at 2.

66. Zeneca Pharmaceuticals (predecessor to AstraZeneca) first provided Dr. McLeskey with fulvestrant in a solid form. *Id.* Dr. McLeskey initially formulated fulvestrant in ethanol and then spiked it into peanut oil to obtain a formulation of 50 mg/mL, which was used to conduct the study of tumor growth depicted in Fig 1A. *Id.* at 5. Zeneca Pharmaceuticals then provided McLeskey with fulvestrant preformulated at 50 mg/mL in a vehicle described as "10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil." *Id.* at 2. Each excipient in the McLeskey formulation is approved for use in

[4] Fulvestrant is a pure antagonist of the estrogen receptor, meaning it has no residual agonist effect on the receptor. This is unlike the existing antiestrogen treatment, tamoxifen, which was an imperfect antagonist of the estrogen receptor. Although tamoxifen blocks most of the activity of endogenous estrogen on the estrogen receptor, tamoxifen still has a slight estrogenic activity. McLeskey proposed that tamoxifen's residual estrogenic activity may lead to resistance in some patients, and a pure antiestrogen might overcome this resistance.

humans.[5] McLeskey used the preformulated fulvestrant in the mouse studies shown in Figs. 1B and 1C. Ex. 1005 at 5.

(a) ***A POSA Would Have Understood that the Formulation in McLeskey Was Expressed in %w/v***

67. The POSA would understand McLeskey to have disclosed excipients in percent weight by volume.

68. Compositions may be described by different systems, including percent weight by volume (%w/v), percent weight by weight (%w/w) and percent volume by volume (%v/v). Rules and conventions in the art would have allowed the POSA to determine that the formulation disclosed in McLeskey was expressed in percent weight by volume (%w/v).

69. When the POSA described a solution containing a solute that is normally a solid,[6] the convention was (and still is) to use %w/v. *See* Ex. 1021 (Remington's) at 6. Even if the solution contains another liquid, the POSA would have followed a convention of expressing concentrations as %w/v, unless

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[5] *See* Ex. 1023 (Handbook of Pharmaceutical Excipients) at 3–4, 6–7, 9, 12; 1021 (Remington's) at 7, 10–11.

[6] Fulvestrant is a solid, as demonstrated by McLeskey. Ex. 1005 at 2 (non-preformulated fulvestrant provided to Dr. McLeskey in a powdered form).

explicitly stated otherwise. The Remington's Pharmaceutical Sciences textbook states:

> "Percentage concentrations of solutions are expressed as follows:
> *Percent weight in weight – (w/w)* expresses the number of g of a constituent in 100 g of solution.
> *Percent weight in volume – (w/v)* expresses the number of g of a constituent in 100 mL of solution, and is used regardless of whether water or another liquid is in the solvent.
> *Percent volume in volume – (v/v)* expresses the number of mL of a constituent in 100 mL of solution.
> The term percent used without qualification means, for mixtures of solids, percent weight in weight; for solutions or suspensions of solids in liquids, percent weight in volume; for solutions of liquids in liquids, percent volume in volume; and for solutions of gases in liquids, percent weight in volume."

Id.; *see also* Exs. 1032 (USP 1995) at 6; 1042 (Martin 1995) at 7 ("The percentage method of expressing the concentration of pharmaceutical solutions is quite common.") and 7 Table 5-2 ("Percent weight-in-volume . . . [Definition] Grams of solute in 100 mL of solution").

70. And there is good reason why solid solutes are reported in %w/v rather than %v/v. Weight is a more precise indicator of an amount of a solid material than is volume because weight accounts for density differences. Consider, for example, a recipe calling for one cup of brown sugar. A loosely packed cup of

sugar and a firmly packed cup of sugar are volumetrically the same, but represent a different weight of brown sugar. That analogy carries through to API used in the pharmaceutical context. Issues such as particle size and packing density can significantly impact volumetric determinations, whereas weight measures do not suffer from the same concerns.

71. Based on the teaching of common references in the art—such as Remington's Pharmaceutical Sciences—because the percent term was used without qualification in the McLeskey disclosure, and because the solute (fulvestrant) is a solid, the preformulation provided by Zeneca Pharmaceuticals and disclosed by McLeskey formulation would have been understood by the POSA to be in units of %weight / volume (%w/v). Although the formulation contained several liquids mixed together, these liquids were all excipients. The POSA would have understood that the unit or percent basis should be determined based on the character of the active pharmaceutical ingredient. Fulvestrant is a solid, and because "[t]he term percent qualification means . . . for solutions or suspensions of solids in liquids, percent weight in volume" (Ex. 1021 (Remington's) at 6), the POSA would have thus understood that the McLeskey formulation contained 50 mg/mL fulvestrant, 10% w/v ethanol, 15% w/v benzyl benzoate, 10% w/v benzyl alcohol, and sufficient castor oil to bring the formulation to volume. Ex. 1005 (McLeskey) at 2.

72. Additional art in the field further confirms that the POSA would have understood that the McLeskey formulation was expressed in %w/v, despite the units not being explicitly specified. As an example, in 1998, Powell—a formulator at the pharmaceutical company Genentech—conducted a survey of excipients and formulations used for parenteral formulation by formulation scientists. Ex. 1043 (Powell). During Powell's survey of pharmaceutics, several manufacturers did not provide units for their formulations. *Id.* When pharmaceutical manufacturers did not specify what kind of percentages they were using, Powell assumed % weight/volume (%w/v), showing that this is the standard convention in the field of formulation. *Id.* at (238).

73. Powell thus confirms that the POSA at the time of '680 patent's priority date would have understood the disclosure in the McLeskey publication to be expressed in %w/v when describing the composition of the fulvestrant formulation.

(b) ***A POSA Would Have Known that the Formulation in McLeskey Was a Solution***

74. The claims of the '680 patent do not require that the administered pharmaceutical formulation be a solution (rather than a suspension). While the Formulation Example in the '680 patent is stated to result in a solution, the claims are not so limited. Nonetheless, the POSA would have understood that the fulvestrant formulation disclosed in McLeskey was a solution.

75. Castor oil, as well as excipients benzyl benzoate, benzyl alcohol, and ethanol, had all been previously used to create *solutions* of fulvestrant. *See*, *e.g.*, Exs. 1007 (Dukes 1989) at 9 (solution of fulvestrant in castor oil and benzyl alcohol); 1025 (Dukes 1992) at 3; 1026 (Dukes 1993) at 2. In contrast, fulvestrant formulations using arachis (peanut) oil formed an oil suspension. Ex. 1008 (Wakeling 1991) at 2 ("ICI 182,780 . . . [was] prepared for administration by diluting an ethanol stock solution into the required volume of arachis oil with gentle warming[.]"); *see also* Ex. 1009 (Wakeling 1992) at Abstract, 4; 1013 (O'Regan 1998) at 2. The POSA would have understood from the prior art that fulvestrant formulated in castor oil formed a solution, whereas fulvestrant formulated in peanut oil formed a suspension. Ex. 1025 (Dukes 1992) at 1, 3 (disclosing that Wakeling formulated fulvestrant as a long-acting suspension in peanut oil, whereas Dukes formulated fulvestrant as a long-acting solution in castor oil). Because castor oil was known to form a solution when solubilizing fulvestrant, especially in conjunction with one or more of the other excipients included in the McLeskey formulation, the POSA would have understood that this formulation was in the form of a solution.

76. Even if the McLeskey formulation was an oil suspension, the POSA would have known that the two types of formulations would have behaved similarly in a human patient. Particularly, the POSA would have known that both

oily solutions and oily suspensions of fulvestrant had long-acting effects. *See* Exs. 1006 (Howell 1996); 1008 (Wakeling 1991); 1009 (Wakeling 1992); 1007 (Dukes 1989); 1025 (Dukes 1992) at 3. Intramuscular suspensions were commonly used in the art and known to be effective. *See, e.g.*, Exs. 1008 (Wakeling 1991); 1009 (Wakeling 1992); 1052 (Davy 1985) at 1; 1053 (Robinson 1946) at 1.

F. Howell 1996 [Ex. 1006]

77. Howell 1996 conducted an investigation of long-term administration of fulvestrant to patients with breast cancer. The purposes of this study were to assess the long-term efficacy and toxicity of fulvestrant (i.e., ICI 182,780) in women with advanced breast cancer and to evaluate the pharmacokinetics of a long-acting formulation used in the study. Howell 1996 described this formulation as "a long-acting formulation contained in a castor oil-based vehicle [that was administered] by monthly i.m. injection (5 ml) into the buttock." Ex. 1006 at 2.

78. The patients in the study received 250 mg of fulvestrant through a monthly i.m. injection. *Id.* Because the patients received a single 5 ml injection each month, the fulvestrant concentration in the formulation can be derived by dividing the total dose of fulvestrant (250 mg) by the injection volume (5 ml). So, it can be concluded that the concentration of fulvestrant in the castor oil-based vehicle was 50 mg/ml.

79. Howell 1996 disclosed the human pharmacokinetics, safety, and efficacy of the long acting castor oil-based depot of fulvestrant. These data indicated that the formulation was long-acting, safe, and was effective in treating breast cancer.

G. EP 0 346 014 ("Dukes 1989") [Ex. 1007]

80. The European patent EP 0 346 014 ("Dukes 1989"), granted to Dukes, teaches formulation of fulvestrant in an oily vehicle of castor oil and benzyl alcohol. Ex. 1007 at 7. Dukes 1989 teaches that such formulations may provide a depot from which the drug leaches out and provides an antiestrogenic effect for 1 to 6 weeks. *Id.*

81. Dukes 1989 disclosed that a formulation of 50 mg/mL fulvestrant, 400 mg benzyl alcohol, and sufficient castor oil to bring the solution to a volume of 1 mL was administered twice, two weeks apart, to mature rats in an intramuscular injection. *Id.* at 9. Dukes 1989 disclosed that the 50 mg/ml fulvestrant in a vehicle of castor oil and benzyl alcohol provided an antiestrogenic effect 2 weeks after injection of the long-acting depot. *Id.* The rats in the fulvestrant depot treatment group had significantly lower uterus weight than controls, with up to 81% inhibition of uterine weight at a test compound dose of 2.5 mg/kg of the long-acting fulvestrant depot injection. *Id.* at 10.

H. Wakeling 1991 [Ex. 1008]

82. In 1991, Wakeling 1991 described the properties of fulvestrant, a potent pure antiestrogen that was new at the time of publication. Ex. 1008. Wakeling 1991 investigated the duration of action of fulvestrant in monkeys and rats. *Id.* at 2; *see also id.* at 3 ("Following the precedent that many steroids administered parenterally in oil have a sustained duration of action, the effect of [fulvestrant] administered as a single s.c. [i.e., subcutaneous] bolus dose in oil suspension was tested in adult ovariectomized rats.").

83. Wakeling 1991 concluded that "[a] single injection of [fulvestrant] provided antitumor efficacy equivalent to that of daily tamoxifen treatment for at least 4 weeks. *Id.* at Abstract; *see also id.* at 6. Wakeling 1991 also noted that fulvestrant had a longer-acting effect than did tamoxifen in the treatment of human cancer tumors in nude mice. *Id.* at 5 ("Note that 2 weeks after the end of [daily oral] tamoxifen treatment tumor growth rate showed evidence of a return to control level whereas, even 3 months after a single dose of [fulvestrant], tumor growth rate remained below that of control.").

84. Wakeling 1991 noted that fulvestrant had an oral potency that was an order of magnitude lower than its potency in parenteral routes of administration. *Id.* at 6. The authors noted that a common means for circumventing poor oral bioavailability was to use an oil depot formulation. *Id.* ("A common means of

circumventing the practical constraints consequent on the poor [oral] bioavailability of steroids is to use parenteral depot formulations with an extended duration of action."). Wakeling 1991 then noted that the predicted efficacy of an oil depot fulvestrant formulation was demonstrated in the nude mouse antitumor studies disclosed in the publication. *Id.*

I. Wakeling 1992 [Ex. 1009]

85. Wakeling 1992 built on Dr. Wakeling's previous research on the pure antiestrogen fulvestrant. Ex. 1009. Wakeling 1992 disclosed that "[s]ustained antioestrogenic effects of [fulvestrant], following a single parenteral dose of ICI 182,780 in oil suspension, were apparent in both rats and pigtail monkeys." *Id.* at Abstract. In particular, Wakeling stated that "[i]n vivo, the antitumour activity of ICI 182,780 was demonstrated with xenografts of MCF-7 and Br10 human breast cancers in athymic mice where, over a 1 month period, a single injection of ICI 182,780 in oil suspension achieved effects comparable with those of daily tamoxifen treatment." *Id.*

86. Wakeling found that the growth of estrogen receptor-positive MCF-7 human breast cancer cell xenografts was blocked completely for at least four weeks by a single subcutaneous injection of 5 mg of a fulvestrant formulation in an oil suspension. *Id.* at 3.

J. Dukes 1992 [Ex. 1025]

87. Dukes 1992 disclosed a long acting depot formulation of fulvestrant in a castor oil vehicle with antiestrogenic activity in monkeys. Ex. 1025. Dukes 1992 investigated the sustained antiuterotrophic action of fulvestrant, shown in Wakeling 1991 [Ex. 1008], using intramuscular administration in monkeys of single doses of fulvestrant formulated in a castor oil-based solution. *Id.* at 3. This long-acting formulation was administered in three i.m. injections at 28-day intervals, and estrogen activity was monitored. *See, e.g., id.* at Abstract.

88. The fulvestrant in the castor oil depot provided dose-dependent antiestrogenic activity in the monkeys. *Id.* For example, a single i.m. injection of 4 mg/kg fulvestrant in monkeys suppressed endometrium thickness to less than 35% of the endometrium thickness of animals in the control group for 2 weeks. *Id.* at 6. A single i.m. injection at 5 mg/kg in monkeys suppressed endometrium thickness to less than 25% for 4 weeks. *Id.* These doses and durations would be expected to be appropriate for clinical use in breast cancer patients. For example, Dukes 1992 states that these results "showed that a dose of 4 mg/kg most closely approximates that required to sustain blockade of oestrogen action for 1 month, a dosing interval likely to be clinically convenient in therapeutic studies in breast cancer patients." *Id.* at 7.

89. Dukes 1992 further investigated the effect of the 4 mg/kg dose after repeated doses. Dukes disclosed that the fulvestrant in a long-acting castor oil-based vehicle completely suppressed endometrium growth for 2 weeks after a first injection. *Id.* After the third injection, antiuterotrophic activity was sustained for between 4 and 5 weeks. *Id.*

90. Dukes 1992 disclosed that the lasting effect of the long-acting fulvestrant formulation was not due to drug accumulation, but instead was due to slow release of the active drug. *Id.* at 8–9. Dukes noted, "[t]o demonstrate that the sustained action of ICI 182,780 in oil reflects a slow release of active drug, the effect was compared with that following injection of a propylene glycol solution which is known to be cleared rapidly . . . [;] blockade of the uterotrophic action of oestradiol was confined strictly to the period of ICI 182,780 treatment." *Id.*

K. Dukes 1993 [Ex. 1026]

91. Dukes 1993 disclosed that a long-acting castor oil-based i.m. depot formulation of fulvestrant had antiestrogenic activity in monkeys. Ex. 1026. Dukes 1993 extended Dr. Dukes's previous research of fulvestrant to adult female monkeys with normal menstrual cycles to study fulvestrant's effects in premenopausal women. *Id.* at Abstract.

92. Dukes 1993 used two fulvestrant formulations for this research:

(1) "a short-acting propylene glycol-based solution (F1) administered once daily i.m. for 25 days" and

(2) "a long-acting castor oil-based solution (F2) given as a single i.m. injection [in the 25-day period]."

Id. at 2. Dukes 1993 demonstrated that the long-acting fulvestrant formulation provided antiestrogenic effects similar to that of the short-acting fulvestrant formulation. Dukes 1993 stated that "[t]hese previous pharmacological findings are entirely consistent with the findings in the present study with respect to the duration of action, the apparent dose–response, and the longer sustained blockade of myometrial than endometrial growth." *Id.* at 7.

VIII. CLAIMS 1-20 OF THE '680 PATENT WERE UNPATENTABLE

A. Ground 1: Claims 1-20 of the '680 Patent Were Obvious Over McLeskey

93. It is my opinion that each claim of the '680 patent was obvious over McLeskey. For reference, below is a chart showing how McLeskey's formulation matches the formulation disclosed in independent claims 1 and 9:

Table 2. Claims of the '680 Patent Versus McLeskey	
'680 Patent Claim (formulation)	**McLeskey Formulation [Ex. 1005 at 2]**
Claims 1, 9: "comprising" (claim 1) / "consisting essentially of (claim 9) about 50 $mgml^{-1}$ fulvestrant about 10% w/v ethanol about 10% w/v benzyl alcohol about 15% w/v benzyl benzoate sufficient amount of castor oil vehicle	**McLeskey Formulation:** 50 $mgml^{-1}$ fulvestrant (preformulated) 10% ethanol 10% benzyl alcohol 15% benzyl benzoate "brought to volume with castor oil"

(a) ***Independent Claim 1 Was Obvious Over McLeskey***

94. Independent claim 1 of the '680 patent recites a method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administering to a human an i.m. injection of a pharmaceutical formulation comprising about 50 $mgml^{-1}$ 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 a castor oil vehicle, wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least 4 weeks after injection. Ex. 1001 at col.12 ll. 42–53.

95. The formulation disclosed by McLeskey in 1998 is an even more precise formulation than the one recited in claim 1 of the '680 patent. McLeskey (Ex. 1005) disclosed a formulation of "50 mg/ml preformulated [fulvestrant] drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil[.]" Ex. 1005 (McLeskey) at 2. As discussed above, a

POSA would have known that the McLeskey formulation was disclosed in %w/v. *See* Section VII.E(a), *supra*. McLeskey's disclosure of a "50 mg/ml^{-1} preformulated [fulvestrant] drug" exactly matches (or falls within) claim 1's recitation of "about 50 mg/ml^{-1} of fulvestrant." McLeskey's disclosure of 10% ethanol, 15% benzyl benzoate, and 10% benzyl alcohol exactly matches claim 1's "about" concentrations of 10% w/v ethanol, 15% w/v benzyl benzoate, and 10% w/v benzyl alcohol. Likewise, McLeskey also disclosed a "50 mg/ml preformulated [fulvestrant] drug," which matches (or falls within the range of) claim 1's "about 50 $mgml^{-1}$ of fulvestrant." And "brought to volume with castor oil," as disclosed in McLeskey, matches the "sufficient amount of a castor oil vehicle" disclosed in claim 1.

96. The POSA, when developing a parenteral formulation of fulvestrant, would have considered available publications that disclosed oil-based vehicles for fulvestrant. McLeskey would have been of relevance to the POSA at least because it disclosed a castor oil-based formulation of fulvestrant suitable for parenteral administration in animals .

97. A POSA would have known that fulvestrant was commonly known in the art to be useful in treating hormonal dependent malignant breast cancer in women, at minimum post-menopausal women. *See* Exs. 1006 (Howell 1996); 1008 (Wakeling 1991); 1009 (Wakeling 1992); 1028 (Wakeling 1993); 1018

(Osborne 1995); 1027 (DeFriend 1994). Thus, the POSA would have understood the fulvestrant formulations disclosed in McLeskey to be useful in treating breast cancer. *See* Section VII.A; *see also* Ex. 1004 (Expert Declaration of Dr. Leslie Oleksowicz, M.D.) ¶¶ 112–133, 163–165.

98. A POSA would have also known that in the clinical setting, fulvestrant must be administered intramuscularly. *See* Section VII.C, *supra*; *see also* Ex. 1013 at 2 ("Clinically, [fulvestrant] must be given by depot intramuscular injection because of low oral potency."). A POSA would therefore be well aware that the formulation disclosed in McLeskey should be administered intramuscularly to perform fulvestrant's known function of treating breast cancer.

99. What is more, the POSA would have expected the McLeskey formulation to effectively solubilize fulvestrant. The POSA would have been well aware that it is insufficient to simply consider a drug solute's solubility in an individual solvent alone. *See* Section IX.A, *infra*. The POSA would have known that the molecular properties of the drug solute and the solvents in a solvent mixture would interact with one another. *See* Section IX.B, *infra*. The POSA would additionally have been able to use routine solubility calculations—which have been known since the 1930s—to predict the effect of adding benzyl benzoate on the solubility of fulvestrant in the solvent mixture disclosed in McLeskey. Ex. 1005 at 2; *see also* Section IX.C, *infra*.

100. The claim recitation "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks" is simply an expression of the desired outcome of administering the claimed formulation in an i.m. injection. Thus, I understand this recitation is not entitled to patentable weight.

101. However, if this recitation is given patentable weight, the POSA would have known that steroids and steroid derivatives have a sustained duration of action when administered parenterally in oil. *See, e.g.*, Ex. 1008 (Wakeling 1991) at 3 (acknowledging "the precedent that many steroids administered parenterally in oil have a sustained duration of action" and noting that this motivated Wakeling to investigate the effect of a long-acting parenteral dose of fulvestrant).

102. More specifically, the prior art disclosed that oil-based fulvestrant formulations achieved a long-acting effect in both animals and humans. Exs. 1006 (Howell 1996) at 3–4, 6 (disclosing continuous release of fulvestrant throughout one-month dosing intervals and blood serum fulvestrant concentration levels in excess of 2.5 ng/ml in humans); 1008 (Wakeling 1991) at Abstract ("A single injection of ICI 182,780 provided antitumour efficacy equivalent to that of daily tamoxifen treatment for at least 4 weeks."); 1025 (Dukes 1992) at Abstract (a single castor oil-based depot injection produced an anti-uterotrophic effect in

monkeys for 3–6 weeks); 1026 (Dukes 1993) at 2 (disclosing both a "short-acting propylene glycol-based solution" for daily administration and a "long-acting castor oil-based solution" for a single injection over 25 days) and 7 (disclosing that the "antiuterotrophic effect of the 4.0 mg/kg [fulvestrant in oil depot] dose was indistinguishable from that of the [daily] short-acting formulation."); 1027 (DeFriend 1994) at 2, 5 (disclosing use of a short-acting propylene glycol-based formulation and stating that "future studies [] are planned with a different, long-acting, formulation of ICI 182780 contained in a castor oil-based vehicle.").

103. Howell 1996 specifically disclosed that a 250 mg injection of fulvestrant in a human patient achieved blood serum concentrations at 30 days of 3.1 ng/mL (after the first injection) and 5.6 ng/mL (after 6 months of injection). The POSA would have understood that serum and plasma concentrations of drugs are generally interchangeable, and Howell's 250 mg injection of fulvestrant in human patients would achieve similar blood plasma concentrations.[7] The human

[7] *See* Ex. 1055 (Uges 1988) at Abstract ("In most cases serum and plasma concentrations of analytes are the same. The choice depends mostly on the policy of the hospital or the availability of the test tubes in the ward."). Serum differs from plasma in that the fibrogen (a soluble protein present in blood plasma) has been allowed to clot and has been removed from the sample. Generally, less sample volume is lost during processing of plasma, so plasma is preferred when

patients achieved a maximum concentration 7 days after injection of 10.5 ng/mL and 12.8 ng/mL, again at 1 and 6 months. Ex. 1006 at 3. Thus, the POSA would understand that the patients achieved fulvestrant blood plasma concentrations above 2.5 ng/mL between at least day 7 and day 30.

104. It would also have been obvious to apply the fulvestrant formulation disclosed in McLeskey to the well-known methods of treating women, at minimum post-menopausal women, with hormonal dependent breast cancer through intramuscular administration. *See* ¶¶ 44, 77–79, *supra*.

105. Therefore, claim 1 of the '680 patent was obvious over McLeskey.

(b) ***Independent Claim 9 Was Obvious over McLeskey***

106. Claim 9 is almost identical to claims 1, except that whereas claim 1 uses the transitional phrase "comprising," claim 9 uses the transitional phrase "consisting essentially of."[8] I have been informed that "comprising" is inclusive or

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limited volumes of blood are available, such as neonates (*see*, *e.g.*, *id.* at 2) and animal studies. Serum is often used in hospitals because clots could form in plasma samples during processing, and there is a risk clotting factors and anticoagulates could interfere with some assays. *Id.* at 2–3.

[8] Claim 9 also omits claim 1's "a sufficient amount of castor oil vehicle." To the extent this omission was intentional, a POSA would still have understood that the recited formulation of "about" 50 $mgml^{-1}$ fulvestrant, 10% w/v ethanol, 10% w/v

open-ended and does not exclude additional, unrecited elements or method steps; "consisting essentially of" excludes any element, step, or ingredient not specified in the claim, unless those elements, steps, or ingredients do not materially affect the basic and novel characteristics of the claimed invention.

107. For the reasons stated above in Section VIII.A(a) (as to independent claim 1), McLeskey disclosed the exact excipients and exact formulation, and thus falls within the "about" recitation, of claim 9. *See also* ¶ 95, *supra.* The formulation disclosed by McLeskey in 1998 is an even more precise formulation than the one recited in claim 1 of the '680 patent. McLeskey (Ex. 1005) disclosed a formulation of "50 mg/ml preformulated [fulvestrant] drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil[.]" Ex. 1005 (McLeskey) at 2. As discussed above, a POSA would have known that the McLeskey formulation was disclosed in %w/v. *See* Section VII.E(a), *supra.* McLeskey's disclosure of a "50 mg/ml^{-1} preformulated [fulvestrant] drug" exactly matches (or falls within) claim 9's recitation of "about 50 mg/ml^{-1} of fulvestrant." McLeskey's disclosure of 10% ethanol, 15% benzyl benzoate, and 10% benzyl alcohol exactly matches claim 9's "about" concentrations of 10% w/v ethanol, 15% w/v benzyl benzoate, and 10% w/v

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benzyl alcohol, and 15% w/v benzyl benzoate did not result in a 100% formulation, and thus that a suitable vehicle, e.g., a castor oil vehicle, could be included.

benzyl alcohol. Likewise, McLeskey also disclosed a "50 mg/ml preformulated [fulvestrant] drug," which matches (or falls within the range of) claim 9's "about 50 $mgml^{-1}$ of fulvestrant."

108. A POSA would have looked to McLeskey, expected the McLeskey formulation to effectively solubilize fulvestrant, and administered the fulvestrant formulation to a human intramuscularly. *See* ¶¶ 96–99, *supra*. A POSA would have also known that a fulvestrant formulation of fulvestrant, ethanol, benzyl alcohol, and benzyl benzoate, as in claim 9—particularly a recited formulation in which the excipient percentages do not result in 100%, *see supra* note 8—should be administered via a suitable pharmaceutical vehicle, e.g., a castor oil vehicle. To the extent claim 9's "wherein" clause is given patentable weight, a POSA would have expected to achieve a 2.5 $nmgl^{-1}$ blood plasma fulvestrant concentration for at least 4 weeks. *Id.* ¶¶ 100–104.

109. Therefore, for the reasons described above (and in Section VIII.A(a), *supra*), claim 9 of the '680 patent was obvious over McLeskey.

(c) ***Dependent Claims 2 and 10 Were Obvious Over McLeskey***

110. Dependent claims 2 and 10 depend from claims 1 and 9, respectively. Claims 2 and 10 express that a blood plasma fulvestrant concentration of 8.5 ng/ml is achieved for 4 weeks after injection.

111. To the extent claims 2 and 10 purport to add an additional patentable element—that a fulvestrant blood concentration of at least 8.5 $ngml^{-1}$ is achieved for at least 4 weeks— it is my opinion that claims 2's and claim 10's recitation is simply an expression of the desired outcome of administering the claimed fulvestrant formulation in an i.m. injection. *See* ¶¶ 40, 100, *supra*. Thus, I understand the recitations of claims 2 and 10 are not entitled to patentable weight.

112. However, even if these recitations are given patentable weight, it is my opinion that claims 2 and 10 were obvious for much the same reason independent claims 1 and 9 were obvious.

113. Before the priority date of the '680 patent, the art disclosed that oil-based fulvestrant formulations achieved a long-acting effect in both animals and humans. *See* ¶¶ 101–103, *supra*. This art disclosed long-acting effects that extended to four weeks after injection. *Id.*, *see also* Exs. 1006 (Howell 1996) at 3–4; 1008 (Wakeling 1991) at Abstract; 1025 (Dukes 1992) at Abstract; 1026 (Dukes 1992) at 2.

114. To the extent claims 2 and 10 are afforded any weight—they recite a blood plasma fulvestrant concentration of 8.5 ng/ml for 4 weeks—it is my opinion that these levels could be reached through routine optimization of the method of treatment. Howell 1996 disclosed blood serum fulvestrant concentrations higher than 8.5 ng/ml extending for at least one week, and higher than approximately 5.5

ng/ml for 4 weeks. Ex. 1006 (Howell 1996) at 3–4. The POSA would have understood that although Howell 1996 reported serum fulvestrant concentrations, the plasma concentrations would have been similar and the values were generally interchangeable. *See* ¶ 103, *supra.* A POSA would also know that fulvestrant formulations in castor oil depots achieved a long-acting effect. *See, e.g., supra* Section VII.D; Exs. 1012; 1007; 1025; 1026; 1018; 1027 at 5. A blood plasma fulvestrant concentration of 8.5 ng/ml could therefore have been achieved through routine optimization of the method of treatment, e.g., by adjusting the dosage or frequency of administration. *See* Ex. 1004 (Expert Declaration of Dr. Leslie Oleksowicz, M.D.) at ¶ 192.

115. Therefore, it is my opinion that claims 2 and 10 of the '680 patent were similarly obvious over McLeskey and the knowledge of a POSA.

(d) ***Dependent Claims 3, 6, 11, and 14 Were Obvious over McLeskey***

116. Dependent claims 3 and 6 depend directly or indirectly, respectively, from independent claim 1. Dependent claims 11 and 14 depend directly or indirectly, respectively, from independent claim 9. Claims 3, 6, 11, and 14 further specify that the benign or malignant disease being treated is breast cancer.

117. To the extent claims 3, 6, 11, and 14 purport to add an additional patentable element of treating breast cancer, as described above, it would have been obvious to use the formulation disclosed in McLeskey to treat patients with

breast cancer. *See* ¶ 97, *supra*; *see also* Section VII.A. Fulvestrant was long known in the art to be efficacious in the treatment of breast cancer. *See* Section VII.A; *see also* Ex. 1004 (Expert Declaration of Dr. Leslie Oleksowicz, M.D.) at ¶¶ 166–168.

118. Thus, claims 3, 6, 11, and 14 of the '680 patent were obvious over McLeskey.

(e) ***Dependent Claims 4, 7, 12, and 15 Were Obvious over McLeskey***

119. Dependent claims 4 and 7 depend directly or indirectly, respectively, from independent claim 1. Dependent claims 12 and 15 depend directly or indirectly, respectively, from independent claim 9. Claims 4, 7, 12, and 15 recite that (1) the total volume of formulation is 5 ml and (2) the fulvestrant formulation is delivered intramuscularly.

120. To the extent claims 4, 7, 12, and 15 purport to add an additional patentable element of 5 ml delivered intramuscularly, it would have been obvious to a POSA to administer a long-acting or "depot" formulation, including this fulvestrant formulation, intramuscularly in the clinical setting. *See* ¶¶ 56–62, 98, 133, *supra*.

121. Likewise, it would have also been obvious to limit an intramuscular injection to 5 mL. A limit on the total intramuscular injection volume of 5 mL was well-known to a POSA at the time. The specification of the '680 patent

acknowledges that "[c]urrently guidelines recommend that no more than 5 mls of liquid is injected intramuscularly in a single injection." Ex. 1001 at col. 5, ll. 64–65. The POSA would understand this statement in the specification to be a statement on the accepted state of the art, not a discovery made by the inventors. Indeed, this statement is consistent with the understanding of a POSA. *See, e.g.*, Ex. 1054 (Newton) at 4. Further, the prior art expressly disclosed intramuscular injections of 5 mL to humans—including i.m. injections of fulvestrant formulations in castor oil—before the priority date of the '680 patent. *See, e.g.*, Ex. 1006 (Howell 1996) at 2–4, 6.

122. Therefore, it is my opinion that claims 4, 7, 12, and 15 of the '680 patent were similarly obvious over McLeskey and the knowledge of a POSA.

(f) ***Dependent Claims 5, 8, 13 and 16 Were Obvious over McLeskey***

123. Dependent claims 5 and 8 depend directly or indirectly, respectively, from independent claim 1. Dependent claims 13 and 16 depend directly or indirectly, respectively, from independent claim 9. Claims 5, 8, 13, and 16 recite that the claimed formulation is administered once monthly.

124. To the extent claims 5, 8, 13, and 16 purport to add an additional patentable element of monthly administration, it would have been obvious to a POSA to administer a fulvestrant formulation, such as that disclosed in McLeskey, to a human monthly. As stated above, it was understood in the art to administer

drugs with low oral availability, such as fulvestrant, via an oil-based "depot" injection, which provided a long-term effect. *See* ¶¶ 59–62, *supra.* Moreover, it was well-established in the prior art to administer a long-acting formulation of fulvestrant to a human on a monthly basis, and that such administration provided sustained effects. *See, e.g.*, Exs. 1006 (Howell 1996) at 3–4; 1008 (Wakeling 1991) at Abstract; 1025 (Dukes 1992) at 3; 1026 (Dukes 1993) at 7; 1028 (Wakeling 1993) at 10; *see also* Ex. 1004 (Expert Declaration of Dr. Leslie Oleksowicz, M.D.) ¶¶ 185–189.

125. Therefore, it is my opinion that claims 5, 8, 13 and 16 of the '680 patent were similarly obvious over McLeskey and the knowledge of a POSA.

(g) ***Dependent Claims 17–20 Were Obvious over McLeskey***

126. Dependent claims 17–18 depend directly or indirectly, respectively, from independent claim 1. Dependent claims 19–20 depend directly or indirectly, respectively, from independent claim 9. Claims 17–20 recite that the claimed formulation is administered in a divided dose.

127. To the extent claims 17–20 purport to add an additional patentable element of a divided dose, for the reasons expressed in the Expert Declaration of Dr. Leslie Oleksowicz, M.D., Ex. 1004, it would have been obvious to a POSA, in light of the prior art, to administer the claimed fulvestrant formulation in a divided dose. Ex. 1004 ¶¶ 181–184.

128. Therefore, it is my opinion that claims 17–20 of the '680 patent were similarly obvious over McLeskey and the knowledge of a POSA.

B. Ground 2: All Claims of the '680 Patent Were Obvious Over Howell 1996 In View of McLeskey

129. It is my opinion that each claim of the '680 patent was obvious over Howell 1996 in view of McLeskey. My discussion of obviousness of the claims of the '680 patent over the McLeskey reference (*see* Section VIII.A, *supra*) is incorporated herein.

(a) *The POSA Would Have Been Motivated to Combine the Howell 1996 and McLeskey References*

130. The claims of the '680 patent claim treating hormonal dependent benign or malignant diseases of the breast or reproductive tract with fulvestrant. That is exactly the subject matter of Howell 1996. Ex. 1006. Howell 1996 is therefore extremely pertinent to the POSA, who would have been attempting to effectively formulate fulvestrant for treating breast cancer in women, particularly post-menopausal women. *See* Ex. 1004 (Expert Declaration of Dr. Leslie Oleksowicz, M.D.) at ¶¶ 55–61, 134, 194–203.

131. Howell 1996 teaches administering a long-acting castor oil-based formulation of fulvestrant in a monthly intramuscular injection to a patient to treat breast cancer. Ex. 1006. After reading Howell 1996, the POSA would have had to find a castor oil-based formulation that would solubilize fulvestrant. The POSA

would have quickly found this formulation in McLeskey. Ex. 1005 at 2. As I discussed above, references like McLeskey would have been highly pertinent to the POSA attempting to effectively formulate a drug. *See* ¶ 64, *supra*. Therefore, the POSA would have looked to McLeskey and would have discovered that 50 mg/mL of fulvestrant was effectively solubilized in "10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil." Ex. 1005 at 2.

(b) ***Independent Claim 1 Was Obvious over Howell 1996 in view of McLeskey***

132. Independent claim 1 of the '680 patent recites a method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administering to a human an i.m. injection of a pharmaceutical formulation comprising about 50 $mgml^{-1}$ 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 a castor oil vehicle, wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least 4 weeks after injection. Ex. 1001 at col.12 ll. 42–53.

133. Howell 1996 disclosed each treatment limitation included in claim 1 of the '680 patent. Howell 1996 disclosed a method of treating breast cancer, which is a hormonal dependent benign or malignant disease of the breast or reproductive tract. Ex. 1006 at 1–7. Howell 1996 disclosed administering this treatment to a human—Howell 1996 administered fulvestrant to women with

advanced breast cancer. *Id.* Howell 1996 disclosed administering the fulvestrant formulation in an intramuscular injection. *Id.* at 1–2, 6. Howell 1996 disclosed a formulation of fulvestrant in castor oil. *Id.* at 2. To the extent the "wherein" clause is given patentable weight, Howell 1996 disclosed attaining a therapeutically significant blood serum fulvestrant concentration level of 2.5 ng/ml for at least 4 weeks after injection.[9] *Id.* at 3–4, 6; *see also* ¶¶ 102–103, *supra.* The POSA would have understood that although Howell 1996 reported serum fulvestrant concentrations, the plasma concentrations would have been similar and the values were generally interchangeable. *See* ¶ 103, *supra.*

134. The element of claim 1 reciting the excipients in a castor oil-based fulvestrant formulation is found in McLeskey. Ex. 1005 at 2. As discussed above, McLeskey disclosed the exact same excipients and a formulation exactly matching the "about" values of claim 1 of the '680 patent. *See* ¶ 95, *supra.* Specifically, the formulation disclosed by McLeskey in 1998 is an even more precise formulation than the one recited in claim 1 of the '680 patent. McLeskey (Ex. 1005) disclosed a formulation of "50 mg/ml preformulated [fulvestrant] drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor

[9] I note, however, that it is my opinion that this claim language is not a limitation, but is instead a desired result of the subject matter of the '680 patent. *See* ¶¶ 40 and 100, *supra.*

oil[.]" Ex. 1005 (McLeskey) at 2. As discussed above, a POSA would have known that the McLeskey formulation was disclosed in %w/v. *See* Section VII.E(a), *supra*. McLeskey's disclosure of a "50 mg/ml^{-1} preformulated [fulvestrant] drug" exactly matches (or falls within) claim 1's recitation of "about 50 mg/ml^{-1} of fulvestrant." McLeskey's disclosure of 10% ethanol, 15% benzyl benzoate, and 10% benzyl alcohol exactly matches claim 1's "about" concentrations of 10% w/v ethanol, 15% w/v benzyl benzoate, and 10% w/v benzyl alcohol. Likewise, McLeskey also disclosed a "50 mg/ml preformulated [fulvestrant] drug," which matches (or falls within the range of) claim 1's "about 50 $mgml^{-1}$ of fulvestrant." And "brought to volume with castor oil," as disclosed in McLeskey, matches the "sufficient amount of a castor oil vehicle" disclosed in claim 1.A POSA would have known that the excipient percentages in the McLeskey formulation were disclosed in %w/v. *See* Section VII.E(a), *supra*. The POSA would have also expected that the McLeskey formulation would effectively solubilize fulvestrant, due to disclosures in the prior art and the POSA's ability to perform routine predictive solubility calculations. *See* Section IX.C, *infra*.

135. McLeskey also disclosed a "50 mg/ml preformulated [fulvestrant] drug," Ex. 1005 at 2, which would have indicated to the POSA that the disclosed formulation effectively dissolved 50 mg/ml of fulvestrant—meaning, a formulation could include 50 mg/ml of fulvestrant, as well as 10% w/v of ethanol, 10% w/v of

benzyl alcohol, 15% w/v of benzyl benzoate, and castor oil. Howell 1996 also disclosed a formulation containing 250 mg of fulvestrant in 5 mL, meaning a concentration of 50 mg/mL of fulvestrant. Ex. 1006 at 2–4, 6.

136. Thus, claim 1 of the '680 patent was obvious over Howell 1996 in view of McLeskey.

(c) ***Independent Claim 9 Was Obvious over Howell 1996 in View of McLeskey***

137. Claim 9 is almost identical to claims 1, except that whereas claim 1 uses the transitional phrase "comprising," claim 9 uses the transitional phrase "consisting essentially of."[10] I have been informed that "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; "consisting essentially of" excludes any element, step, or ingredient not specified in the claim, unless those elements, steps, or ingredients do not materially affect the basic and novel characteristics of the claimed invention.

138. For the reasons stated above in Section VIII.A(a) (regarding claim 1), Section VIII.A(b) (regarding claim 2), and ¶¶ 133–135, *supra*, Howell 1996 and McLeskey disclosed all elements of claim 9 of the '680 patent, and a POSA would have considered both references. A POSA would have looked to the McLeskey, considered the exact formulation, expected the McLeskey formulation to

[10] *See supra* n.8.

effectively solubilize fulvestrant, and administered the fulvestrant formulation to a human intramuscularly. *See* ¶¶ 96–99, *supra*. A POSA would have also known that a fulvestrant formulation of fulvestrant, ethanol, benzyl alcohol, and benzyl benzoate, as in claim 9 should be administered via a suitable pharmaceutical vehicle, e.g., a castor oil vehicle. *See* ¶ 108 and n.8, *supra*.

139. To the extent claim 9's "wherein" clause is given patentable weight, a POSA would have expected to achieve a 2.5 $nmgl^{-1}$ blood plasma fulvestrant concentration for at least 4 weeks. *See* ¶¶ 100–104, *supra*. Therefore, for the reasons described above (*see* Section VIII.A(a) and ¶ 133, *supra*), claim 9 was obvious over McLeskey.

140. To the extent claim 9 does not explicitly include a castor oil vehicle, a POSA would have known that the listed fulvestrant formulation of about 50 mg/ml fulvestrant, about 10% w/v ethanol, about 10% w/v benzyl alcohol, and about 15% w/v benzyl benzoate—which would be expected to solubilize the fulvestrant compound, *see* Sections IX.B–C, *infra*, and which did not result in a 100% formulation—could be administered via a suitable pharmaceutical vehicle, e.g., a castor oil vehicle, as disclosed in McLeskey (Ex. 1005 at 2) and Howell 1996 (Ex. 1006 at 2).

141. Thus, claim 9 of the '680 patent was obvious over Howell 1996 in view of McLeskey.

(d) ***Dependent Claims 2 and 10 Were Obvious Over Howell in View of McLeskey***

142. Dependent claims 2 and 10 depend from claims 1 and 9, respectively. Claims 2 and 10 express that a blood plasma fulvestrant concentration of 8.5 ng/ml is achieved for 4 weeks after injection.

143. For the reasons stated above in Section VIII.A(a)–(b) and VIII.B(b)–(c), Howell 1996 and McLeskey disclosed all elements of claims 1 and 9 of the '680 patent, and a POSA would have considered both references.

144. As stated above in Section VIII.A(c), to the extent claims 2 and 10 purport to add an additional patentable element—that a fulvestrant blood concentration of at least 8.5 $ngml^{-1}$ is achieved for at least 4 weeks—it is my opinion that claims 2's and claim 10's recitation is simply an expression of the desired outcome of administering the claimed fulvestrant formulation in an i.m. injection. *See* ¶¶ 40, 100, *supra*. Thus, I understand the recitations of claims 2 and 10 are not entitled to patentable weight.

145. However, even if these recitations are given patentable weight, it is my opinion that claims 2 and 10 were obvious for much the same reason independent claims 1 and 9 were obvious and for the same reasons given above regarding claims 2 and 10, *see* Section VIII.A(c), .

146. Before the priority date of the '680 patent, the art disclosed that oil-based fulvestrant formulations achieved a long-acting effect in both animals and

humans. *See* ¶¶ 101–103, *supra*. This art disclosed long-acting effects that extended to four weeks after injection. *Id.*, *see also* Exs. 1006 (Howell 1996) at 3–4; 1008 (Wakeling 1991) at Abstract; 1025 (Dukes 1992) at Abstract; 1026 (Dukes 1992) at 2.

147. To the extent claims 2 and 10 are afforded any weight—they recite a blood plasma fulvestrant concentration of 8.5 ng/ml for 4 weeks—it is my opinion that these levels could be reached through routine optimization of the method of treatment. Howell 1996 disclosed blood serum fulvestrant concentrations higher than 8.5 ng/ml extending for at least one week, and higher than approximately 5.5 ng/ml for 4 weeks. Ex. 1006 (Howell 1996) at 3–4. The POSA would have understood that although Howell 1996 reported serum fulvestrant concentrations, the plasma concentrations would have been similar and the values were generally interchangeable. *See* ¶ 103, *supra*. A POSA would also know that fulvestrant formulations in castor oil depots achieved a long-acting effect. *See, e.g.*, *supra* Section VII.D; Exs. 1012; 1007; 1025; 1026; 1018; 1027 at 5. A blood plasma fulvestrant concentration of 8.5 ng/ml could therefore have been achieved through routine optimization of the method of treatment, e.g., by adjusting the dosage or frequency of administration. *See* Ex. 1004 (Expert Declaration of Dr. Leslie Oleksowicz, M.D.) at ¶ 192.

148. Therefore, it is my opinion that claims 2 an 10 of the '680 patent were similarly obvious over Howell 1996, McLeskey, and the knowledge of a POSA.

(e) ***Dependent Claims 3, 6, 11, and 14 Were Obvious over Howell 1996 in View of McLeskey***

149. Dependent claims 3 and 6 depend directly or indirectly, respectively, from independent claim 1. Dependent claims 11 and 14 depend directly or indirectly, respectively, from independent claim 9. Claims 3, 6, 11, and 14 further specify that the benign or malignant disease being treated is breast cancer.

150. To the extent claims 3, 6, 11, and 14 purport to add an additional patentable element of treating breast cancer, as described above, it would have been obvious to use the formulation disclosed in McLeskey to treat patients with breast cancer. *See* ¶ 97, *supra*; *see also* Sections VII.A, VIII.A(d); *see also* Ex. 1004 (Expert Declaration of Dr. Leslie Oleksowicz, M.D.) at ¶¶ 166–168. Fulvestrant was long known in the art to be efficacious in the treatment of breast cancer. *See* Section VII.A.

151. Thus, claims 3, 6, 11, and 14 of the '680 patent were obvious over Howell 1996 and McLeskey.

(f) ***Dependent Claims 4, 7, 12 and 15 Were Obvious over Howell 1996 in View of McLeskey***

152. Dependent claims 4 and 7 depend directly or indirectly, respectively, from independent claim 1. Dependent claims 12 and 15 depend directly or

indirectly, respectively, from independent claim 9. Claims 4, 7, 12, and 15 recite that (1) the total volume of formulation is 5 ml and (2) the fulvestrant formulation is delivered intramuscularly.

153. To the extent claims 4, 7, 12, and 15 purport to add an additional patentable element of 5 ml delivered intramuscularly, it would have been obvious to a POSA to administer a long-acting or "depot" formulation, including this fulvestrant formulation, intramuscularly in the clinical setting. *See* ¶¶ 98, 133, and Section VIII.A(e), *supra*.

154. Likewise, it would have also been obvious to limit an intramuscular injection to 5 mL. A limit on the total intramuscular injection volume of 5 mL was well-known to a POSA at the time. The specification of the '680 patent acknowledges that "[c]urrently guidelines recommend that no more than 5 mls of liquid is injected intramuscularly in a single injection." Ex. 1001 at col. 5, ll. 64–65. The POSA would understand this statement in the specification to be a statement on the accepted state of the art, not a discovery made by the inventors. Indeed, this statement is consistent with the understanding of a POSA. *See, e.g.*, Ex. 1054 (Newton) at 4. Further, the prior art expressly disclosed intramuscular injections of 5 mL to humans—including i.m. injections of fulvestrant formulations in castor oil—before the priority date of the '680 patent. *See, e.g.*, Ex. 1006 (Howell 1996) at 2–4, 6.

155. Therefore, it is my opinion that claims 4, 7, 12, and 15 of the '680 patent were similarly obvious over Howell 1996, McLeskey, and the knowledge of a POSA.

(g) *Dependent Claims 5, 8, 13 and 16 Were Obvious over McLeskey*

156. Dependent claims 5 and 8 depend directly or indirectly, respectively, from independent claim 1. Dependent claims 13 and 16 depend directly or indirectly, respectively, from independent claim 9. Claims 5, 8, 13, and 16 recite that the claimed formulation is administered once monthly.

157. To the extent claims 5, 8, 13, and 16 purport to add an additional patentable element of monthly administration, it would have been obvious to a POSA to administer a fulvestrant formulation, such as that disclosed in McLeskey, to a human monthly. As stated above, it was understood in the art to administer drugs with low oral availability, such as fulvestrant, via an oil-based "depot" injection, which provided a long-term effect. *See* ¶¶ 59–62, 124, *supra*. Moreover, it was well-established in the prior art to administer a long-acting formulation of fulvestrant to a human on a monthly basis, and that such administration provided sustained effects. *See, e.g.*, Exs. 1006 (Howell 1996) at 3–4; 1008 (Wakeling 1991) at Abstract; 1025 (Dukes 1992) at 3; 1026 (Dukes 1993) at 7; 1028 (Wakeling 1993) at 10; *see also* Ex. 1004 (Expert Declaration of Dr. Leslie Oleksowicz, M.D.) ¶¶ 185–189, 215–219.

158. Therefore, it is my opinion that claims 5, 8, 13 and 16 of the '680 patent were similarly obvious over Howell 1996, McLeskey, and the knowledge of a POSA.

(h) ***Dependent Claims 17–20 Were Obvious over McLeskey***

159. Dependent claims 17–18 depend directly or indirectly, respectively, from independent claim 1. Dependent claims 19–20 depend directly or indirectly, respectively, from independent claim 9. Claims 17–20 recite that the claimed formulation is administered in a divided dose.

160. To the extent claims 17–20 purport to add an additional patentable element of a divided dose, for the reasons expressed in the Expert Declaration of Dr. Leslie Oleksowicz, M.D., Ex. 1004, it would have been obvious to a POSA, in light of the prior art, to administer the claimed fulvestrant formulation in a divided dose. Ex. 1004 ¶¶ 181–184, 211–214.

161. Therefore, it is my opinion that claims 17–20 of the '680 patent were similarly obvious over Howell 1996, McLeskey, and the knowledge of a POSA.

IX. THE CLAIMS OF THE '680 PATENT DID NOT ACHIEVE ANY UNEXPECTED RESULT

162. I understand that AstraZeneca has contended that the formulation recited in the method claims of the '680 patent achieves an unexpectedly superior solubility because fulvestrant is more soluble in the claimed formulation than in

castor oil, benzyl alcohol, or benzyl benzoate alone. I disagree with that contention.

163. AstraZeneca has represented that it was surprising that the introduction of a non-aqueous ester solvent—such as benzyl benzoate—increased the solubility of fulvestrant in the entire solvent mixture of castor oil, benzyl alcohol, and ethanol. *See, e.g.*, Ex. 1001 at col. 6, ll. 8–19. On the contrary, the literature well known to the POSA established that a solute can have increased solubility in a mixture of solvents, despite the fact that the solute may not have high solubility in one or more of the individual solvents in the solvent mixture. Therefore, the supposed "challenges" set forth in the '680 patent do not find support in any publication specific to drug formulation and they are therefore immaterial in my opinion.

A. A POSA Would Have Understood that Solubility of a Drug Does Not Depend Solely on Its Solubility in Each Solvent Individually

164. When developing a formulation, the POSA would not have solely considered individual solubility of a solute in one solvent when determining potential formulation components. In addition, the POSA would not have excluded a potential solvent for use in a solvent blend based solely on the solubility of the drug in that individual solvent alone. The POSA would have been aware that solvent mixtures often provide better solubility than pure solvents, and that a solute is often much more soluble in mixtures of solvents than it is in the

pure solvent. *See, e.g.*, Ex. 1044 (Barton 1991) at 34 ("Practical good solvents may be blends of poor solvents or even of nonsolvents[.]").

165. The POSA would have been aware that solvents have different energetic interactions with solutes, and mixtures of solvents can minimize the differences in these energies between the solute and solvent to maximize solubility. *See* Ex. 1045 (Hansen 1969) at 2. The POSA would have known that it was common that an optimum solvent blend may contain a "poor" solvent (i.e., one that poorly solubilizes a solute on its own).

(a) ***Examples of Increased Solubility of a Solute in a Mixture of Solvents Were Disclosed in the Art***

166. Several examples had been disclosed in the art of a solute having higher solubility in a mixture of solvents than in each individual solvent. For example, although the steroid testosterone propionate was poorly soluble in cyclohexane, its solubility in a mixture of octanol and cyclohexane was greater than its solubility in either solvent individually. Ex. 1046 (Martin 1982) at 5.

167. In another example, the solubility of the drug theophylline was studied in dioxane and water. Despite the solubility of theophylline in water being less than 1/3 its solubility in dioxane, the addition of even a small amount of water improved theophylline's solubility beyond its solubility in either individual solvent. Ex. 1047 (Martin 1980) at 3.

168. Further, although phenanthrene (a backbone molecule of many hydrophobic drugs) was poorly soluble in cyclohexane and relatively soluble in methylene iodide, adding cyclohexane to methylene iodide dramatically improved the solubility of phenanthrene. Ex. 1048 (Gordon 1952) at 2.

169. In summary, the POSA would have been aware that even though a pure solvent may not provide sufficient solubility of a drug on its own, mixtures of that solvent with other solvents could provide suitable highly concentrated formulations. Thus, the POSA would not exclude a solvent from further formulation development based on an initial survey or prior knowledge of poor solubility in the pure solvent.

B. A POSA Would Have Expected that the Addition of Benzyl Benzoate Would Improve the Solubility of Fulvestrant

(a) *The Solubility of a Solute in a Solvent (or Mixture of Solvents) Depends on Molecular Forces*

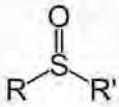
170. The solubility of a drug in a solvent or mixture of solvents depends on the cohesive energy between molecules, which represents the molecular forces holding each substance together. Exs. 1049 (Hancock 1997) at 1–2; 1042 (Martin 1995) at 4. Solubility is governed by the general principle "like dissolves like" (e.g., oily lipophilic solutes generally dissolve best in oils, and polar ionic compounds dissolve best in aqueous solutions). *See, e.g.*, Ex. 1042 (Martin 1995) at 10. Molecules in a solute have an attraction—or a cohesive energy—for each

other and for themselves that holds them together. For a solute to dissolve in a solvent, the solvent must overcome the cohesion of the solute's intermolecular bonds with like solute molecules, and at the same time, the solvent must break its own intermolecular bonds with like solvent molecules in order to interact with the solute. This is best accomplished when the solvent and solute have attractive forces that are similar to one another.

171. However, the adage "like dissolves like" in terms of polarity alone does not explain conflicting observations, for example, when an oily compound dissolves poorly in nonpolar oil, but addition of polar co-solvents improves solubility. Indeed, there are other molecular forces, including hydrogen bonding, polarity, and London dispersion forces, that can rationally explain solubility trends. *See, e.g.*, Exs. 1050 (Hildebrand 1936); 1045 (Hansen 1969). In predicting solubility, therefore, the POSA would have taken into account intermolecular forces such as hydrogen bonding nature (the number of hydrogen bonds a molecule has the potential to form) and the number of polar groups.

(b) ***Intermolecular Forces Between Fulvestrant and the Excipients in the '680 Patent Claims Would Have Led a POSA to Predict that Adding Benzyl Benzoate Would Have Improved the Solubility of Fulvestrant***

172. Fulvestrant is generally a lipophilic molecule, but despite being highly lipophilic, fulvestrant has properties that impart certain polarity and hydrogen

bonding nature to the molecule. In fulvestrant, the sulfinyl group () imparts some polarity and hydrogen bonding nature to the otherwise highly lipophilic molecule. Sulfinyl groups have a significant dipolar nature, having a positive charge at the S atom and a negative charge at the O atom, and they have a free electron pair.

173. The solvents disclosed in the '680 patent claims and the McLeskey formulation are useful in oily solutions, but they also impart some polarity and hydrogen bonding nature to the solvent mixture. Fulvestrant was already known in the art to be highly soluble in benzyl alcohol, ethanol, and castor oil. *See* Ex. 1001 ('680 patent) at col. 5, ll. 30–48. Castor oil has increased hydrogen bonding and polar dipole character compared to other vegetable oils (such as corn or peanut oil), due to the hydroxyl functional group in ricinoleic acid. *See id.* at 31–36; *see also* Ex. 1022 (Riffkin) at 3. Benzyl benzoate, like castor oil, adds hydrogen bonding and polar dipole character to a solvent blend due to its ester group. The POSA would have therefore expected that adding benzyl benzoate to a solution of castor oil, benzyl alcohol, and ethanol would actually improve the solubility of fulvestrant in the solvent mixture, because it would impart additional hydrogen bonding and polarity to the solvent mixture, rendering the solvent mixture's molecular properties more similar to those of fulvestrant.

C. To Confirm the POSA's Expectation that the Addition of Benzyl Benzoate Would Increase the Solubility of Fulvestrant in the Solvent Mixture, the POSA Could Have Performed Routine Solubility Calculations

174. At the priority date, the POSA would have knowledge of routine optimization of solvent mixtures for increasing the solubility of a pharmaceutical solute, i.e., the drug, in pharmaceutically acceptable solvents, including prediction of solubility of solutes in solvents *a priori*. Solubility parameters could be calculated in order to determine the optimum solvent blend for dissolving a drug solute. *See, e.g.*, Exs. 1049 (Hancock 1997); 1045 (Hansen 1969); 1050 (Hildebrand 1936). These solubility parameters quantify the cohesive energy holding each substance together. Ex. 1049 (Hancock 1997) at 2.

175. Solubility theory calculations were commonly used in the art of pharmaceutical formulation. The POSA would have recognized the value that Hildebrand solubility approaches have in predicting pharmaceutical drug solubility in the early stages of formulation and would have regularly applied these methods in the routine optimization of formulations. In fact, before the priority date of the '680 patent, Dr. Raymond C. Rowe, a senior scientist at Zeneca Pharmaceuticals (which merged to become AstraZeneca in 1999), explained that "the most common use of solubility parameters in the decelopment [sic] of a pharmaceutical dosage form is in predicting how materials will interact when combined in multi-component formulations." Ex. 1049 (Hancock 1997) at 13. Dr. Rowe summarizes

that "[a]n awareness of the widespread availability of solubility parameters for pharmaceutical materials and their potential use in designing optimal dosage forms is likely to be of great value to the formulation scientist." *Id.* at 18. I am in agreement with Dr. Rowe that the POSA at the time of the priority date of the '680 patent would be aware of the widespread availability of solubility parameter methods to design optimal dosage forms.

X. CONCLUSION

176. For the foregoing reasons, it is my opinion that claims 1–20 of the '680 patent were obvious over McLeskey, as well as obvious over Howell 1996 in view of McLeskey. Independent claims 1 and 9 of the '680 patent disclose the exact excipients that were previously disclosed in McLeskey, and McLeskey disclosed percentages of those excipients matching the "about" recitations of claims 1 and 9. All of the additional limitations of the claims are either disclosed in Howell 1996, were well known to the POSA at the priority date, or both.

177. Therefore it is my opinion that claims 1–20 of the '680 patent were obvious.

178. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Dated: June 29, 2016 By: 

M. Laird Forrest, Ph.D.

EXHIBIT A

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Academic Experience

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Associate Professor in the Department of Medicinal Chemistry (courtesy), University of Kansas, 12/2015-present
Associate Professor in the Department of Chemistry (courtesy), University of Kansas, 11/2013-present
Research Associate Professor (volunteer), Department of Internal Medicine, Division of Dermatology, University of Kansas Medical Center, 6/2011-6/2015 (listed appointments were at Asst. Prof. level prior to 8/2013)
Assistant Professor, Department of Pharmaceutical Chemistry, University of Kansas, 1/2007-8/2013
Adjunct Assistant Professor, Dept. of Pharmaceutical Sciences, Washington State University, Pullman, 11/2006-11/2013
Postdoctoral Fellow, Division of Pharmaceutical Sciences, University of Wisconsin, Madison, 2004-2006
Graduate Research Assistant, Department of Chemical Engineering, UIUC, 1998-2003

Other Professional Experience

Nanopharm LLC (d/b/a HylaPharm), co-founder, Chief Operating Officer, 2011-present
HylaPharm is developing injected and locally administered anti-cancer chemotherapeutics.
Exogenesis Corporation, Member of Scientific and Medical Advisory Board, 2009-present
Exogenesis is developing and commercializing nanoscale surface modification for improving the safety and efficacy of implantable medical devices
Patent Engineer/Writer, Beem Patent Law Firm, Chicago, IL, 2003-2004
Drafted and assisted in prosecution of patent applications, provided in-house scientific expert support.
Software Engineer/Consultant, Packaging Corporation of America (multiple sites), 1994-present
Developed and managed custom software for analysis of real-time manufacturing quality control systems and integration with product tracking in business data systems.
Expert witness/consultant
Medac Pharma v. Antares Pharma, expert declaration (2015)
Par Pharma v. TWI Pharma, expert declaration (2015)

Awards and Honors

University of Kansas Leading Light award, 2014
Japan Society for Promotion of Science (JSPS) Visiting Scholar Fellow, 2010
American Cancer Society Research Scholar, 2008-2012
American Association of Colleges of Pharmacy, New Investigators Award, 2007
PhRMA Foundation Postdoctoral Fellow, 2006
Controlled Release Society Annual Meeting, Glasgow, Scotland.
Student poster abstract award (unable to attend/accept), 2003
American Institute of Chemical Engineers Annual Conference, Reno, NV
Pharmaceutical and Biotechnology Program Student Paper Award, 2001
Carriers in Gene Therapy Session Speaker Award, 2001
Auburn P&P Foundation Scholarship; Tenneco Engineering Scholarship, 1994-1998

Teaching

Full courses

Biopharmaceutics and Drug Delivery, PHCH626, yearly Spring 2011-present, *Course coordinator and instructor*
Introduction of Clinical Chemistry PHCH667; yearly Spring 2007-2010, *Course coordinator and instructor*
Pharmaceutical Equilibria PHCH862/3; yearly Fall 2008-present, *Course coordinator and instructor*

Short courses

Short course on Drug Delivery (15 lectures / 1 credit hr), *Course developer and instructor*
Shandong University, China (July 2009)
Tsukuba University, Japan (July 2009)
Short course on Drug Formulation and Basic Pharmacokinetics (15 lecture hours/1 credit hr), *Couse developer and instructor*
Tsukuba University, Japan (August 2010)

Partial courses and invited lectures

Drug Delivery PHCH 715; Fall 2007, 2009, 2011, 2013
Emerging Trends in Pharmaceutical Chemistry PHCH 511; Fall 2007, Fall 2008, Fall 2010, 2012, 2014 (guest lecturer)
Introduction to Nanotechnology, C&PE 656; Spring/Fall 2009-2014 (guest lecturer)
Sigma Xi Continuing Education series, KUMC Fall 2007 (guest lecturer).

Patents

1. Forrest ML, Cai S, Zhang T, Senadheera SPSN, Groer C, Aires D, "Drug delivery compositions and methods." US Pat. Prov. Application 62/274,508 (filed 1/4/2016)
2. Forrest ML, Yunqi Zhao, Shaofeng Duan, Ti Zhang, "Targeted mTOR Inhibitor." US Pat. Prov. Application 62/120,215 (filed 2/24/2015).
3. Kwon, G.S. and M.L. Forrest, "Micelle composition of polymer and passenger drug." US Pat 9,107,814 (granted 8/18/2015).
4. Forrest ML, Cai S, Duan S, Zhang T, Yang Q, "Drug and imaging agent delivery compositions and methods" US Pat. 8,802,235. (granted 4/4/2014)
5. Rowe P, Forrest ML, Moulder R, Cai S, "Preparations for enhancement of hair growth" US Pat. Application (filed 1/20/2015)
6. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" US Pat. 8,088,412 (granted 1/3/2012) (International filings 1/30/2009)
7. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" Korean Patent 10-1224711 (granted 2/18/2013)
8. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" Japanese Patent 5,302,340 (granted 6/28/2013)
9. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" Chinese Patent 101965201 B (granted 10/23/2013)
10. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" CIP 13/341,282 (filed 1/3/2012)
11. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" France Brevet No. 2242514
12. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" Germany DBP No. 60 2009 033 907
13. Forrest ML, Cohen MS, Cai S, "Intralymphatic chemotherapy drug carriers" U.K. Patent No. 2242514
14. Kwon, G.S, and M.L. Forrest, "Micelle composition of polymer and passenger drug." US Pat. 8,173,167 (granted 5/11/12)
15. Kwon, G.S., M.L. Forrest, and N.M. Davies. "Micelle encapsulation of therapeutic agents." US App 20100203114

Peer Reviewed Publications (chronological order)

List also available as:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41384976/?sort=date&direction=ascending

1. Forrest, M.L., D.W. Pack. "On the Kinetics of Polyplex Endocytic Trafficking: Implications for Gene Delivery Vector Design." *Mol. Ther.* 6: 57-66 (2002). PMID: 12095304
2. Forrest, M.L., J.T. Koerber, and D.W. Pack. "A Degradable Polyethylenimine Derivative with Low Toxicity for Highly Efficient Gene Delivery." *Bioconjug. Chem.* 14: 934-940 (2003). PMID: 13129396
3. Forrest, M.L., G.E. Meister, J.T. Koerber, D.W. Pack. "Polyethylenimine Derivatives with Reduced Buffering Capacity and Enhanced Transfection Efficiency." *Pharm. Res.* 21: 365-371 (2004). PMID: 15032320
4. Forrest, M.L., N. Gabrielson, D.W. Pack. "Cyclodextrin-polyethylenimine conjugates for targeted in vitro gene delivery." *Biotechnol. Bioeng.* 89: 416-423 (2005). PMID: 15627256
5. Kwon, G.S. and M.L. Forrest. "Amphiphilic Block Copolymer Micelles for Nanoscale Drug Delivery." *Drug Dev. Res.* 67: 15-22 (2006).

6. Forrest, M.L., C.-Y. Won, A.W. Waseem, G.S. Kwon. "In vitro Release of the mTOR Inhibitor Rapamycin from Poly(ethylene glycol)-b-Poly(ε-caprolactone) Micelles." *J. Control. Release* 110:370-377 (2006). PMID: 16298448 *Highest cited paper in this journal for 2006.*
7. Forrest, M.L., A. Zhao, C.-Y. Won, A.W. Waseem, G.S. Kwon. "Lipophilic prodrugs of Hsp90 inhibitor geldanamycin for nanoencapsulation in poly(ethylene glycol)-beta-poly(sigma-caprolactone) micelles." *J. Control. Release* 116:139-149 (2006). PMID: 16926059
8. Xiong, M.P., M.L. Forrest, A.L. Karls, G.S. Kwon. "Biotin-triggered release of PEG-avidin from biotinylated-PEI enhances in vitro gene expression." *Bioconjug. Chem.*18:746-753 (2007). PMID: 17375897
9. Yáñez, J.A., M.L. Forrest, Y. Ohgami, G.S. Kwon, N.M. Davies. "Pharmacometrics and Delivery of Novel Nanoformulated PEG-b-Poly(ε-caprolactone) Micelles of Rapamycin." *Cancer Chemo. Pharmacol.* 2007 61(1):133-144 (2008). PMID: 17393166 PMCID: PMC2259393
10. Xiong, M.P., Y. Bae, S. Fukushima, M.L. Forrest, N. Nishiyama, K. Kataoka, G.S. Kwon. "pH-Responsive Multi-PEGylated Dual Cationic Nanoparticles Enable Charge Modulations for Safe Gene Delivery." *ChemMedChem* 2(9): 1321-1327 (2007). PMID: 17579918
11. Xiong, M.P., M.L. Forrest, N.M. Davies, G.S. Kwon. "Poly(Aspartate-g-PEI800), a polyethylenimine analogue of low toxicity and high transfection efficiency for gene delivery." *Biomaterials* 28:4889-4900 (2007). PMID: 17692910.
12. Forrest, M.L., J.A. Yáñez, C.M. Remsberg, Y. Ohgami, G.S. Kwon, N.M. Davies. "Paclitaxel prodrugs with sustained release and high solubility in poly(ethylene glycol)-b-poly(ε-caprolactone) micelle nanocarriers: pharmacokinetic disposition, tolerability and cytotoxicity." *Pharm. Res.* 25:194-206 (2008). PMID:17912488.
13. M.L. Forrest, G.S. Kwon. "Clinical developments in drug delivery nanotechnology." *Adv. Drug Deliv. Rev.* 60(8): 861-862 (2008). PMID: 18358557.
14. S. Cai, Y. Xie, T. Bagby, M.S. Cohen, M.L. Forrest. "Intralymphatic chemotherapy using a hyaluronan-cisplatin conjugate." *J. Surg. Res.* 147(2): 247-252 (2008). PMID: 18498877. **Featured on issue cover.** PMCID: PMC2430723.
15. M.P. Xiong, J.A. Yáñez, C.M. Remsberg, Y. Ohgami, G.S. Kwon, N.M. Davies, M.L. Forrest. "Formulation of a geldanamycin prodrug in mPEG-b-PCL micelles greatly enhances tolerability and pharmacokinetics in rats." *J. Control. Rel.* 129(1):33-40 (2008). PMID: 18456363 PMCID: PMC2492396
16. K.R. Vega-Villa, J.A. Yáñez, C.M. Remsberg, M.L. Forrest, N.M. Davies. "Clinical Toxicities of Nanocarrier Systems." *Adv. Drug Deliv. Rev.* 60(8):929-938 (2008). PMID: 18313790
17. K.L. Aillon, Y. Xie, N. El-Gendy, C.J. Berkland, M.L. Forrest. "Effects of nanomaterial physicochemical properties on in vivo toxicity." *Adv. Drug. Deliv. Rev.*, 61(6):457-66 (2009). PMID 19386275. PMCID: PMC2743376
18. M.P. Xiong, J.A. Yáñez, G.S. Kwon, N.M. Davies, M.L. Forrest. "A cremophor-free formulation for tanespirmycin (17-AAG) using PEO-b-PDLLA micelles: characterization and pharmacokinetics in rats." *J. Pharm. Sci.* 98(4):1577-86 (2009). PMID 18752263 PMCID: PMC2649998
19. Xie, Y, M.S. Cohen, M.L. Forrest. "Drug Delivery to the Lymphatic System: Importance in Future Cancer Diagnosis and Therapies." *Expert Opin. Drug Deliv.*, 6:785-92 (2009). PMID: 19563270. PMCID: PMC3102644.
20. S.K. Nune, P. Gunda, P.K. Thallapally, Y.Y. Lin, M.L. Forrest, C.J. Berkland. "Nanoparticles for biomedical imaging." *Expert Opin. Drug Deliv.* 6(11):1175-94 (2009). PMID: 19743894. PMCID: PMC3097035.
21. M.S. Cohen, S. Cai, M.L. Forrest. "A Novel Intralymphatic Nanocarrier-Delivery System for Cisplatin Therapy in Breast Cancer with Improved Tumor Efficacy and Lower Systemic Toxicity In Vivo." *Am. J. Surg.*, 198(6):781-6 (2009). PMID 19969129. PMCID: PMC2791715.
22. S. Cai, Y. Xie, N.M. Davies, M.S. Cohen, M.L. Forrest. "Pharmacokinetics and disposition of a localized lymphatic polymeric hyaluronan conjugate of cisplatin in rats." *J. Pharm. Sci.*, 99(6):2664-71 (2010). PMID: 19960530
23. R. Ndolo, M.L. Forrest, J.P. Krise. "The role of lysosomes in limiting drug toxicity in mice." *J. Pharmacol. Exp. Ther.* 333(1):120-8 (2010). PMID: 20056778 PMCID: PMC2846018
24. D.A. Rao, M.L. Forrest, A.W. Alani, G.S. Kwon, J.R. Robinson. "Biodegradable PLGA based nanoparticles for sustained regional lymphatic drug delivery." *J. Pharm. Sci.*, 99(4):2018-31 (2010). PMID: 19902520
25. Y. Xie, K.L Aillon, S. Cai, J.M. Christian, N.M. Davies, C.J. Berkland, M.L. Forrest. "Pulmonary delivery of cisplatin-hyaluronan conjugates via endotracheal instillation for the treatment of lung cancer." *Intl. J. Pharm.* 392(1-2):156-63 (2010). PMID: 20363303 PMCID: PMC2873163
26. S. Cai, S. Thati, T.R. Bagby, H-M. Diab, N.M. Davies, M.S. Cohen, M.L. Forrest. "Localized doxorubicin chemotherapy with a biopolymeric nanocarrier improves survival and reduces toxicity in xenografts of human breast cancer." *J. Control. Rel.* 146(2):212-218 (2010). PMID: 20403395 PMCID: PMC2918704
27. Y. Xie, S. Duan, M.L. Forrest. "Alkyne- and 1,6-elimination- succinimidyl carbonate- terminated heterobifunctional poly(ethylene glycol) for reversible "click" PEGylation." *Drug Discov. Ther.* 4(4):240-245 (2010). PMID: 21949558 PMCID: PMC3178183
28. S. Cai, N.M. Davies, M.S. Cohen, M.L. Forrest. "Carried-based intralymphatic cisplatin chemotherapy for the treatment of metastatic squamous cell carcinoma of the head & neck." *Ther. Deliv.* 1(2):237-245 (2010). PMID: 21339844 PMCID: PMC3039877

29. R. A. Ndolo, D.T. Jacobs, M.L. Forrest, J.P. Krise. "Intracellular distribution-based anticancer drug targeting: exploiting a lysosomal acidification defect associated with cancer cells." *Mol. Cell Pharmacol.* 2(4):131-126 (2010). PMID: 21274418 PMCID: PMC3026327
30. J.A. Yáñez, C.M. Remsberg, C.L. Sayre, M.L. Forrest, N.M. Davies. "Flip-flop pharmacokinetics – reversal of disposition. Challenges and opportunities during drug development." *Ther. Deliv.* 2(5):643-672 (2011). PMID: 21837267 PMCID: PMC3152312
31. S.K. Nune, P. Gunda, B.K. Majeti, P.K. Thallapally, M.L. Forrest. "Advances in lymphatic imaging and drug delivery." *Adv. Drug. Deliv. Rev.* 63(10-11):867-85 (2011). PMID: 21718728. PMCID: 3164439.
32. S. Cai, Q. Yang, M.L. Forrest. "Lymphatic drug delivery using engineered liposomes and solid lipid nanoparticles." *Adv. Drug. Deliv. Rev.* 63(10-11):901-908 (2011). PMID: 21712055. PMCID: PMC3164476.
33. M.S. Cohen, M.L. Forrest. "Lymphatic drug delivery: Therapy, Imaging and Nanotechnology." *Adv. Drug. Deliv. Rev.* 63(10-11):865-866 (2011). PMID: 21669240
34. S.M. Cohen, R. Mukerji, S. Cai, I. Damjanov, M.L Forrest*, M.S. Cohen*. "Subcutaneous delivery of nanoconjugated doxorubicin and cisplatin for locally advanced breast cancer demonstrate improved efficacy and decreased toxicity at lower doses than standard systemic combination therapy in vivo." *Am. J. Surg.* 202(6):646-653 (2011) ** co-corresponding authors* PMID: 21982998.
35. V. Shum, N. Gabrielson, M.L. Forrest, D.W. Pack. "The effects of PVP(Fe(III)) Catalyst on polymer molecular weight and gene delivery via biodegradable cross-linked polyethylenimine." *Pharm. Res.* 29(2):500-10 (2011). PMID: 21892707 PMCID: PMC3465843
36. S. Cai, T. Bagby, M.L.Forrest. "Development of regional chemotherapies: feasibility, safety and efficacy in clinical use and preclinical studies." *Ther. Deliv.* 2(11):1467-1484 (2011). PMID: 22229080 PMCID: PMC3249754
37. Q. Yang, H. Cui, S. Cai, X. Yang, M.L. Forrest. "In vivo photoacoustic imaging of chemotherapy-induced apoptosis in squamous cell carcinoma using a near-infrared caspase-9 probe" *J. Biomed. Optics.* 16(11)116026 (2011) PMID: 22112131 PMCID: PMC3221716
Included in: Virtual Journal of Biological Physics, 22(9) (2011).
38. Y. Luan, Q. Yang, Y. Xie, S. Duan, S. Cai, M.L. Forrest. "A Sensitive Near-Infrared Fluorescent Probe for Caspase: Synthesis and Application in Cell Imaging." *Drug Discov. Ther.* 5(5):220-226 (2011). PMID: 22282719 PMCID: PMC3265084
39. S. Sharifi, S. Behzadi, S. Laurent, M.L. Forrest, P. Stroeve, M. Mahmoudi. "Toxicity of Nanomaterials." *Chem. Soc. Rev.* 41: 2323-2343 (2012). PMID: 22170510 **Featured as most read article in Dec11 and Jan12.**
40. S. Duan, S. Cai, Q. Yang, M. L. Forrest. "Multi-arm polymeric nanocarrier as a nitric oxide delivery platform for chemotherapy of head and neck squamous cell carcinoma" *Biomaterials* 33(11):3243-3253 (2012). PMID: 22281420 PMCID: PMC3572206
41. S. Duan, S. Cai, Y. Xie, T.R. Bagby, M.L. Forrest. "Synthesis and characterization of a multi-arm poly(acrylic acid) star polymer for application in delivery of cisplatin and a nitric oxide." *J. Polym. Sci. A Polym. Chem.*. 50(13): 2715-24 (2012).
42. Y. Zhao, S. Duan, X. Zeng, C. Liu, B. Li, M.L. Forrest. "Prodrug strategy for PSMA-targeted delivery of TGX-221 to prostate cancer cells" *Mol. Pharm.* 9(6):1705-16 (2012). PMID: 22494444 PMCID: PMC3601665
43. T. R. Bagby, S. Cai, S. Thati, S. Duan, D.J. Aires, M.L. Forrest. "Impact of Molecular Weight on Lymphatic Drainage of a Biopolymer-Based Imaging Agent." *Pharmaceutics* 4, 276-295 (2012). PMID: 24300232 PMCID: PMC3834911
44. E.A. Mohamed, M. M. Meshali, C.M. Remsberg, Yunqi Zhao, T.M. Borg, A. Monem, M. Foda, N.M. Davies, M.L. Forrest. "Vorinostat with Sustained Release and High Solubility in Poly(ethylene glycol)-b-poly(DL-lactic acid) Micelle Nanocarriers: Characterization and Effects on Pharmacokinetics in Rat Serum and Urine" *J. Pharm. Sci.* 101(10):3787-98 (2012). PMID: 22806441
45. R. Ndolo, Y. Luan, S. Duan, M.L. Forrest, J. Krise. "Lysosomotropic Properties of Weakly Basic Anticancer Agents Promote Cancer Cell Selectivity" *PLoS One* 7(11):e49366 (2012). PMID 23145164 PMCID: PMC3492287
46. C. Remsberg, Y. Zhao, J. Takemoto, R. Bertram, N. Davies, M.L. Forrest. "Pharmacokinetic Evaluation of a DSPE-PEG2000 Micellar Formulation of Ridaforolimus in Rat." *Pharmaceutics* 5(1):81-91 (2012)
47. R. Venable, D. Worley, D. Gustafson, R. Hansen, E.J. Ehrhart, D. Aires, S. Cai, M. Cohen, M.L. Forrest. "Hyaluronan cisplatin conjugate in five dogs with soft tissue sarcomas." *Am. J. Vet. Res.* 73(12):1969-76 (2012). PMID: 23176425 PMCID: PMC3778682
48. T.R. Bagby, S. Duan, S. Cai, S. Thati, C. Berkland, D. Aires, M.L. Forrest. "Lymphatic trafficking kinetics and near-infrared imaging using star polymer architectures with controlled anionic character". *Eur. J. Pharm. Sci.* 47(1):287-94 (2013). PMID 22546180 PMCID: PMC4301975
49. A.J. Mellot, M.L. Forrest, M.S. Detamore. "Physical non-viral gene delivery methods for tissue engineering." *Ann. Biomed. Eng.* 41(3):446-68 (2013) PMID: 23099792
50. K. Devarajan, M.L. Forrest, M.S. Detamore, H. Staecker. "Adenovector Mediated Delivery to Human Umbilical Cord Mesenchymal Stromal Cells Induces Inner Ear Cell Phenotype." *Cellular Reprogramming* 15(1):43-54 (2013). PMID: 23379581 PMCID: PMC4298749

51. S. Cohen, N. Rockefeller, R. Makerji, D. Durham, M. Forrest, S. Cai, M. Cohen, Y. Shnayder. "Efficacy and Toxicity of Peritumoral Delivery of Nanoconjugated Cisplatin in an In Vivo Murine Model of Head and Neck Squamous Cell Carcinoma." *JAMA Otolaryngology-Head & Neck Surgery* 139(4):382-7 (2013). PMID: 23599074 PMCID: PMC4306558
52.
53. T. Zhang, H. Cui, H-C. Chang, X. Yang, M.L. Forrest. "Photoacoustic imaging of biological tissues with radiation damaged nanodiamonds as a near infrared optical contrast agent." *Journal of Biomedical Optics*. 18(2):26018 (2013). PMID: 23400417 PMCID: PMC3569583
54. J. Sestak, M. Mullins, L. Northrup, S. Thati, M.L. Forrest, T. Siahaan, C. Berkland. "Single-step grafting of aminooxy-peptides to hyaluronan: A simple approach to multifunctional therapeutics for experimental autoimmune encephalomyelitis." *Journal of Controlled Release*. 168(3)334-40 (2013). PMID: 23541930 PMCID: PMC3672265
55. Q. Yang, D.J. Aires, S. Cai, G.R. Fraga, D. Zhang, C.Z. Li, M.L. Forrest. "In vivo efficacy of nano hyaluronan-conjugated cisplatin for treatment of murine melanoma." *J. Drugs Dermatol.* 13(3):283-7 (2014). PMID: 24595572 PMCID: PMC4344317
56. Mellott AJ, Godsey ME, Shinogle HE, Moore DS, Forrest ML, Detamore MS. "Improving viability and transfection efficiency with human umbilical cord Wharton's jelly cells through use of a ROCK inhibitor," *Cellular Reprogramming* 16(2):91-7 (2014). PMID: 24552552 PMCID: PMC3967373
57. C. Louizos, J.A. Yanez, M.L. Forrest, N.M. Davies. "Deconvoluting the Hysteresis Loop Conundrum in Pharmacokinetic / Pharmacodynamic Relationships" *J. Pharm. Pharm. Sci.* 17(1):34-91 (2014). PMID: 24735761 PMCID: PMC4332569
58. Y. Zhao, T. Zhang, S. Duan, N.M. Davies, M.L.Forrest. "CD44-Tropic Polymeric Nanocarrier for Breast Cancer Targeted Rapamycin Chemotherapy". *Nanomedicine: NBM* 10(6):1221-30 (2014). PMID: 24637218 PMCID: PMC4119834
59. T. Zhang, H. Cui, C-Y Fang, K. Cheng, X. Yang, H-C Chang, M.L. Forrest. "Targeted nanodiamonds as phenotype specific photoacoustic contrast agents for breast cancer." *Nanomedicine (London)* 10(6):1221-30 (2014). PMID: 25723091 PMCID: PMC4703108
60. S. Cai, A. Alhowyan, Q. Yang, W.C.M. Forrest, Y. Shnayder, M.L. Forrest. "Cellular Uptake and Internalization of Hyaluronan-based Doxorubicin and Cisplatin Conjugates." *J. Drug Targeting*, 22(7):648-57 (2014). PMID: 24892741
61. S. Thati, C. Kruel, B. Hartwell, J. Sestak, T. Siahaan, M.L. Forrest, C. Berkland. "Routes of Administration and Dose Optimization of Soluble Antigen Arrays in Mice with Experimental Autoimmune Encephalomyelitis." *J. Pharm. Sci.* 104(2):714-21 (2015). PMID: 25447242 PMCID: PMC4312227
62. R. Chen, Y. Zhao, Y. Huang, W. Jiang, JB. Thrasher, P. Terranova, M.L. Forrest, B. Li. "Nanomicellar TGX221 blocks xenografts tumor growth of prostate cancer in nude mice." *Prostate* doi:10.1002/pros.22941 (2015). PMID: 25620467 PMCID: PMC4376584
63. Q. Yang, K.R. Moulder, M.S. Cohen, S. Cai, M.L. Forrest. "Cabozantinib Loaded DSPE-PEG2000 Micelles as Delivery System: Formulation, Characterization and Cytotoxicity Evaluation." *BAOJ Pharmaceutical Sciences* 1.pii:001 (2015). PMID: 25688382 PMCID: PMC4327881
64. Mellott AJ, Devarajan K, Shinogle HE, Moore DS, Talata Z, Laurence JS, Forrest ML, Noji S, Tanaka E, Staecker H, Detamore MS, "Non-viral reprogramming of human Wharton's jelly cells reveals differences between ATOH1 homologues," *Tissue Engineering Part A*, 1(11-12):1795-809 (2015). PMID: 25760435 PMCID: PMC4449705
65. Chakraborty, Aishik; Mucci, Nicolas; Tan, Ming; Steckley, Ashleigh; Zhang, Ti; Forrest, M. Laird; Dhar, Prajnaparamita. "Phospholipid Composition Modulates Carbon Nanodiamond Induced Alterations in Phospholipid Domain Formation." *Langmuir*, 31(18):5093-104 (2015) PMID: 25876023 PMCID: PMC4702515
66. Q Yang, M. Gong, S. Cai, T. Zhang, J.T. Douglas, V. Chikan, N.M. Davies, P. Lee, I.- Y. Choi, S. Ren, M.L. Forrest. "Combining hard and soft magnetism into a single core-shell nanoparticle to achieve both hyperthermia and image contrast." *Therapeutic Delivery*, 6(10):1195-1210 (2015) PMID: 26606855 PMCID: PMC4702516
67. S. Cai, T. Zhang, W.C. Forrest, Y. Qiuhong, C. Groer, E. Mohr, D.J. Aires, M. S.M. Axiak-Bechtel, B.K. Flesner, C.J. Henry, K.A. Selting, D. Tate, J.A. Swarz, J.N. Bryan, M.L. Forrest. "Phase I/II Clinical Trial of Hyaluronan-Cisplatin Nanoconjugate for the Treatment of Spontaneous Canine Cancers." *American Journal Veterinary Research, Accepted 2015. NIHMS748091*
68. M.W. Sim, P.T. Grogan, C. Subramanian, C.R. Bradford, T.E. Carey, M.L. Forrest, M.E. Prince, M.S. Cohen. "Effects of Peritumoral Nanoconjugated Cisplatin on Laryngeal Cancer Stem Cells." *The Laryngoscope. Accepted, 2015*. PMID: 26690734. *NIHMS738632*

Books/Special Journal Issues as Editor

1. M.L. Forrest and G.S. Kwon (co-editors) "Clinical developments in drug delivery nanotechnology." *Advanced Drug Delivery Reviews*, Elsevier (Philadelphia, PA USA), 2008.

2. M.L. Forrest and M.S. Cohen (co-editors) "The Lymphatic System: Therapy, Imaging and Nanotechnology." *Advanced Drug Delivery Reviews*, Elsevier (Philadelphia, PA USA), 2011.
3. M.L Forrest and J. Ramsey (co-editors). "Nanoparticles for Delivery of Biotherapeutics." Future Science Ltd. (London), 2015.

Book chapters (peer reviewed)

1. Liu, R.L., M.L. Forrest, and G.S. Kwon. "Micellization and Drug Solubility Enhancement" in *Water Insoluble Drug Formulation*, 2nd ed. Editor R. Liu. CRC Press (Boca Raton, FL) (2008).
2. Hart, D.S., Yunqi Zhao, M.L. Forrest. "Polyethylene glycol polyester block copolymers: Biocompatible carriers for nanoparticulate drug delivery" in *Handbook of Harnessing Biomaterials in Nanomedicine*, Ed. Dan Peer. Taylor & Francis publishing, (Oxford, UK)(2011).
3. J.A. Yáñez, D.R. Brooks, M.L. Forrest, N.M. Davies. "Pharmacokinetic Behavior of Orally Administered Drugs" in *Oral Bioavailability: Basics Principles, Advanced Concepts and Applications*, Eds. M. Hu and X. Li. Wiley Press (Hoboken, NJ) (2011).
4. T. Zhang, M.L. Forrest. "Biotherapeutic applications of metallic nanoparticles." *Nanoparticles for Delivery of Biotherapeutics*, Future Science Ltd. (London), publishing 2015.
5. Q. Yang, M.L. Forrest. "Drug delivery to the lymphatic system." In *Drug Delivery: Principles and Applications, Second Edition*, Eds. B. Wang, T. Siahaan. Wiley Press (Hoboken, NJ), publishing 2015.

Conference Abstracts, Papers, Proceedings and Posters

1. Forrest, M.L, D. W. Pack. "Quantitation of endolysosomal trafficking of polyplex gene delivery vehicles." *Proceedings of the International Symposium on Controlled Release of Bioactive Materials* 28, 607 (2001).
2. Forrest, M.L, J.T. Koerber, D.W. Pack. "Highly Efficient, Biodegradable Polyethylenimine Gene Delivery Vehicles." *Proceedings of the International Symposium on Controlled Release of Bioactive Materials* 30, 588 (2003).
3. Balija, A.M., M. L. Forrest, D.W. Pack, and S.C. Zimmerman. "Dendritic Trojan horse." *Abstracts of Papers (American Chemical Society Meeting)* 228: U63 267-ORGN Part 2, Aug. 22 (2004).
4. Forrest, M.L., N. Gabrielson, D.W. Pack. "Reduction of polyethylenimine bufferings capacity enhances in-vitro gene delivery activity." *Molecular Therapy* 9:S138 (2004).
5. Forrest, M.L., S. Tu, C.-Y. Won, W. Malick, G.S. Kwon. "Nanoencapsulation of Hydrophobic Paclitaxel Prodrugs in Poly(ethylene glycol)-block-poly(ε-caprolactone) Micelles." *Proceedings of the International Symposium on Controlled Release of Bioactive Materials* 30 (2006).
6. Yáñez, J. C. Remsberg, G. Kwon, N. Davies, M.L. Forrest. "Pharmacokinetics, Delivery, and Tolerability of Novel Nanoencapsulated PEG-b-Poly(ε -caprolactone) Micelles of Geldanamycin Prodrugs in Rats." *AAPS J* 9:W4427 (2007).
7. Forrest, M.L., J. Yáñez, M. Xiong, G.S. Kwon, N. Davies. "Pharmacokinetics and Characterization of 17-AAG Geldanamycin Analogue (Tanespimycin) in a Poly(ethylene oxide)-b-Poly(D-lactic acid) Micelle Nanocarrier." *AAPS J* 9:W4405 (2007).
8. C. Remsberg, C., J. Yáñez, G. Kwon, N. Davies, M.L. Forrest. "To encapsulate a synthesized paclitaxel prodrug in amphiphilic block co-polymer micelles of PEG-b-PCL and to determine the pharmacokinetics and tissue distribution of paclitaxel prodrug (PAX7'C6) solubilized in PEG-b-PCL compared to Taxol." *AAPS J* 9:W4406 (2007).
9. Forrest, M.L. and D.W. Pack. "DNA-Polymer Complexes for Gene Therapy: Discovering the Barriers to Efficient Delivery." Poster presentation at the University of Illinois Biotechnology Symposium, Urbana, IL, November 1999.
10. Forrest, M.L. and D.W. Pack. "Quantitation of Polyplex pH Microenvironment as a Tool for Elucidating Gene Delivery Mechanism." Paper at Pharmaceutical and Biotechnology Program, American Institute of Chemical Engineering National Meeting, Reno, NV, November 2001.
11. Forrest, M.L. and D.W. Pack. "Nano-Complexes of Polymer and DNA: 'Artificial Viruses'." Poster at the Nanotechnology Industrial Symposium, University of Illinois, Urbana, IL, May 2003.
12. Forrest, M.L. and D.W. Pack. "Non-Viral Gene Delivery Vectors Based on Modified Polyethylenimine" and "Highly Efficient, Biodegradable Polyethylenimine Gene Delivery Vehicles." Posters at the 30th Annual Meeting & Exposition of the Controlled Release Society, Glasgow, Scotland, July 2003.
13. Forrest, M.L. and G.S. Kwon. "Hydrolysable Prodrugs of Geldanamycin for Efficient Nanoencapsulation and Sustained Release." Poster at the American Association of Pharmaceutical Scientists Annual Meeting and Exposition, Nashville, TN, November 2005.

14. Forrest, M.L. and G.S. Kwon. "Hydrolysable Prodrugs of Geldanamycin for Efficient Nanoencapsulation and Sustained Release." and "Nanocarriers for Controlled Delivery of Therapeutic Agents." Poster at American Institute of Chemical Engineers Annual Conference, Cleveland, OH, November 2005.
15. Yáñez, J.A., M.L. Forrest, Y. Ohgami, G.S. Kwon, N.M. Davies. "Pharmacometrics and Delivery of Novel Nanoformulated PEG-b-Poly(ε-caprolactone) Micelles of Rapamycin." Poster at American Association of Pharmaceutical Scientists Annual Meeting, San Antonio, TX, October 2006.
16. Forrest, M.L., J.A. Yáñez, C.M. Remsberg, G.S. Kwon, N.M. Davies. "Nanocarrier Formulation of a Geldanamycin Prodrug in ABC Micelles: Pharmacokinetics and Tolerability in Rats." Poster at Utah 13th Drug Delivery Symposium, Salt Lake City, UT, February 2007.
17. Forrest, M.L., J.A. Yáñez, C.M. Remsberg, G.S. Kwon, N.M. Davies. "Pharmacokinetics of Nanoencapsulated Paclitaxel Hexonate Prodrug in Poly(ethylene glycol)-block-poly(epsilon-caprolactone) Micelles." Poster at 34th Annual Meeting of the Controlled Release Society, Long Beach, CA, July 2007.
18. Xiong, M.P., J.A. Yáñez, G.S. Kwon, N.M. Davies, M.L. Forrest. "A Cremophor-free Formulation for 17-AAG (tanespimycin) using PEO-b-PDLA Micelles: Characterization and Pharmacokinetics in Rats." Poster at 34th Annual Meeting of the Controlled Release Society, Long Beach, CA, July 2007.
19. Forrest, M.L., J.A. Yáñez, C.M. Remsberg, G.S. Kwon, N.M. Davies. "Pharmacokinetics of Nanoencapsulated Paclitaxel Hexonate Prodrug in Poly(ethylene glycol)-block-poly(epsilon-caprolactone) Micelles." Poster at 34th Annual Meeting of the Controlled Release Society, Long Beach, CA, July 2007.
20. M.S. Cohen, H. Diab, S. Cai, Y. Xie, M.L. Forrest. "Intralymphatic delivery system for treatment of breast cancer." Presented at American Society of Clinical Oncology – 2007 Breast Cancer Symposium, San Francisco, CA, September 7-8, 2007.
21. Yáñez, J.A., C.M. Remsberg, G.S. Kwon, N.M. Davies, M.L. Forrest. "Pharmacokinetics, Delivery, and Tolerability of Novel Nanoencapsulated PEG-b-Poly(epsilon-caprolactone) Micelles of Geldanamycin Prodrugs in Rats." Presented at American Association of Pharmaceutical Scientists Annual Meeting, San Diego, CA, November, 2007.
22. Remsberg, C.M., J.A. Yáñez, G.S. Kwon, N.M. Davies, M.L. Forrest. "Pharmacokinetic and Tissue Distribution Analysis of a Paclitaxel Prodrug Nanoencapsulated in PEG-b-Poly(epsilon-caprolactone) Micelles." Presented at American Association of Pharmaceutical Scientists Annual Meeting, San Diego, CA, November, 2007.
23. Forrest, M.L., J.A. Yáñez, M.P. Xiong, G.S. Kwon, N.M. Davies. "Pharmacokinetics and Characterization of 17-AAG Geldanamycin Analogue (Tanespimycin) in a Poly(ethylene oxide)-b-Poly(D-lactic acid) Micelle Nanocarrier." Presented at American Association of Pharmaceutical Scientists Annual Meeting, San Diego, CA, November, 2007.
24. Cai, S., Y. Xie, H. Diab, M.S. Cohen, M.L. Forrest. "Nanocarrier delivery of cisplatin to the lymphatics: In vitro and in vivo evaluation in rodents." Presented at KUMC Masonic Cancer Center Annual Meeting, December 1, 2007.
25. Cai, S., Y. Xie, T. Bagby, M.S. Cohen, M.L. Forrest. "A Hyaluronan nanocarrier for intralymphatic drug delivery: synthesis, characterization, and pharmacokinetics in rats." Presented at American Association for Cancer Research Annual Meeting, San Diego, April 14, 2008.
26. Cai, S., M.S. Cohen, M.L. Forrest. "Intralymphatic treatment of breast cancer: synthesis, characterization and pharmacokinetics in rodents." Presented at Abbott Labs, Abbott Park, IL, June 13, 2008.
27. M.S. Cohen, S. Cai, M.L. Forrest. "Intralymphatic nanocarrier chemotherapy for breast cancer: Improved delivery to locoregional lymph nodes." Presented at AACR Translational Cancer Medicine: Cancer Clinical Trials and Personalized Medicine conference, Monterey, CA, July 21, 2008.
28. T. Bagby, M.L. Forrest. "Development of Stable Melphalan Formulations for Melanoma." Presented at KU Cancer Center Research Symposium, Kansas City, November 7, 2008.
29. Y. Xie, K.L. Aillon,C.J. Berkland, M.L.Forrest. "Pulmonary Delivery of Cisplatin-Hyaluronan Conjugates for the Treatment of Lung Cancer: Synthesis, Pharmacokinetics, and Tissue Distribution in Rats." Presented at 2008 Cancer Center Research Symposium, Kansas City, November 7, 2008.
30. S. Cai, Y. Xie, T.R. Bagby, M.S. Cohen, M.L. Forrest. "Intralymphatic drug delivery for treatment of breast cancer and head and neck cancer" Presented at The University of Kansas Cancer Center Symposium at the University of Kansas Medical Center, Kansas City, November 7, 2008.
31. S. Thati, S. Cai, T.R. Bagby, M.S. Cohen, M.L. Forrest. "Intralymphatic drug delivery for treatment of breast cancer: Synthesis, characterization, pharmacokinetics and anti-cancer activity in rodents" Presented at The University of Kansas Cancer Center Symposium at the University of Kansas Medical Center, Kansas City, November 7, 2008.
32. S. Cai, Y. Xie, T.R. Bagby, M.S. Cohen, M.L. Forrest. "Intralymphatic drug delivery for treatment of breast cancer: Synthesis, characterization, and pharmacokinetics in rodents." Presented at Higuchi Bioscience Talks 2008 at University of Kansas, Lawrence, December 5, 2008.

33. T.R. Bagby, Y. Xie, M.L. Forrest. "Reversible Shielding of Viruses for Cancer Gene Therapy." Presented at the 14th International Symposium on Recent Advances in Drug Delivery Systems: Drug Carriers-Progress Beyond Delivery, Salt Lake City, UT, February 16, 2009.
34. Y. Xie, K.L. Aillon, C. Berkland, M.L. Forrest. "Nanocarrier delivery system for chemotherapeutic treatment of lung cancer." ." Presented at the 14th International Symposium on Recent Advances in Drug Delivery Systems: Drug Carriers-Progress Beyond Delivery, Salt Lake City, UT, February 16, 2009.
35. S. Cai, Y. Xie, T.R. Bagby, S. Thati, B.J. Johnston, M.S. Cohen , M.L. Forrest. "Intralymphatic drug delivery for treatment of breast cancer and head and neck cancer: synthesis, characterization, pharmacokinetics and anti-cancer activity in rodents." Presented at 14th international symposium on recent advances in drug delivery systems, Salt Lake City, UT, February 16, 2009.
36. Forrest, M.L. "Drug nanocarriers for intralymphatic chemotherapy of breast cancer." Presented at INBRE Conference, Oklahoma City, OK, May 28, 2009.
37. T.R. Bagby and M.L. Forrest. "Lymphatic Imaging of Mice." Presented at The University of Kansas Department of Pharmaceutical Chemistry Fall Retreat, Lawrence, KS, October 15, 2009.
38. T.R. Bagby, S. Cai, S. Thati, Y. Xie, N.M. Davies, M.S. Cohen and M.L. Forrest. "Localized Doxorubicin Chemotherapy with a Biopolymeric Nanocarrier Improves Survival and Reduces Toxicity in Xenografts of Human Breast Cancer." Presented at the Faculty Research Day at the University of Kansas Medical Center, Kansas City, KS, November 3, 2009.
39. Remsberg, C.M., J.K. Takemoto, R.M. Bertram, M.L. Forrest, N.M. Davies. "Development of a novel micelle formulation and pharmacometrics of the mTOR inhibitor, deforolimus." Presented at Canadian Society for Pharmaceutical Sciences in Richmond, British Columbia, June 2-5, 2010.
40. Remsberg, C.M., J.K. Takemoto, R.M. Bertram, M.L. Forrest, N.M. Davies. "Nanoformulation development and pharmacometrics of the histone deacetylase inhibitor vorinostat." Presented at Canadian Society for Pharmaceutical Sciences in Richmond, BC, June 2-5, 2010.
41. S. Cai, S. Duan, Q. Yang, M.L. Forrest. "Lymphatic Delivery of Cisplatin and Nitric Oxide Prodrug JS-K for the Treatment of Metastatic Head and Neck Squamous Cell Cancer." Presented at Department of Pharmaceutical Chemistry Fall Retreat Symposium, University of Kansas, Baldwin City, Kansas, October 14, 2010
42. S. Cai, M.L. Forrest. "Lymphatic Drug Delivery for the Treatment of Metastatic Cancers." Presented at School of Pharmacy Graduate Honors Symposium, University of Kansas, Lawrence, Kansas, April 15, 2010
43. T.R. Bagby, S. Thati, S. Cai, and M.L. Forrest. "Effect of Molecular Weight on Lymphatic Drainage Patterns and Kinetics of Localized Drug Carriers." Presented at Pharmaceutics Graduate Student Research Meeting, Columbus, Ohio, June 18, 2010.
44. Q. Yang, S. Cai, T.R. Bagby, S. Duan, M.L. Forrest. "Encapsulation of anticancer drugs and imaging agents in nanoparticles for lymphatic cancer treatment." Presented at Department of Pharmaceutical Chemistry Fall Retreat Symposium, Baldwin city, KS, October 14, 2010
45. T.R. Bagby, S. Thati, S. Duan, S. Cai, and M.L. Forrest. "Effect of Molecular Weight and Charge on Lymphatic Drainage Patterns and Kinetics of Localized Drug Carriers Using Whole Body Fluorescent Imaging." Presented at the Fourth Annual University of Kansas Department of Pharmaceutical Chemistry Fall Retreat, Lawrence, KS, October 15, 2010.
46. Y. Zhao, S. Duan, M.L. Forrest. "PSMA-targeted Nanocarriers for Delivery of TGX-221 to Prostate Cancer Cells." Presented at Department of Pharmaceutical Chemistry Fall Retreat Symposium, Baldwin city, KS, October 14, 2010
47. Duan, S.; S. Cai; T.R. Bagby; M.L. Forrest. "Synthesis of sugar and carbonate star polymers for localized chemotheraphy". Presented at the 45th Midwest Regional Meeting of the American Chemical Society, Wichita, KS, October 27-30, 2010.
48. Takemoto, J.K., C.M. Remsberg, M.L. Forrest, N.M. Davies. "Nanomicellar delivery pharmacokinetics and pharmacodynamics of the histone deacetylase inhibitor suberoylanilide hydroxamic acid." Presented at the American Association of Pharmaceutical Scientists Annual Meeting and Exposition, New Orleans, LA, November 13-14, 2010.
49. Remsberg, C.M., M.L. Forrest, N.M. Davies. "Quantitative determination of ridaforolimus, a mTOR inhibitor, in rat plasma using LC/ESI/MS." Presented at the FIP Pharmaceutical Sciences 2010 World Congress, American Association of Pharmaceutical Scientists Annual Meeting and Exposition, New Orleans, LA, November 13-14, 2010.
50. Cai, S., Y. Xie, S. Thati, T.R. Bagby, M.S. Cohen, M.L. Forrest. "Lymphatic delivery of cisplatin for the treatment of metastatic head and neck squamous cell cancer." Presented at Globalization of Pharmaceutics Education Network (GPEN), University of North Carolina, Chapel Hill, NC, November 10-12, 2010.

51. Bagby, T.R., S. Thati, S. Duan, S. Cai, M.L. Forrest. "Effect of Molecular Weight and Charge on Lymphatic Drainage Patterns and Kinetics of Localized Drug Carriers." Presented at Globalization of Pharmaceutics Education Network (GPEN), University of North Carolina, Chapel Hill, NC, November 10-12, 2010.
52. S. Cai, S. Duan, Q. Yang, M.L. Forrest. "Targeted Drug Platform for Combination Nitric Oxide and Platinum Chemotherapy of Head and Neck Cancer." Presented at Chemical Biology NIH Training Grant Symposium, University of Kansas, Lawrence, Kansas, December 7, 2010
53. S. Cai, S. Duan, M.S. Cohen, M.L. Forrest. "Targeted Drug Platform for Combination Nitric Oxide and Platinum Chemotherapy of Head and Neck Cancer." Presented at Kansas IDeA Network of Biomedical Research Excellence Symposium, Kansas City, Kansas, January 15, 2011
54. S. Cai, M.L. Forrest. "Development of Drug Delivery Platforms for Locoregional Treatment of Carcinomas." Presented at Kansas IDeA Network of Biomedical Research Excellence Symposium, Kansas City, Kansas, January 15, 2011.
55. S. Cohen, M. Cohen, R. Mukerji, S. Cai, I. Damjanov, M.L. Forrest. "Subcutaneous Delivery of Nanoconjugated Doxorubicin/Cisplatin for Locally Advanced Breast Cancer Demonstrates Improved Efficacy and Decreased Toxicity Over Standard Systemic." Resident, Postdoc, Fellows Research Day, Kansas City, Kansas, May 5, 2011.
56. M.L. Forrest, S. Cai, S. Duan, M.S. Cohen, Q. Yang. "Nitric oxide-releasing nanoparticle combination therapy to overcome drug resistance in platinum-resistant breast cancers." Presented at American Society of Clinical Oncology Breast Symposium, San Francisco, CA, September 9, 2011.
57. S. M. Cohen, R. Mukerji, S. Cai, I. Damjanov, M.L. Forrest (presenter), M.S. Cohen. "Evaluation of complete pathologic response and histologic toxicity using a subcutaneous delivery system with combination nanoconjugated doxorubicin and cisplatin for locally advanced breast cancer in vivo." Presented at American Society of Clinical Oncology Breast Symposium, San Francisco, CA, September 9, 2011.
58. K. Devarajan, M.L. Forrest, H. Staecker, M.S. Detamore. "Adenoviral mediated gene delivery to human umbilical cord mesenchymal stem cells for inner ear hair cell differentiation." Biomedical Engineering Society, Hartford, CT, October, 2011.
59. C.L. Sayre, S.E. Martinez, E.A. Mohamed, M.M. Meshali, C.M. Remsberg, Y. Zhao, T. M. Borg, A.M.M. Foda, J.K. Takemoto, M.L. Forrest, N.M. Davies. "Vorinostat with sustained released and high solubility in poly(ethylene glycol)-b-poly(DL-lactic acid) micelle nanocarriers: characterization and effects on pharmacokinetics in rat serum and urine." Canadian Society for Pharmaceutical Sciences Annual Symposium, Toronto, June 2012.
60. S. Cai, Q. Yang, S. Siller, D. Worley, L. Schneider, D. Aires, M. Cohen, M.L. Forrest. "A safe and efficacious approach to cisplatin chemotherapy: loco-regional injection of HylaPlat in canines." American Association of Pharmaceutical Scientists Annual Meeting, Chicago, IL, October, 2012.
61. Forrest, M.L. "Formulation development and pharmacokinetics of subcutaneously injected HylaPlat in spontaneous canine cancers" International Society for Hyalurnan Sciences. Oklahoma City, OK. June 3, 2013.
62. T. Zhang, Forrest, M.L. "Nanodiamond-based contrast agents for photoacoustic imaging." SPIE International Society for optics and photonics. San Diego, CA. August 25, 2013.
63. S. Cai, D. Vartia, M. Forrest, J. Bryan, D. Aires, M.L. Forrest. "A safe and efficacious approach to cisplatin chemotherapy: loco-regional injection of HylaPlat in canines." American Association of Cancer Research Annual Meeting, San Diego, CA, April 2014.
64. S. Cai, W.C. Forrest, J. Bryan, D. Aires, M.L. Forrest. "Development of Locoregional Polymeric Cisplatin Chemotherapy: Clinical Trials in Canines with Spontaneous Cancers" Controlled Release Society Annual Meeting, Chicago, IL, June 2014.
65. M. L. Forrest, S. Cai, W.C. Forrest, T. Zhang, M. Cohen, J. Bryan, D. Aires. "Development of Locoregional Polymeric Cisplatin Chemotherapy: Clinical Trials in Canines with Spontaneous Cancers," American Association for Pharmaceutical Sciences (AAPS) Annual Conference, San Diego, CA, November 2014
66. P.T. White, C. Subramanian, P.T. Grogan, S. Cai, M.L. Forrest, M.S. Cohen. "Nanoparticle-targeting of breast cancer stem cells improves efficacy and durability of chemotherapy." Association for Academic Surgery Congress, Las Vegas, NV, February 2015.
67. S. Ishiguro, D. Uppalapati, S. Cai, J. Hodge, L. Forrest, M. Tamura. "A local chemotherapy with hyaluronan-cisplatin conjugate significantly attenuates growth of lung adenocarcinoma xenografts in mouse model," American Association for Cancer Research (AACR) Annual Conference, Philadelphia, PA, April 22, 2015.

Invited Lectures

1. Forrest, M.L. and G.S. Kwon. "Phospholipid Micelles for Chemotherapeutic Drug Delivery." Invited lecture for Engineering Seminar Series, University of Kansas, Lawrence, KS, March 10, 2005.

2. Forrest, M.L. and G.S. Kwon. "Nanoencapsulation of Chemotherapeutics." Invited lecture for Pharmaceutical Sciences Seminar Series, Washington State University, Pullman, WA, September 9, 2005.
3. Forrest, M.L. and G.S. Kwon. "Development of Nanotechnologies for Drug and Gene Delivery." Invited lecture for Chemical Engineering, Florida State University, April 25, 2006.
4. Forrest, M.L. "Stability of Sirolimus in oxidative environments." Invited lecture for Exogenesis Inc., Cambridge, MA, April 25, 2007.
5. Forrest, M.L. "Emerging nanotherapeutics for cancer." Invited lecture for Sigma Xi Seminar Series, School of Medicine, University of Kansas Medical Center, Kansas City, KS, September 3, 2007.
6. Forrest, M.L. "Nanocarrier technologies for cancer imaging and treatment." Invited lecture for Engineering Seminar Series, University of Kansas, Lawrence, KS, October 19, 2007.
7. Forrest, M.L. "Nanocarrier technology in the treatment and diagnosis of cancer." Invited lecture for Department of Chemistry, Missouri State University, Springfield, MO, October 29, 2007.
8. Forrest, M.L. "New routes for chemotherapeutic intervention using nanotechnology." Invited lecture for Department of Molecular and integrative physiology, University of Kansas Medical Center, Kansas City, MO, February 4, 2008.
9. Forrest, M.L. "Trailblazing new pathways in cancer therapy", Invited lecture for Department of Chemical Engineering, Oklahoma State University, Stillwater, OK, October 7, 2008.
10. Forrest, M.L. "Lymphatic chemotherapy for localized cancers", Invited lecture for Department of Oral Biology, University of Missouri, Kansas City, KS, December 6, 2008.
11. Forrest, M.L. "Drug delivery technology and new treatments in cancer." Invited lecture for Department of Chemistry, University of Central Arkansas, Conway, AR, November 20, 2008.
12. Forrest, M.L. "Design of nanocarriers for novel routes of therapy." Invited lecture for Department of Bioengineering, University of Kansas, KS, April 10, 2009.
13. Forrest, M.L. "Drug nanocarriers for intralymphatic chemotherapy of breast cancer." INBRE Conference, Oklahoma City, OK, May 28, 2009.
14. Forrest, M.L. "Targeted Nanopharmaceuticals for Localized Carcinomas", Tsukuba University, Tsukuba City, Japan, July 15, 2009.
15. Forrest, M.L. "Nanotechnology Treatments for Cancer", Shandong University, Jinan, China, July 27, 2009.
16. Forrest, M.L. "Nanotechnology and Future Therapeutics in Cancer Treatment", Washington State University, Pullman, WA, August 3, 2009.
17. Forrest, M.L., "Development of Nanocarrier Platforms for Locally Advanced Carcinomas", Washington State University, Pullman, WA, August 7, 2009.
18. Forrest, M.L. "Localizing drug delivery to reduce toxicity and improve efficacy." NSF IUCRC, Atlanta, GA, November 20, 2009.
19. Forrest, M.L. "Engineered nanomaterials in drug delivery." Department of Materials Science Technology, Graduate School of Industrial Science and Technology, Tokyo University of Science, Tokyo, Japan, June 9, 2010.
20. Forrest, M.L. "Nanoconjugate formulation for treatment of locally advanced cancers." Department of Biomolecular Engineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, Tokyo, Japan, June 11, 2010.
21. Forrest, M.L. "Nanoconjugate formulation for treatment of locally advanced cancers." Bioengineering Laboratory, RIKEN Institute, Wako, Japan, June 15, 2010.
22. Forrest, M.L. "Engineered nanomaterials in drug delivery." Bioengineering Department, Tokyo University of Agriculture, Tokyo, Japan, June 22, 2010.
23. Forrest, M.L. "Star polymers for localized drug delivery." Graduate School of Medicine, University of Tokyo, Tokyo, Japan, June 23, 2010.
24. Forrest, M.L. "Lymphatic drug targeting systems." Biomaterials Engineering Research Institute, Tokyo Medical and Dental, Tokyo, Japan, June 28, 2010.
25. Forrest, M.L. "Localized chemotherapy using polymeric nanocarriers." Department of Translational Medicine, National Cancer Center, Tokyo, Japan, July 1, 2010.
26. Forrest, M.L. "Nanoparticle engineering for targeted drug delivery." School of Engineering, Tsukuba University, Tsukuba City, Japan, July 6, 2010.
27. Forrest, M.L. "Hyaluronan nanocarriers in drug delivery." Department of Biophysical Chemistry, Kyoto Pharmaceutical University, Kyoto, Japan, July 8, 2010.

28. Forrest, M.L. "Star polymers for localized drug delivery." Department of Drug Delivery Research and Institute for Innovative NanoBio Drug Delivery and Development, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan, July 9, 2010.
29. Forrest, M.L. "Localized chemotherapy using polymeric nanocarriers." Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Osaka, Japan, July 12, 2010.
30. Forrest, M.L. "Nanoparticle strategies for treatment of head and neck and breast cancers." Department of Biomedical Engineering, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan, July 13, 2010.
31. Forrest, M.L. "Star polymers for localized drug delivery." Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Osaka, Japan, July 14, 2010.
32. Forrest, M.L. "Localized chemotherapy using polymeric nanocarriers." Osaka Prefecture University, Osaka, Japan, July 15, 2010.
33. Forrest, M.L. "Localized chemotherapy using polymeric nanocarriers." Department of Applied Chemistry and Bioengineering, Graduate School of Engineering, Osaka City University, Osaka, Japan, July 16, 2010.
34. Forrest, M.L. "Multi-branched polymer design for drug delivery." Department of Applied Chemistry, Hiroshima University, Hiroshima, Japan, July 17, 2010.
35. Forrest, M.L. "Localized nanoparticle chemotherapy." Institute for Materials Chemistry and Engineering." Kyushu University, Fukuoka, Japan, July 20, 2010.
36. Forrest, M.L. "Targeted chemotherapy in the lymphatic system." Hokkaido University, Sapporo, Japan, July 27, 2010.
37. Forrest, M.L. "Targeted drug delivery to the lymphatics and functional imaging of tumor response." Affiliated Hospital of Guangdong Medical College, Zhanjiang, China, June 3, 2011.
38. Forrest, M.L. "Targeted chemotherapy platform for veterinarian oncology." University of Missouri, Rolla, October 7, 2011.
39. Forrest, M.L. "Localized chemotherapy for anti-cancer treatment and rapid in vivo imaging of therapeutic response." University of Kentucky, Dept. Pharmaceutics Sciences, Lexington, KY, November 4, 2011.
40. Forrest, M.L. "Development of localized cancer treatments and measurement of therapeutic response." University of Manitoba, School of Pharmacy, Winnipeg, Canada, April 11, 2012.
41. Forrest, M.L. "Localized anti-cancer treatment via lymphatic targeting." Midwest Regional Meeting of the American Chemical Society (MWMB), Omaha, Nebraska, October 25, 2012.
42. Forrest, M.L. "Localized anti-cancer treatment via lymphatic targeting." KINBRE External Advisory Committee, Kansas City, KS, April 17, 2013.
43. Forrest, M.L. "Localized anti-cancer chemotherapy." International Advanced Drug Delivery Symposium. Taipei, Taiwan, May 2, 2013.
44. Forrest, M.L. "Formulation development and pharmacokinetics of subcutaneously injected HylaPlat in spontaneous canine cancers" International Society for Hyalurnan Sciences. Oklahoma City, OK. June 3, 2013.
45. Forrest, M.L. "Locally targeted anti-cancer therapy." University of Missouri – Kansas City. Kansas City, MO. April 27, 2014.
46. Forrest, M.L. "Locally targeted platinum chemotherapy." Kansas State University, Manhattan, KS. October 5, 2015.

Conference Podium Presentations (chronological order)

1. M.L. Forrest, D.W. Pack. "Quantitative assay for polyplex release from endolysosomes: implications for design of gene delivery vehicles." AIChE Annual Meeting, Los Angeles, CA, November 13, 2000.
2. M.L. Forrest, D.W. Pack. "Quantitation of endolysosomal trafficking of polyplex gene delivery vehicles." 28th International Symposium on Controlled Release of Bioactive Materials, San Diego, California, June 27, 2001.
3. Forrest, M.L. and D.W. Pack. "Intelligent Design of Gene Delivery Vehicles: Is Endosomal Buffering Necessary?" American Institute of Chemical Engineering National Meeting, Reno, NV, November 2001.
4. Forrest, M.L. and D.W. Pack. "A Degradable Derivative of Polyethylenimine that Provides Higher Gene Transfer Efficiency and Negligible Cytotoxicity." American Institute of Chemical Engineering Annual National Meeting, Indianapolis, IN, November 2002.
5. M.L. Forrest, J.T. Koerber, D.W. Pack. "Non-viral gene delivery vectors based on modified polyethylenimine." 30th International Symposium on Controlled Release of Bioactive Materials, Glasgow, Scotland, June 22, 2003.
6. M.L. Forrest, J.T. Koerber, D.W. Pack. "Highly efficient, biodegradable polyethylenimine gene delivery vehicles." 30th International Symposium on Controlled Release of Bioactive Materials, Glasgow, Scotland, June 22, 2003.

7. M.L. Forrest, J.T. Koerber, and D.W. Pack. "Enhancement of PEI-mediated gene delivery by acetylation of primary and secondary amines." AIChE Annual Meeting, San Francisco, CA, November 20, 2003.
8. N. Gabrielson, M.L. Forrest, and D.W. Pack. "Reduction of polyethylenimine buffering capacity enhances in-vitro gene delivery activity." American Society of Gene Therapy 7th Annual Meeting, Minneapolis, MN, June 4, 2004.
9. M. L. Forrest. "Drug nanocarriers for intralymphatic chemotherapy of breast cancer." INBRE Conference, Oklahoma City, OK, May 28, 2009.
10. Forrest, M.L. "Nanoconjugate Formulation for Localized Chemotherapy." NanoDDS, Indianapolis, IN, October 6, 2009.
11. Forrest, M.L. "Star Polymers for Lymphatic Delivery." American Chemical Society Midwest Regional Annual Meeting, Iowa City, IA, October 23, 2009.
12. S. Cai, M.L. Forrest. "Development of Drug Delivery Platforms for Locoregional Treatment of Carcinomas." Presented at Kansas IDeA Network of Biomedical Research Excellence Symposium, Kansas City, Kansas, January 15, 2011
13. Forrest, M.L., T. Zhang. "Nanodiamond-based contrast agents for photoacoustic imaging." International Society for Optics and Photonics (SPIE), San Diego, CA, August 27, 2013.
14. Forrest, M.L. "Locoregional hyaluronan cisplatin (HylaPlat) in spontaneous canine cancers." International Society for Hyaluronan Sciences (ISHAS), Oklahoma City, OK, June 6, 2013.

Thesis Committees

Thesis committee chair:

PhD: Taryn Bagby (Pharm Chem, 2012), Shuang Cai (Pharm Chem, 2011), Ryan Moulder (Pharm Chem), Ninad Varkhede (Pharm Chem), Qiuhong Yang (Pharm Chem, 2014), Ti Zhang (Pharm Chem, 2015), Yunqi Zhao (Pharm Chem, 2013)

MS: David Hart (Pharm Chem, 2007), Peter Kleindl (Bioengineering, expected 2016), Ryan Moulder (Bioengineering, 2015), Alisha Simonian (Pharm Chem), Evelyn Yanez (Pharm Chem)

Thesis committee member:

PhD: Rosemary Ndolo (Pharm Chem, 2012), Julian Kissman (Pharm Chem, 2009), Chuda Chittasupho (Pharm Chem, 2012) Ryan Funk (Pharm Chem), Supang Kondee (Pharm Chem, 2011), Kwame Nti-Addae (Pharm Chem, 2008), Zahra Mohammadi (Chem Engr), Erik Vankampen (Chem Engr), Tiffany Suekama (Bioengineering, 2014), Jacob Staley (Bioengineering), Amir Fakhari (Bioengineering, 2011), Huizhong Cui (Bioengineering, 2012), Janggun Jo (Bioengineering, 2014), Lindsey Ott (Bioengineering, 2014), Anahita Khanlari (Chem Engr, 2014), Adam Mellott (Chem Engr, 2014), Saba Ghazvini (Bioegineering, tbd)

MS: Vivian Robertson (Pharm Chem, 2013), Mark Bailey (Bioengineering, 2010), Keerthana Devarajan (Bioengineering, 2011)

Student advising (undergraduate researchers)

Pharmacy: Grace Ulrich, Lei Cheung, Abby Petrulis

Chemical Engineering: He Li, Shara Thatti, Connor Bybee, Jason Christian, Hanny Sawaf, Benjamin Johnston, Brian Kim, Francis Pamatmat, Carolynn Stone, Ryan Moulder, Sebastian Bohn, Vignish Raghumraman, John Gerber, Joe Rasmussen, Michael Choi, Eva Mohr (Mechanical), Hannah Leiker, Reese Willis (Chemistry),

Summer URP: Grace Ulrich, Yomna Badawi, Shih-Hsuan Huang

Postdoctoral Scientists (includes visiting scientists)

Shuang Cai, Padmaja Gunda, Yumei Xie, Yepeng Luan, Shaofeng Duan, Sanjeewa Senadheera

Employment of graduates (includes persons employed but have not yet completed all degree requirements):

Taryn Bagby (Formulation Scientist, Mallinckordt Pharmaceuticals)
Shuang Cai (Principal Scientist, HylaPharm)
Shaofeng Duan (Associate Professor, Henan University, China)
Padmaja Gunda (Instructor, Washington State University)
David Hart (Research & Development Manager, PhytoTechnology Laboratories)
Yepeng Luan (Postdoctoral Research Scientist, University of Georgia)
Alisha Simonian (Product Development Scientist, Ohr Pharmaceutical Inc)
Yumei Xie (Postdoctoral Research Associate, Pacific Northwest National Laboratory)
Evelyn Yanez (Senior Research Associate, Genetech)
Ti Zhang (Research Scientist, HylaPharm)

Yunqi Zhao (Assistant Professor, Kunming University, China)

Professional Activities

Peer review (Funding Agencies, ad-hoc unless noted otherwise):

American Cancer Society, Drug development study section *ad hoc reviewer (2012-2014), full member (2014-2019)*
National Institutes of Health (NIH), *NCI RC1 2009, NCI R43(SBIR) 2011, NIGMS(MBRS) 2010-2013, NCI SBIR 2014, R15 2014, NCI SBIR 2015,NIH UH2/3 2015, NIH R01/R21Bioengineering Sciences and Technologies (BST) 2015*
National Science Centre (NARODOWE CENTRUM NAUKI), Poland, 2013
United Kingdom Association for International Cancer Research (AICR), *2010*
Canadian National Sciences and Engineering Research Council (NSERC), *2008*
Netherlands Technology Foundation (STW), *2009*
Hong Kong Innovation and Technology Support Programme (ITSP), *2008*
University of Houston Gear Program, *2007*

Peer review (Publications):

Ad hoc Editor for issue of Advanced Drug Delivery Reviews (2 issues, 2008 and 2011)

Ad hoc reviewer for: Advanced Drug Delivery Reviews, Biomacromolecules, Biomaterials, Biomedical Chromatography, Biopharmaceutics & Drug Disposition, Biophysical Chemistry, Clinical Pharmacokinetics, Drug Development and Industrial Pharmacy, European Journal of Pharmaceutics and Biopharmaceutics, International Journal of Pharmaceutics, Journal of Biomaterials Research, Journal of the American Chemical Society, Journal of Biomaterials Science: Polymer Edition, Journal of Biomedical Materials Research Part A, Journal of Chromatography B, Journal of Controlled Release, Journal of Pharmaceutical Sciences, Journal of Pharmacy and Pharmaceutical Sciences, Phytotherapy Research

Member: American Association of Pharmaceutical Scientists (active), American Association for Cancer Research (inactive), American Institute of Chemical Engineers (inactive)

Service

DEPARTMENT

Graduate student admissions committee, Spring 2007-present
Coordinator for Higuchi Awards to 6th year pharmacy students, Spring 2007-present
Coordinator for Enz Awards to 6th year pharmacy students, Spring 2007-present
Graduate student recruiting at Midwest American Chemical Society meeting, October 2009, 2010, 2012
Participant (presenter) with Eric Munson in Atlanta NSF-industry meeting for I/UCRC CPMF (Industry/University Cooperative Research Center for Center for Pharmaceutical Manufacturing and Formulation), November 2009
Graduate student recruiting at Central Arkansas University, November 2008
Faculty retreat planning committee member, Spring 2007
Graduate student recruiting at Missouri State University, October 2007

SCHOOL

PharmD admissions committee member, 2010-present
PharmD and MBA dual degree admissions committee member, Spring 2008-present
Pharmaceutical Chemistry Chair 5-year review committee, 2014-15

UNIVERSITY

Animal Care Advisory Council, November 2013-present
Vice-Chair of Institutional Animal Care and Use Committee (IACUC) (October 2011 – August 2013)
Chair of IACUC protocol development subcommittee, July 2009 – August 2013
IACUC member January 2007-August 2013
Interviewer for University Assessment of General Education, Spring 2007 and 2008
Student recruiter for KU at Annual Biomedical Research Conference for Minority Students (ABRCMS), St. Louis, 2011; Nashville, TN, 2013

LOCAL, STATE, REGIONAL

Invited speaker at Kansas City Chapter of American Cancer Society fundraising dinner, August 2009 (unable to attend)
Judge at PSGRM Annual Conference, Kansas City, June 2007
Judge at Annual Biomedical Research Conference for Minority Students (ABRCMS), November 2011, 2013

NATIONAL

Reviewer and study section member for American Cancer Society (ACS), Cancer Drug Development panel, 2012-

present (currently full study section member)
Reviewer National Institutes of Health (NIH), R01/R21 proposal review: Bioengineering Sciences and Technologies (BST) study section, ad hoc, 2015.
Reviewer National Institutes of Heath (NIH), NCI proposal review: cancer detection, diagnosis, and treatment technologies for global health (UH phase 2 and 3), ad hoc, 2015
Reviewer National Institutes of Heath (NIH), SBIR contract review: cancer stem cell culture systems (Phase 1 and Phase 2), ad hoc, 2015
Reviewer National Institutes of Health (NIH), SBIR contract review: cancer stem cell treatments(Phase 1 and Phase 2), ad hoc, 2014
Reviewer for National Institutes of Health (NIH) R15, ad hoc, 2014
Reviewer for National Institutes of Health (NIH), SBIR contract review panel: anticancer antibodies, ad hoc 2011
Reviewer for National Institutes of Health (NIH), MBRS review panel, ad hoc 2010, 2012
Reviewer for National Institutes of Health (NIH), RC1 grants, ad hoc 2009
Member of Scientific and Medical Advisory Board, Exogenesis Corporation, Billerica, MA, 2009-present
Member and participant in national meetings – American Chemical Society, 2009-present
Member and participant in national meetings – American Association of Pharmaceutical Sciences, 2005-present
Member and participant in national and international meetings, abstract reviewer – Controlled Release Society, 2002-2014
Member and participant in national meetings – American Institute of Chemical Engineers, 2000-2005
Reviewer for Advanced Drug Delivery Reviews, Biomacromolecules, Biomaterials, Biomedical Chromatography, Biopharmaceutics & Drug Disposition, Biophysical Chemistry, Clinical Pharmacokinetics, Drug Development and Industrial Pharmacy, European Journal of Pharmaceutics and Biopharmaceutics, International Journal of Pharmaceutics, Journal of Biomaterials Research, Journal of Biomaterials Science: Polymer Edition, Journal of Biomedical Materials Research Part A, Journal of Chromatography B, Journal of Controlled Release, Journal of Pharmaceutical Sciences, Journal of Pharmacy and Pharmaceutical Sciences, Phytotherapy Research, Nanomaterials
Reviewer for University of Houston Gear Program, ad hoc 2007

INTERNATIONAL
Reviewer for National Science Centre (NARODOWE CENTRUM NAUKI), Poland, ad hoc 2013
Editorial Board member, Journal of Pharmaceutics, 2012-2013
Reviewer for Icelandic Research Fund, ad hoc 2012
Reviewer for Association for International Cancer Research (AICR), United Kingdom; ad hoc 2010
Developed, organized and taught short course (1 full credit hour) "Drug Delivery systems"
Tsukuba University, Tsukuba, Japan (July 2009 and 2010)
Shandong University, Jinan, China (July 2009)
Reviewer for Hong Kong Innovation and Technology Support Programme (ITSP), ad hoc 2008
Theme issue editor for Advanced Drug Delivery Reviews, 2 theme issues, 2008 and 2009
Reviewer for Canadian National Sciences and Engineering Research Council (NSERC), ad hoc 2007
Reviewer for Netherlands Technology Foundation (STW), ad hoc 2007 and 2008

Grants

Active

1R01CA173292-01 (PI:Forrest) 03/01/13 – 2/28/18
National Institute of Health/National Cancer Institute
Title: Biomaterials for treatment of head and neck cancers
Role: PI

1U01FD005285 (lead PI: Volkin, Co-PI:Forrest) 10/1/14-9/30/17
FDA (Food and Drug Administration)
Title: Development of an Integrated Mathematical Model for Comparative Characterization of Complex Molecules

National Institutes of Health (NIH) / National Cancer Institute (NCI) 9/10/2015-6/10/2016
Contract Number: HHSN261201500047C (NCI control # N43-CO-2015-0047)
Targeted nanoparticle treatment for breast cancer stem cells
Role: co-investigator/PI subaward

Industrial Contract (PI: Forrest) 05/01/12- 04/30/14
HylaPharm LLC
Translation development of intralymphatic chemotherapy
Role: Principal investigator

Proof of Concept Award (PI: Forrest) 5/1/2015-4/30/2016
University of Kansas Commercialization and Technology Center
Development of therapy for triple negative breast cancer
Role: PI

Proof of Concept Jay Award (PI: Forrest) 7/1/2015-6/30/2016
Higuchi Biosciences Center
Mechanistic understanding of oxidation of therapeutic proteins after subcutaneous administration
Role: PI

Kansas State University – College of Veterinary Medicine & Veterinary Health Center 6/1/15-5/31/16
Proof-of-concept study locoregionally administering a nanotherapeutic formulation of hyaluronan conjugated cisplatin to dogs with naturally-occurring metastatic apocrine gland anal sac adenocarcinoma
Role: co-investigator

Recently completed (last 3 years)
Proof of Concept Award (PI: Rowe) 4/1/2014-6/30/2015
University of Kansas Commercialization and Technology Center
Formulation for enhanced hair growth
Role: Co-PI

RSG-08-133-01-CDD (PI: Forrest) 07/01/08-06/30/13
American Cancer Society, Research Scholar Grant
Targeted drug carriers for melanoma therapy
Role: Principal Investigator

1P30CA168524-01 (PI: Jensen) 12/10/12 – 8/09/13
NIH Acad. 0, Su. 0
KU Cancer bridge award for R01 submissions
Role: PI on subaward

KG090481 Susan G. Komen Foundation, Career Catalyst Grant (PI: M.S. Cohen) 7/1/09-6/30/12 *Nanocarrier-based Targeted Chemotherapy for Improved Drug Therapy in Locally Advanced Breast Cancer.* (role: Co-investigator)

Department of Defense Prostate Cancer Idea Award (PI: B. L) 10/01/09 – 09/30/12
Targeted delivery of nanoparticle-encapsulated p110beta-specific inhibitor for prostate cancer intervention
The goal is to develop a new formulation of signal transduction inhibitors for prostate cancer using nanocarriers.
(role: Co-investigator)

1R56AI091996 (PI: Berkland) 08/15/12 – 07/31/15
Targeted nanoscale antigen arrays for treating autoimmune diseases
NIH

Pilot award (PI: Forrest) 1/30/2013-1/29/2014
Kansas Biosciences Authority
Preclinical studies of a nanoconjugate drug
Role: Principal investigator

EXHIBIT B

Exhibit	Description
1001	U.S. Patent No. 8,329,680
1002	File History For U.S. Patent No. 8,329,680
1005	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," CLIN. CANCER RESEARCH 4:697–711 (1998) ("McLeskey")
1006	Howell *et al.*, "Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer," BRIT. J. CANCER 74:300–08 (1996) ("Howell 1996")
1007	EP 0 346 014 (Dukes), published 12/13/1989 ("Dukes 1989")
1008	Wakeling et al., "A Potent Specific Pure Antiestrogen with Clinical Potential," 51 CANCER RESEARCH 3867–3873 (1991) ("Wakeling 1991")
1009	Alan E. Wakeling & Jean Bowler, "ICI 182,780: A New Antioestrogen with Clinical Potential," 43 J. STEROID BIOCHEM. MOLEC. BIOL. 173–177 (1992) ("Wakeling 1992")
1010	Spiegel & Noseworthy, "Use of Nonaqueous Solvents in Parenteral Products," 52(10) J. Pharm. Sci. 917–927 (1963) ("Spiegel & Noseworthy")
1011	Order, *AstraZeneca Pharmaceuticals LP v. Sandoz Inc.*, No. 14–03547 (D.N.J. July 29, 2015), ECF No. 102
1012	A. Howell, "Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer," LANCET 345: 29–30 (1995) ("Howell 1995")
1013	O'Regan et al., "Effects of the Antiestrogens Tamoxifen, Toremifene, and ICI 182,780 on Endometrial Cancer Growth," 90 J. NAT'L CANCER INST. 1552–1558 (1998) ("O'Regan 1998")
1014	Lu e*t al.*, "The effects of aromatase inhibitors and antiestrogens in the nude mouse model," BREAST CANCER RESEARCH & TREATMENT 50:63–71 (1998) ("Lu 1998")

1016	Poyser, "Effects of onapristone, tamoxifen and ICI 182780 on uterine prostaglandin production and luteal function in nonpregnant guinea-pigs," 98 J. REPRODUCTION AND FERTILITY 307–312 (1993) ("Poyser")
1018	Osborne et al., "Comparison of the Effects of a Pure Steroidal Antiestrogen With Those of Tamoxifen in a Model of Human Breast Cancer," 87 J. NAT'L CANCER INST. 746–750 (1995) ("Osborne 1995")
1019	U.S. Patent RE 28,690 ("Lehmann")
1020	GB 1 569 286 ("GB '286")
1021	REMINGTON'S PHARMACEUTICAL SCIENCES (excerpts) (Alfonso R. Gennaro ed., 18th ed. 1990) ("Remington's")
1022	Riffkin, "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones," 53 J. PHARM. SCI. 891–895 (1964) ("Riffkin")
1023	HANDBOOK OF PHARMACEUTICAL EXCIPIENTS 7–9, 35–39, 82–83 (Ainley Wade & Paul J. Weller eds., 2d ed. 1994)
1024	PHARMACEUTICAL DOSAGE FORMS: PARENTERAL MEDICATIONS Vol. 1 (Kenneth E. Avis et al. eds., 2d ed. 1992)
1025	Dukes *et al.*, "Antiuterotrophic effects of a pure antioestrogen, ICI 182,780: magnetic resonance imaging of the uterus in ovariectomized monkeys," 135 J. ENDOCRINOLOGY 239–247 (1992) ("Dukes 1992")
1026	Dukes *et al.*, "Antiuterotrophic effects of the pure antiestrogen ICI 182,780 in adult female monkeys (*Macaca nemestrina*): quantitative magnetic resonance imaging," 138 J. ENDOCRINOLOGY 203–209 (1993) ("Dukes 1993")
1027	DeFriend *et al.*, "Investigation of a New Pure Antiestrogen (ICI 182780) in Women with Primary Breast Cancer," 54 CANCER RESEARCH 408–414 (1994) ("DeFriend 1994")
1028	Alan E. Wakeling, "The future of new pure antiestrogens in clinical breast cancer," 25 BREAST CANCER RESEARCH & TREATMENT 1–9 (1993) ("Wakeling 1993")
1029	U.S. Patent No. 4,659,516 ("'516 patent")

1030	Lu *et al.*, "The effect of combining aromatase inhibitors with antiestrogens on tumor growth in a nude mouse model for breast cancer," BREAST CANCER RESEARCH & TREATMENT 57:183–192 (1999) ("Lu 1999")
1032	UNITED STATES PHARMACOPEIA XXIV, NAT'L FORMULARY XIX 14 (2000) ("USP 24")
1037	James C. Boylan et al., *Parenteral Products*, *in* MODERN PHARMACEUTICS (Gilbert S. Banker & Christopher T. Rhodes eds., 3d ed. rev. 1996) ("Modern Pharmaceutics")
1040	U.S. Patent No. 4,229,626 (Schülze et al.), issued 10/10/1978 ("Schülze")
1041	U.S. Patent No. 4,310,523 (Neumann), issued 1/12/1982 ("Neumann")
1042	ALFRED MARTIN, PHYSICAL PHARMACY: PHYSICAL CHEMISTRY PRINCIPLES IN THE PHARMACEUTICAL SCIENCES (4th ed. 1995) ("Martin 1995")
1043	Powell et al., "Compendium of Excipients for Parenteral Formulations," 52(5) PDA J. PHARM. SCI. & TECH. 238–311 (1998) ("Powell")
1044	ALLAN F.M. BARTON, HANDBOOK OF SOLUBILITY PARAMETERS AND OTHER COHESION PARAMETERS (2d ed. 1991) ("Barton 1991")
1045	Hansen, "The Universality of the Solubility Parameter," 8(1) I & EC PRODUCT RESEARCH AND DEVELOPMENT 2–11 (1969) ("Hansen 1969")
1046	Martin et al., "Extended Hildebrand Solubility Approach: Testosterone and Testosterone Propionate in Binary Solvents," 71(12) J. PHARM. SCI. 1334–1340 (1982) ("Martin 1982")
1047	Martin et al., "Extended Hildebrand Solubility Approach: Solubility of Theophylline in Polar Binary Solvents," 69(5) J. PHARM. SCI. 487–491 (1980) ("Martin 1980")
1048	Gordon & Scott, "Enhanced Solubility in Solvent Mixtures. I. The System Phenanthrene—Cyclohexane—Methylene Iodide," (1952) ("Gordon 1952")
1049	Hancock et al., "The use of solubility parameters in

	pharmaceutical dosage form design," 148 INT'L J. PHARMACEUTICS 1–21 (1997) ("Hancock 1997")
1050	Hildebrand, "Dipole Attraction and Hydrogen Bond Formation in Their Relation to Solubility," 83(2141) SCIENCE 21–24 (1936) ("Hildebrand 1936")
1051	Waynforth et al., "Good Practice Guidelines: Administration of Substances (Rat, Mouse, Guinea Pig, Rabbit)," 1(1) LABORATORY OF ANIMAL SCIENCE ASSOCIATION GOOD PRACTICE GUIDELINES 1–4 (1998) ("Waynforth 1998")
1052	Davy et al., "A pharmacokinetic evaluation of IM administration of bleomycin oil suspension," 14 CANCER CHEMOTHERAPY PHARMACOLOGY 274–276 (1985) ("Davy 1985")
1053	Robinson et al., "Procaine Penicillin: Therapeutic Efficiency and a Comparative Study of the Absorption of Suspensions in Oil and in Oil Plus Aluminum Monostearate and of an Aqueous Suspension Containing Sodium Carboxylmethylcellulose," 33(10) J. LAB. CLIN. MED. 1232–40 (1948) ("Robinson 1948")
1054	Newton, "Reviewing the 'Big Three' Injection Routes," 22(2) NURSING 34–41 (1992) ("Newton")
1055	Uges, "Plasma or serum in therapeutic drug monitoring and clinical toxicology," 10 PHARMACEUTISCH WEEKBLAD SCIENTIFIC EDITION 185–88 (1988) ("Uges 1988")