UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INNOPHARMA LICENSING, LLC

Petitioner

v.

ASTRAZENECA AB

Patent Owner

Case IPR2017-00900

U.S. Patent 8,329,680 B2

DECLARATION OF RONALD J. SAWCHUK, PH.D. IN SUPPORT OF PATENT OWNER'S PRELIMINARY RESPONSE

I, Ronald J. Sawchuk, Ph.D., do hereby make the following declaration:

I) INTRODUCTION

1. I am over the age of eighteen and competent to make this declaration.

2. I have been retained as an expert witness on behalf of AstraZeneca AB for the above-captioned *inter partes* review (IPR). I am being compensated at my customary rate of $875 per hour for my consultation in connection with this matter. My compensation is in no way dependent on the outcome of my analysis or opinions rendered in this matter.

II) QUALIFICATIONS AND EXPERIENCE

3. My name is Ronald J. Sawchuk, Ph.D. I am a Professor of Pharmaceutics, Emeritus, and Morse Alumni Distinguished Teaching Professor. I also served as the Director of the Bioanalytic and Pharmacokinetic Services Laboratory at the University of Minnesota until August of 2014 when I completed a drug development contract at the University. I have studied and carried out clinical and pre-clinical research in the field of pharmacokinetics and biopharmaceutics for over forty years.

4. I joined the University of Minnesota in 1971 as an Instructor in Pharmaceutics after having obtained a Bachelor and Masters of Science Degree from the University of Toronto in 1963 and 1996, respectively, and completing my Doctoral Degree (Ph.D.) in Pharmaceutical Chemistry (pharmacokinetics

emphasis) at the University of California, San Francisco, which was granted in 1972.

5. At the University of Minnesota I served as an Assistant Professor of Pharmaceutics from 1972 to 1977, an Associate Professor of Pharmaceutics from 1977 to 1983, and a full Professor of Pharmaceutics from 1983 until my retirement in July of 2010. During this period, I was course director for instruction in pharmacokinetics, clinical pharmacokinetics, advanced pharmacokinetics, and pharmacokinetic modeling and simulation. I was also a participating instructor in biopharmaceutics, and advanced pharmacokinetics. I continue to provide lectures relating to preclinical and clinical pharmacokinetics to scientists in the pharmaceutical industry.

6. I also served as a member of the graduate programs in Pharmaceutics, Neurosciences, and Experimental and Clinical Pharmacology. From 1983 to 1989 and 1991 to 1994, I was the Director of Graduate Studies in Pharmaceutics at the University. From 1982 to 1995, I also served as Director of the Clinical Pharmacokinetics Laboratory at the College of Pharmacy at the University of Minnesota. From 1998 to 1999 I served as the Head of the Department of Pharmaceutics at the University of Minnesota.

7. Although I have formally retired from the University, my Graduate Faculty appointment in the Department of Pharmaceutics is still in effect, allowing

me to teach graduate students in the program. I have advised on the order of forty graduate students, postdoctoral fellows, and visiting scholars, on projects relating to preclinical and clinical pharmacokinetics, biopharmaceutics, and bioanalytical chemistry.

8. A major focus of my research was preclinical and clinical pharmacokinetics. I have been involved with many different preclinical and clinical human trials, and in particular with the analysis of the pharmacokinetic and other data generated during those trials. I also focused my research on drug bioavailability and bioequivalence. I have taught, and continue to teach, pharmacokinetics, and pharmacokinetic modeling and simulation in professional, graduate, and elective courses at the University of Minnesota and to the pharmaceutical industry. This instruction includes lectures on the assessment of bioavailability and bioequivalence.

9. I have expertise in the determination of pharmacokinetic parameters and metrics for orally administered drugs, bioanalytical chemistry, biopharmaceutics, and pharmacodynamics. I have devoted a large part of my career to the study of the pharmacokinetics of drugs. And, in addition to authoring numerous publications in this area, I have received funding from various sources in the public and private sector to support my research in pharmacokinetics, including support from the National Institutes of Health ("NIH") and the U.S. Food and Drug

Administration ("FDA").

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

11. I have been a member of numerous scientific and clinical societies. I am a Fellow of the American Association of Pharmaceutical Scientists and of the American Association for the Advancement of Science. I have been a member of the International Society of Anti-infective Pharmacology and the International Society for the Study of Xenobiotics (ISSX). I served a three-year term as a member-at-large on the American Association of Pharmaceutical Scientists (AAPS) Executive Council.

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

13. I am a named author on over 100 refereed scientific publications, several book chapters and over 170 abstracts, which have been presented at

scientific meetings. I have also co-edited a book on drug bioavailability and given hundreds of invited lectures.

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

15. My academic background and work experience are summarized in my *curriculum vitae*, attached to this declaration as Exhibit A.

16. In the past four years, I have testified in the following litigation: *Ferring v.* Watson (July 17, 2013); *Ferring v.* Watson and Apotex (Jan 21-30, 2014); *Shire v.* Actavis et al. (Feb 13, 2014); *Astra-Zeneca v.* Sandoz et al. (June 5, 2015); *BMS* v. Teva (August 25, 2015); *Astra-Zeneca* v. Sandoz et al. (March 23, 2016); and *Astra-Zeneca* v. Sagent and Glenmark (July 11-14, 2016).

III) MY UNDERSTANDING OF THE PROCEEDING

17. I have been informed that this proceeding is an *inter partes* review ("IPR") before the Patent Trial and Appeal Board of the United States Patent and Trademark Office ("the Board"). I have been informed that an IPR is a proceeding to review the patentability of one or more issued claims in a United States patent on the grounds that the patent is the same as or rendered obvious in view of the prior art.

18. I understand that InnoPharma Licensing, LLC ("InnoPharma") has

challenged AstraZeneca-owned U.S. Patent No. 8,329,680, which relates to a method of treating hormonal dependent disease of the breast or reproductive tract, and, more specifically hormonal dependent breast cancer.

19. I have been informed that InnoPharma filed a Petition (IPR2017-00900, Paper 1) ("Petition") requesting IPR of U.S. Patent No. 8,329,680 (the "'680 Patent"), which issued to John R. Evans and Rosalind U. Grundy on December 11, 2012 and is assigned to AstraZeneca AB. I have reviewed the Petition, and understand that it alleges that claims 1-3 and 6 of the '680 Patent are unpatentable over Howell 1996 (Ex. 1007) and, alternatively, over the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008), the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008) and O'Regan (Ex. 1009), and the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008), O'Regan (Ex. 1009), and DeFriend (Ex. 1038).

IV) MATERIALS CONSIDERED

20. In preparing this declaration, I reviewed the Howell 1996 (**Ex. 1007**), McLeskey (**Ex. 1008**), O'Regan (**Ex. 1009**) and DeFriend (**Ex. 1038**); the '680 Patent (**Ex. 1001**); the declaration of Dr. Bergstrom (**Ex. 1013**); and the other exhibits listed in Exhibit B.

V) MY OPINIONS AND THEIR BASES

21. In this declaration, I was asked to provide opinions concerning:

A. The qualifications of a person of ordinary skill in the art as of January 10, 2000;

B. The state of the art as of January 10, 2000;

C. The claim limitations "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks" (Claims 1 and 3) and "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$," (Claims 2 and 6); and

D. The declaration of Dr. Richard Bergstrom, Ph.D. (Ex. 1013) ("Bergstrom Decl.") and exhibits cited therein.

22. As part of this opinion, I considered the level of ordinary skill in the art around January 2000, which represents the filing date of GB 0000313, to which the '680 Patent claims priority.

23. Based on my review of the materials identified above in Section IV) as well as the materials listed in Exhibit B, and my knowledge and experience, my opinions are as follows:

VI) SUMMARY OF APPLICABLE LEGAL CONSIDERATIONS

24. Counsel for AstraZeneca requested that I express my opinions with certain guidelines in mind, which are set forth below.

25. For this declaration I have been asked to use January 10, 2000 as the relevant date for my analysis.

26. AstraZeneca's counsel informed me that my analysis must be done through the eyes of the "person of ordinary skill in the art" as of January 10, 2000. I understand from AstraZeneca's counsel that a person of ordinary skill in the art is a hypothetical person, who has the characteristics of an ordinary artisan including ordinary creativity.

27. Factually, in my opinion, a person of ordinary skill in the art in 2000 would have been a person having a bachelor's or advanced degree in a discipline such as pharmacy, pharmaceutical sciences, endocrinology, medicine or related disciplines, and having at least two years of practical experience in drug development and/or drug delivery, or the clinical treatment of hormonal dependent diseases of the breast and/or reproductive tract. Because drug formulation and development is complicated and multidisciplinary, it would require a team of individuals including, at least, medical doctors, formulators and pharmacokineticists.

28. Unless expressly stated otherwise, all of the opinions provided in this declaration are made from the perspective of a person of ordinary skill in the art as of January 10, 2000.

VII) CLAIM CONSTRUCTION

29. All of the claims of the '680 Patent are expressly directed to methods of treatment. The methods of treatment include choice of an active ingredient, a method of administration (i.e., a combination of excipients and active injected intramuscularly), and the amount of the active to be delivered to the blood in a sustained release fashion to treat hormonal dependent disease of the breast and reproductive tract.

30. I agree with Dr. Bergstrom that the therapeutically significant blood plasma fulvestrant concentration terms in the '680 Patent claims are limitations of the claims. Bergstrom Decl. ¶ 65. These limitations are in claims 1 and 2: "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks"; "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$."

31. A person of skill in the art would understand these limitations to mean that the specified blood plasma fulvestrant concentrations of at least 2.5 $ngml^{-1}$ or 8.5 $ngml^{-1}$ are achieved and maintained for the specified amount of time, i.e., at least 4 weeks. This is consistent with the Board's finding in *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, Case IPR2016-01325, Paper No. 11 (P.T.A.B. Dec. 14, 2016) . Ex. 1011 (PTAB Decision) at 18 ("[W]e interpret 'achieves' in the wherein clauses as meaning that the concentration of fulvestrant

in a patient's blood plasma is at or above the specified minimum concentration for the specified time period.").

32. Further, these limitations give meaning to and provide defining characteristics of the method of treatment. Indeed, as the Board previously held, "rather than merely stating the result of intramuscularly administering the recited formulation, [] the wherein clause dictates both the administration duration and dose of the formulation, i.e., an amount sufficient to provide a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks." Ex. 1011 at 17. And, "[t]hat these parameters are further limited in claim[] 2, [] ('the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$') further indicates that the wherein clauses provide defining characteristics." *Id.*

VIII) THE STATE OF THE ART AS OF JANUARY 10, 2000

A) Drug Delivery And Pharmacokinetics

33. Drug targeting and duration of delivery are two important aspects of drug delivery. Drug targeting concerns identifying a specific organ or tissue to which the drug is to be delivered, while duration of delivery refers to how long the drug is present in the target organ or tissue.

34. Here, the point of the formulations set forth in the challenged patent claims is to deliver specified blood plasma levels of the drug fulvestrant for

specified times.

35. In terms of duration, one conventional distinction involves the difference between immediate and sustained released formulations.

36. "Immediate release" means the active pharmaceutical ingredient is released without a delay from its dosage form after it is administered. Most conventional oral formulations, such as tablets or capsules, are designed for immediate release of active pharmaceutical ingredients upon administration in order to rapidly obtain complete absorption.

37. Characteristic of immediate release formulations is a relatively rapid rise in the blood plasma drug levels—to an early and high peak—followed by a relatively rapid decrease in those levels.

38. In contrast, sustained-release formulations are characterized by a relatively slow rise in blood plasma drug levels which peak later, and are followed by a relatively prolonged decrease in those levels. These formulations are also often referred to as extended-release formulations.

39. With "sustained release" "blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced, because a more even blood level is maintained." Ex. 2134 (Lachman's) at 5. "Sustained-release systems include any drug delivery system that achieves slow release of drug over an extended period of time. . .The objective in designing a sustained-release system

is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level." Ex. 2080 (Remington's) at 6.

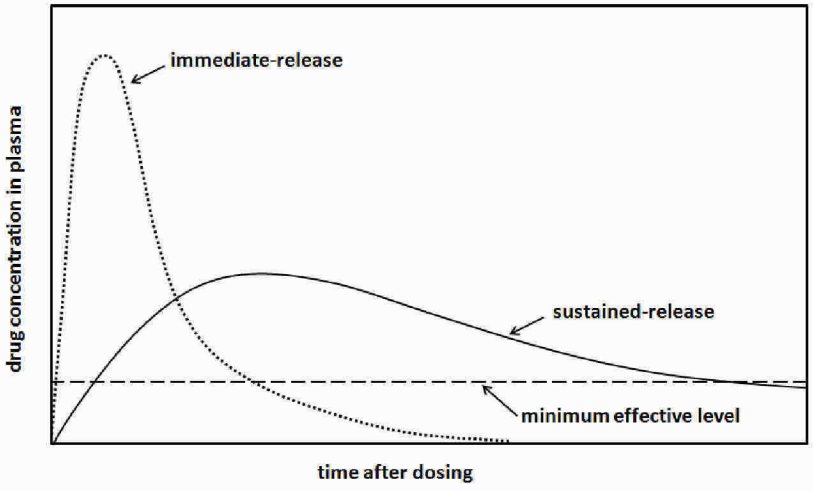
40. Without question, a person of ordinary skill would have understood that a "sustained-release" formulation is "designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectable dosage forms, this period may vary from days to months." Ex. 2134 (Lachman's) at 5. In other words, sustained release formulations are "designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose." *Id.*

41. Many sustained-release formulations are described in terms of a specific minimum drug concentration ("at least concentration X") that is achieved and maintained over a particular period of time (e.g., hours, a day, a week, two weeks, a month).

42. The study of the time-course of blood plasma levels of a drug following administration of a particular formulation/active pharmaceutical ingredient is called pharmacokinetics. Amongst other things, pharmacokinetics offers a means by which to compare the rate and extent of drug exposure provided by different formulations and/or dosing of the same active pharmaceutical ingredient.

43. This rate and extent of drug exposure requires in vivo pharmacokinetic studies. In a clinical study setting, pharmacokineticists determine the concentration of drug in a subject's plasma over time (by periodically drawing blood) in order to understand how the body processes the drug as it is being absorbed from a given formulation after it has been administered. Typically a graph of plasma drug concentrations as a function of time is generated. This graph is referred to as a "concentration-time course" or "concentration-time curve." And, a variety of analytical methods can then be used to study the results.

44. The figure below illustrates the difference between the time-course of a sustained-(solid curve) and immediate-release (dotted curve) formulation for a single dose. In contrast to an immediate-release formulation, the sustained-release formulation exhibits a prolonged period during which plasma concentrations are maintained in a specified range (e.g., above some minimum effective level).



B) Pharmacokinetics, Pharmacodynamics, And The Development Of Drugs Through Clinical Trials

45. Clinical trials are conducted in a series of steps, referred to as Phases. If a drug is found to be "successful" in a given Phase, it is permitted to continue to the next. Typically there are three such Phases, referred to as Phase I, II and III, respectively.

46. The disciplines of pharmacokinetics and pharmacodynamics are important areas of activity throughout clinical development.

47. Pharmacokinetics is essentially the study of the relationship between the dose, or dosing regimen that is used in animals or humans, and the plasma or serum concentrations of the drug that are produced. The profile of plasma concentrations or levels observed depends upon the rate and extent of absorption of the drug from its dosage form into the subject's bloodstream, in addition to how it is distributed within the body, and how rapidly and efficiently it is clear from the body by the organs of elimination.

48. Related to pharmacokinetics are bioavailability and bioanalytical chemistry. Bioavailability is a measure of the rate and extent of absorption of a drug into systemic blood, in animals or humans. The extent of absorption is typically characterized by the area under the curve ("AUC") in the blood plasma following either a single dose or upon multiple dosing over a specified duration. The rate of absorption is usually characterized by the maximum concentration of

the drug observed in plasma, and the time at which this maximum is observed. These parameters or metrics are referred to as "C_{max}" and "T_{max}," respectively. Bioanalytical chemistry involves the quantitative analysis of biological fluids (e.g., plasma, whole blood, urine, and cerebrospinal fluid) for endogenous, e.g., hormones, and exogenous compounds, e.g., drugs and metabolites. This field includes the measurement and analysis of drug levels in plasma, which provides data used to calculate many pharmacokinetic parameters or metrics, such as AUC, C_{max}, and T_{max}.

49. Of note, systemic exposure to a drug may be described in terms of the blood serum or plasma concentrations of the drug during continuous therapy (e.g., the steady-state plasma concentration, Css), or the area under the blood plasma concentration-time curve (the AUC).

50. Pharmacodynamics involves the study of the potential relationship between plasma levels of a drug and the biological effects produced. These include both the desired therapeutic responses (efficacy) and side effects or adverse events. Although efficacy (the desired therapeutic response) may be linked to plasma levels, this relationship is often very difficult to identify for a variety of reasons including the complex and usually unknown mechanisms of action for many drugs. For example, a disequilibrium in the concentrations of the drug at the measurement site (i.e. the blood plasma or serum) and those in what is referred to

as an "effect compartment" often complicates the relationship between drug levels and therapeutic response. In this case, there may be a significant delay in the response, such that effects occur much later than expected based upon the pattern of plasma levels of the drug. Other examples include a situation where there is a complicated cascade of events that must occur over time (e.g., changes in the level and activity of clotting factors resulting from the administration of an anticoagulant that interferes with the "clotting cascade") before a response to the drug is observed.

51. A careful analysis of the relationship between plasma drug levels and the effects that the drug produces is required to establish any "pharmacokinetic-pharmacodynamic" link and typically requires careful and detailed observations of the results of numerous clinical studies. Significant data (usually including data from Phase III clinical trials) and a careful analysis of the relationship between plasma drug levels and the effects that a drug produces is required to establish any "pharmacokinetic-pharmacodynamic" link. Indeed, as Dr. Bergstrom correctly notes (Ex. 1013 ¶ 38), large numbers of patients are needed to establish a pharmacokinetic-pharmacodynamic link. I agree.

C) Targeted Blood Plasma Drug Concentrations During Therapy

52. If a relationship between plasma concentrations and response—efficacy and/or adverse effects—can be established for a drug, that may allow for

the development of a strategy involving achieving and maintaining a target concentration or a target range of concentrations for individual patients.

53. This target(s) corresponds with the greatest likelihood of therapeutic success. Stated differently, ranges of serum or plasma concentrations of a drug which are known to be therapeutically significant can be used prospectively to establish a dosing regimen for patients.

54. It may be important to monitor plasma concentrations in individual patients during therapy if one wishes to ensure that those levels are within the therapeutic range, in particular if for some reason the patient's medical condition or genomic class warrants it. However, this is not always necessary, for example, if the field's experience with the drug product and dosing regimen has established the typical blood plasma drug concentrations obtained. In any event, clinicians who have the responsibility for the care of patients in oncology are typically well informed about monitoring patient response, including assessing therapeutic efficacy, and the incidence of troublesome drug related side effects, and making a change in his or her drug therapy as the situation requires it.

55. The minimum effective plasma concentration of a drug (MEC), may also be considered to be a minimum target concentration for a patient receiving medication on a multiple dosing regimen. A minimum toxic concentration of a drug (MTC), if established, would represent the upper end of this target range. The

range of plasma concentrations between the MEC and MTC is referred to as the "therapeutic window." Patient factors, such as differences in receptor density, protein binding, and disease state, may contribute to variability in this range in some patients. Nevertheless, therapeutic windows are considered for many drugs to represent a range of concentrations within which the likelihood of a desired clinical effect is relatively high, and that of unacceptable toxicity is relatively low.

56. It should be noted that response to some drugs changes with plasma drug concentrations closely in time. For other drugs the response may change more slowly than the plasma concentrations; this may result from an equilibrium delay between drug levels in the bloodstream and those at the site of action in the body, as alluded to above. Such a delay may result in a slow onset of effect, and may allow the desired response to continue with the same intensity even though the plasma drug concentrations are decreasing. Whether drug effects are closely associated in time with plasma drug levels, or exhibit a delay in onset or an extended duration of action that is unexpected in view of declining plasma levels, depends on the mechanism of action of the drug. Detailed pharmacokinetic—pharmacodynamic modeling studies are often necessary to understand any linkage between plasma drug concentrations and the response (e.g., the desired therapeutic effects) observed for a particular drug.

IX) OVERVIEW OF THE '680 PATENT PROSECUTION HISTORY

57. There are a number of inaccuracies in Dr. Bergstrom's description of the prosecution history. I am the author of the Declaration Under 37 C.F.R. § 1.132 of Ronald J. Sawchuk, dated January 13, 2012 and filed during the prosecution of the '680 patent (Ex. 1019) (the "Sawchuk Declaration"). The Sawchuk Declaration is discussed below.

A) The Sawchuk Declaration Describes Numerous Differences That Exist Between McLeskey and the Patent Claims

58. With respect to the information in McLeskey regarding the castor oil fulvestrant composition, the Sawchuk Declaration explains that "[i]n a liquid composition, when a solute or cosolvent is a liquid, it is often convenient to express its concentration as a volume percent, i.e., % v/v." Ex. 1019 at ¶ 17. Citing numerous prior art examples where that is the case, i.e., prior art references that express the concentration of liquid solutes or cosolvents in liquid compositions as volume percent (% v/v), the Sawchuk Declaration states my belief that "one of ordinary skill in the art would have concluded the McLeskey castor oil composition was described in volume/volume units (% v/v)." Ex. 1019 at ¶ 17. In reaching that opinion in the Sawchuk Declaration, I did not consider the patents because they are not part of the state of the art "prior to January 10, 2000." Ex. 1019 at ¶ 15. I do, however, note that Dr. McLeskey herself testified she believed the McLeskey castor oil composition described to be in volume/volume units (% v/v). Ex. 2043 at ¶ 8.

59. With respect to Dr. Bergstrom's paragraphs 53-56, I understand these paragraphs to be related to Dr. Bergstrom's opinions regarding validity of the challenged claims. Accordingly I address these points below in my analysis of why, in my opinion, the claimed therapeutically significant blood plasma fulvestrant concentrations are novel and why one of ordinary skill in the art would neither combine Howell and McLeskey, nor be motivated to find or reasonably expect any formulation described in McLeskey to exhibit the same or similar pharmacokinetics described in Howell.

B) The Gellert Declaration and the Sawchuk Declaration Are Consistent and Both Support the Patentability of the Challenged Claims

60. In paragraphs 57-62, Dr. Bergstrom attempts to re-write certain facts of the prosecution history of the '680 patent prosecution to suggest that the Sawchuk Declaration was inconsistent with the Declaration Under 37 C.F.R. § 1.132 of Paul Richard Gellert, dated August 8, 2008 and filed during the prosecution of the '160 patent (Ex. 1020) (the "Gellert Declaration").[1] Contrary to Dr. Bergstrom's assertions, the facts of the prosecution history clearly establish the Gellert and Sawchuk declarations are consistent, and both support the patentability of the challenged claims. Based on the clear facts in the prosecution history, Dr. Bergstrom is incorrect.

[1] The Gellert Declaration was attached as an exhibit to the Sawchuk Declaration. *See* Ex. 1019 at page 27.

61. First, the Gellert and Sawchuk declarations are written from different perspectives. Unlike the Gellert Declaration, the Sawchuk Declaration is written from the perspective of one of ordinary skill in the art without the benefit of the inventors' confidential research. The purpose of the Sawchuk Declaration was to "explain how a person of ordinary skill in that art at that time [i.e., ***prior to*** January 10, 2000] would have understood the references cited in the Office Action and how such a person would have interpreted certain experimental results related to various fulvestrant formulations." Ex. 1019 at ¶ 15.

62. On the other hand, the Gellert Declaration, which is not prior art, is written by an internal AstraZeneca scientist familiar with the work of the inventors and clearly begins with the invention in mind. Ex. 1020 at ¶ 11. ("In about early 2000, ***a person responsible for developing a sustained release injectable formulation suitable for administration to humans for a new steroidal compound such as fulvestrant***, would have had specialized training and experience in developing pharmaceutical formulations and methods for their administration. ***In developing such a formulation for fulvestrant***, the objective would have been to formulate an intramuscular (IM) injection that would provide for the satisfactory sustained release of fulvestrant over a period of at least two weeks and preferably over a period of at least four weeks to reduce the frequency of administration, and would have a target fulvestrant content of at least 45 mg/mL so as to provide a

fulvestrant dose of at least 250 mg in a single 5-6 mL injection. ***From my personal experience*** and knowledge of the literature at about that time, I believe that such an experienced formulator would likely have approached the task of developing a formulation for fulvestrant in about the following manner.") (emphasis added)).

63. The Gellert declaration even sets forth the inventors' own unpublished data and experimentation. Ex. 1020 at ¶13 ("[A]n aqueous suspension of fulvestrant resulted in extensive local tissue irritation at the injection site as well as a poor release profile, such as reported in paragraph [0042] of the Evans Application."), ¶16 ("[F]ulvestrant had extremely low solubility in water, low solubility in most oils . . . such as reported in Table 2 of the Evans Application."), ¶20 ("This is confirmed in Table 4 of the Evans Application[.]"), ¶21 ("[b]ased on the solubility data determined in the preformulation screen (such as reported in Table 2) of the Evans Application"). In other words, using data generated by the inventors, Dr. Gellert explained how the inventors themselves were ***surprised*** by the result of their work—that is, the results of their experimentation could not have been reasonably predicted.

64. Again, Dr. Gellert begins not at the point where one of ordinary skill would have started, but rather, the Gellert Declaration begins with the much narrower objective "to investigate intramuscular injection of an aqueous or oil

suspension of fulvestrant." Ex. 1020 at ¶ 13. As Dr. Gellert describes, only after significant, unpublished experimentation did the inventors discover that "injection of an aqueous suspension of fulvestrant resulted in extensive local tissue irritation at the injection site as well as a poor release profile." Ex. 1020 at ¶ 13. Dr. Gellert continues that significant experimentation would have been required to "conduct[] a preformulation solubility screen, separately measuring the solubility of fulvestrant in a range of pure solvents." Ex. 1020 at ¶ 16. Then, the Gellert Declaration explains, significant experimentation would have been needed to determine appropriate concentrations of various combinations of potential solvents in order to solubilize the desired concentration of fulvestrant. Ex. 1020 at ¶¶ 22-24. Yet, as Dr. Gellert describes, even conducting all of these experiments would not lead to benzyl benzoate, because benzyl benzoate "would be expected to have a negative effect on fulvestrant solubility since fulvestrant was even less soluble in benzyl benzoate than in castor oil." Ex. 1020 at ¶ 24. Importantly, none of this information was taught in the prior art.

65. It is clear that the purpose of the Gellert declaration was to explain how an experienced formulator, having in hand results from internal, confidential experimentation conducted by the AstraZeneca inventors, and ***not known in the art***, "would likely have approached the task of developing a formulation for fulvestrant" and nonetheless have been ***unable*** to reasonably predict the outcome.

See e.g., Ex. 1020 at ¶13 ("[A]n aqueous suspension of fulvestrant resulted in extensive local tissue irritation at the injection site as well as a poor release profile, such as reported in paragraph [0042] of the Evans Application."); at ¶16 ("[F]ulvestrant had extremely low solubility in water, low solubility in most oils . . . such as reported in Table 2 of the Evans Application."), ¶20 ("This is confirmed in Table 4 of the Evans Application[.]"); and at ¶21 ("[b]ased on the solubility data determined in the preformulation screen (such as reported in Table 2) of the Evans Application"). In other words, using data generated by the inventors, Dr. Gellert ***explained how the inventors themselves were surprised by the result of their work***. *See e.g.*, Ex. 1020 at ¶ 6 ("I have evaluated the transcription and other errors against the original application disclosures and conclude that these do not change the ultimate conclusions made from the data as originally reported. The addition of 15% w/v benzyl benzoate to compositions having total alcohol concentrations in castor oil of 10%, 15%, 20% and 30% w/v ***unexpectedly*** provides a positive effect on fulvestrant solubility, significantly increasing the solubility of fulvestrant in the compositions despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil."); *see also* at ¶ 25 ("Under these circumstances, the discovery by Evans *et al.*, that the addition of benzyl benzoate to the castor oil/alcohol mixture actually increases the solubility of fulvestrant such that more fulvestrant could be dissolved in a given volume of formulation, was ***unexpected***

and truly surprising. This positive benzyl benzoate effect on fulvestrant solubility in the resulting formulation is shown in Table 3 of the specification (and is not changed by the above-noted corrections), and is confirmed and demonstrated over a broader range of formulation composition by the additional set of experiments conducted under my guidance and discussed in paragraphs 7-9 above, the results of which are reported in Attachments C.").

66. And, again, this analysis assumed such a person has the same objective that the inventors had: "to formulate an intramuscular (IM) injection that would provide for the satisfactory sustained release of fulvestrant over a period of at least two weeks and preferably over a period of at least four weeks to reduce the frequency of administration, and would have a target fulvestrant content of at least 45 mg/mL so as to provide a fulvestrant dose of at least 250 mg in a single 5-6 mL injection." Ex. 1020 at ¶¶ 17, 24.

67. Indeed, the Gellert Declaration explains in detail why ***even with*** the benefit of having in hand the inventors' internal, confidential research, the addition of benzyl benzoate was surprising. Ex. 1020 at ¶ 24. Importantly, contrary to Dr. Bergstrom's assertion (Bergstrom ¶ 59), nowhere does Dr. Gellert suggest that a person of ordinary skill in the art would have been motivated to achieve and maintain any specific blood plasma levels of fulvestrant—and, in my opinion, there would not have been any such motivation especially given the results set forth in

Howell. *See generally* Ex. 1020.

68. Accordingly, the Gellert and Sawchuk declarations logically ***cannot*** be contradictory, as asserted by Dr. Bergstrom (Bergstrom ¶¶ 57-61), because they are written from different perspectives.

69. Second, the Gellert and Sawchuk declarations both state that oil suspension formulations would have been a reasonable starting point. The Sawchuk Declaration—which again was written from the perspective of the skilled artisan without the benefit of the inventors' internal, confidential research—states that a suspension would have been "among the most favored formulations to select for further development." Ex. 1019 at ¶ 41. The Gellert Declaration is in agreement, stating that "a reasonable starting point would have been to investigate intramuscular injection of an aqueous or oil suspension of fulvestrant." Ex. 1020 at ¶ 13. Accordingly, the Gellert and Sawchuk declarations are consistent on this point, contrary to Dr. Bergstrom's assertions otherwise (Bergstrom at ¶ 57).

70. Third, the Gellert and Sawchuk declarations are not contradictory with respect to the Dukes formulation. And, importantly, neither declaration suggests that Dukes would have led one of ordinary skill in the art, directly or indirectly, to McLeskey.

71. According to the Gellert declaration, the Dukes formulation would have been a consideration "based on the solubility data determined in the

[inventors' internal, confidential] preformulation screen (such as reported in Table 2 of the Evans Application), ethanol and/or benzyl alcohol would have been seen as the best co-solvent candidates for raising the fulvestrant solubility to the 45 mg/mL target in the castor oil vehicle, and would also function to lower the viscosity of the resulting formulation and make it easier to inject." Ex. 1020 at ¶ 21. ("Consistent with this solubility data, Dukes (US '814) added 40% w/v benzyl alcohol in order to dissolve 50 mg/mL fulvestrant in the castor oil-based formulation used in the experimental rat studies of his Example 3. It thus would have been apparent that 40% w/v benzyl alcohol could function as a co-solvent in castor oil to achieve the target fulvestrant concentration.").

72. In the Sawchuk Declaration, I simply stated: "*Dukes* discloses two different fulvestrant compositions for intramuscular injection, one containing fulvestrant dissolved 'in a mixture of propylene glycol: ethanol: water: poloxamer 407' administered daily by intramuscular injection to rats. Dukes (Exhibit 4) at Example 2, p. 8. The second composition contained 50 mg of fulvestrant, '400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml.' *Id.* at Example 3, p. 9. For each composition, Dukes reports that 'at all doses tested the compound [fulvestrant] selectively inhibits the action of the animals' endogenous oestrogen on their uteri.' *Id.* at Examples 2 & 3, pp. 8-9." Ex. 1019 at ¶ 39.

73. Finally, not only are the declarations not inconsistent, I specifically considered, cited, and attached as an exhibit to my declaration, the Gellert Declaration. In explaining why one of skill in the art "would not have had a reasonable expectation that the McLeskey castor oil composition would have been effective when given as an intramuscular injection, such as in the method of treatment recited in the claims" I specifically point to the Gellert Declaration as describing the extensive formulation research involved. Ex. 1019 ¶¶ 57-69. "As part of the discussion of the development of methods of treatment involving the administration of fulvestrant, the Gellert Declaration states that 'the experienced formulator would want to minimize the amount of co-solvents and excipients in any injectable formulation.'" Ex. 1019 at ¶ 60 (citing Ex. 1020 at ¶ 22). "Thus, even if the McLeskey castor oil composition had been considered as a potentially useful formulation in the development of a method of treatment for humans, one of ordinary skill in the art would have performed additional formulation studies to obtain a composition with suitable characteristics for the desired route of administration. The Gellert Declaration explains one of the rationales to perform those additional studies[.]" Ex. 1019 at ¶ 61 (citing Ex. 1020 at ¶ 22).

74. As I explain in the Sawchuk Declaration, "[r]egardless of how high or low the cosolvent concentrations are in a given formulation, the preparation of formulations in which a drug such as fulvestrant can be solubilized is not sufficient

to ensure the desired therapeutic effect when such formulation is administered to patients. . . . [S]uitable experiments are needed to determine the pharmacokinetic performance of any candidate formulation(s)." Ex. 1019 at ¶ 62. In other words, the concentration of drug in the formulation is not the most important or relevant consideration. I go on in my declaration to explain "it is understood that an animal model for drug dosage form performance may provide some discrimination among candidate dosage forms in development. Thus, the plasma concentration profile should reflect changes in the release characteristics of the drug from the formulation. That type of pharmacokinetic data could be used to characterize important variables in the development of a suitable method of treatment. For drugs that are difficult to formulate, such as fulvestrant, the pharmacokinetic data could be useful to investigate the most promising formulation for the desired route of administration." Ex. 1019 at ¶ 63.

75. As an example, I cite to PCT Application Publication No. WO 03/006064 (Ex. 1037), which illustrates the point that different formulations have different pharmacokinetic profiles and, thus, "[d]epending on the overall objective of the administration of fulvestrant, some of the fulvestrant formulations . . . would be more desirable than others for that given purpose and, based on the relevant pharmacokinetic profiles, one of ordinary skill in the art would be able to select one of those fulvestrant formulations for further development and/or testing." Ex.

1019 at ¶ 66. "However, one of ordinary skill in the art would not have been able to determine whether a given fulvestrant formulation injected intramuscularly as in WO 03/006064 would have had the desired pharmacokinetic profile until such in vivo pharmacokinetic studies were carried out. The testing of various formulations having different compositions, as portrayed in Figures 1, 2A and 2B, would typically be undertaken during the development of a dosage form in order to ensure an optimal method of treatment using a drug that is difficult to formulate. Such studies would be expected to demonstrate differences in the blood plasma concentrations of a test drug, and would allow the investigators to identify factors that would enhance the performance of the formulation." Ex. 1019 at ¶ 67. And, "[t]herefore, when considering the differences in pharmacokinetic profiles demonstrated in the example from WO 03/006064, it becomes clear that one of ordinary skill in the art knowing only the composition of a given formulation administered subcutaneously, but having no pharmacokinetic data following its intramuscular administration, would have had no expectation, one way or another, that the formulation would be effective when administered intramuscularly in a given method of treatment." Ex. 1019 at ¶ 68.

X) REFERENCES CITED BY DR. BERGSTROM

76. Dr. Bergstrom selects only a few, very specific references as showing the scope of prior art at the time of the invention. Ex. 1013 at ¶¶ 83-98. This

retrospective selection ignores the perspective that a skilled artisan would have had at the time of invention. The references in Dr. Bergstrom's Declaration are not representative of the full scope or content of the prior art, nor of the knowledge or skill of a person of ordinary skill in the art at the time of the invention. I address each of the references cited below.

A) Howell (Ex. 1007)

77. In *Pharmacokinetics, Pharmacological And Anti-Tumour Effects Of The Specific Anti-Oestrogen ICI 182780 In Women With Advanced Breast Cancer*, 74 Br. J. Cancer 300 (1996) (Ex. 1007) ("Howell") the authors report on a very small clinical trial involving fulvestrant in 19 patients with advanced breast cancer resistant to tamoxifen. Ex. 1007 at 1.

78. Howell does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Howell administered a dose of 250 mg but explicitly suggests that "lower doses of the drug may be effective in maintaining therapeutic serum drug levels." As such, an ordinary researcher would have been motivated to use lower doses. Howell does not disclose the composition of the administered formulation of fulvestrant and the skilled artisan would not be able to use the data in Howell to obtain the claimed method of treatment.

79. Howell identifies the objectives of the Phase II study as: "to assess the

long-term efficacy and toxicity of [fulvestrant] in patients with advanced breast cancer, and to evaluate the pharmacokinetics of the long-acting formulation used [in the study]." Ex. 1007 at 1.

80. Fulvestrant was given monthly in a castor-oil based vehicle as a long-acting intramuscular injection of 5 ml. Ex. 1007 at 2. There is no disclosure of the composition of the formulation used or the various proportion(s) of excipients contained therein.

81. To assess drug safety, four of the 19 patients received 100 mg during the first month and then 250 mg from the second month on. Fifteen of the 19 received 250 mg monthly from the outset of the study. Eleven of the 19 patients were treated for at least six months. Ex. 1007 at Table 1. Mean C_{max} (i.e., the mean of the maximums observed) of fulvestrant were identified as approximately 10.5 ng/mL during the first month and 12.6 ng/mL during the sixth month (Ex. 1007 at 1) and then later as 12.8 ng/mL (Ex. 1007 at 3). Mean end-of-month levels were approximately 3.1 ng/mL for the first month, and 5.6 ng/mL for the sixth month. Ex. 1007 at 3. Thirteen of 19 (68%) patients exhibited a "partial response" or "no change" to fulvestrant (7 patients had "partial responses;" 6 showed "no change"). Ex. 1007 at Table II .

82. Contrary to the assertions made by Dr. Bergstrom (Ex. 1013 ¶ 86), Howell does not teach or disclose "significant detail concerning the formulation,

route of administration, and dosing regimen for fulvestrant." Ex. 1013 ¶ 86. Nor does Howell "disclose[] the exact 'therapeutically significant blood plasma fulvestrant concentration' recited in claim 2 of the '122 patent and claims 3 and 6 of the '680 patent and the 'blood plasma fulvestrant concentration' recited in claims 19 and 20 of the '139 patent" as Dr. Bergstrom boldly asserts (Ex. 1013 ¶ 87), and I note he makes such assertions without basis or support. Further, I do not understand Dr. Bergstrom's basis for asserting the results of the study reported in Howell were "positive" or that "numerous . . . other details about fulvestrant . . . would have been considered positive" by a person of ordinary skill in the art. Ex. 1013 ¶¶ 84, 85. In any event I disagree with Dr. Bergstrom's unsupported characterization of Howell as "positive."

83. Importantly, the authors of Howell do not draw the conclusions Dr. Bergstrom does now in retrospect. The authors do not conclude or even hypothesize that there is a target blood plasma concentration level that ***should*** be achieved in future studies based on their results. They do not discuss the period of time over which such levels should be maintained. And, the authors do not recommend a dosing regimen. A person of ordinary skill in the art would have recognized that Howell was a preliminary, early clinical study in which clinicians were only just beginning to gather relevant clinical data. And, a person of ordinary skill in the art would have recognized that none of the conclusions Dr. Bergstrom

draws because the Howell publication explicitly indicates (in words and data) that no pharmacokinetic-pharmacodynamic link had been established.

84. Although the maximum serum levels of fulvestrant during both the first and six months of treatment were tabulated, pre-dose fulvestrant concentrations were not reported—meaning one does not know what the fulvestrant blood serum levels were in those patients, and no conclusions can be made as to each individual's levels.

85. The authors do report "[f]rom studies on inhibition of endometrial proliferation in the monkey and inhibition of tumor proliferation in a previous phase I study, it was ***predicted*** that serum levels of ICI 182780 in the range of 2-3 ng ml^{-1} were consistent with a therapeutic effect in patients with advanced breast cancer." Ex. 1007 at 6 (emphasis added). But, there are several important issues that must be noted.

86. First, ***the authors do not conclude*** that 2-3 ng ml^{-1} ***should be targeted*** in the future. In fact, they suggest, based on the reported pharmacokinetic data, that the starting doses used in their study may have been too high. Specifically, the authors note "there was evidence of drug accumulation after multiple dosing, such that after 6 months treatment there was an 80% increase in mean end of month drug levels and a 50% increase in the AUC compared with data from month 1. These data suggest that ***lower doses of the drug*** may be effective in maintaining

therapeutic serum drug levels, although further clinical studies are required to confirm this hypothesis." Ex. 1007 at 6 (emphasis added). Second, unlike Dr. Bergstrom, the authors ***avoid*** drawing a conclusion regarding any correlation between blood plasma levels and efficacy. The authors conclude "a direct pharmacokinetic-pharmacodynamic link is ***not*** proven with the ***few*** patients studied to date." Ex. 1007 at 6. I agree with the authors of Howell and note this would have left a person of ordinary skill in the art completely in the dark as to what or even whether to target any given blood plasma concentration. And because this was the ***first*** clinical study involving fulvestrant given monthly in a "castor-oil based vehicle," and there was only a very limited number of patients receiving a fixed dose whose data were reported through the sixth month, i.e., 11 patients (Ex. 1007 at 3)—a person of ordinary skill in the art would have understood any alleged pharmacokinetic-pharmacodynamic link, even if it had been identified (which it was not), to be very preliminary. Moreover, again I agree with the authors that the pharmacokinetic data simply do not support such a link. As the authors stated "there was ***no significant difference*** in the median C_{max} and AUC between ***responders and non-responders*** to treatment (Table II). After 6 months of treatment there was ***no significant difference*** between C_{max} and AUC for patients who had a ***partial reponse*** [sic] (PR) ***compared with those with a no change*** (NC) ***response***." Ex. 1007 at 3 (emphasis added); *see also* Table II ("There were no

significant differences in drug kinetics between responders and non-responders."). In fact, as discussed below, in conducting his analysis, Dr. Bergstrom completely ignores this express analysis done by the authors themselves, and worse, Dr. Bergstrom reached his conclusion with the results of the Patents-in-Suit in mind. Last, it would have been unclear to a person of ordinary skill in the art what the statement regarding 2-3 ng ml^{-1} is based upon. The authors state that "[p]harmacokinetic data concerning the release characteristics of the drug into serum in this study were found to be similar to those previously demonstrated in adult female monkeys." Ex. 1007 at 6. The authors cite to a 1993 paper by Dukes et al., but no pharmacokinetic data in monkeys were reported in that paper. *See generally* Dukes et al., *Antiuterotrophic Effects of the Pure Antioestrogen ICI 182,780 in Adult Female Monkeys (*Macaca nemestrina*): Quantitative Magnetic Resonance Imaging*, 138 J. Endocrinology 203 (1993) (Ex. 1057) ("Dukes 1993"). And, although the authors reference a "previous phase I study" they do not identify which one of two potential articles in their reference list they are referring to: DeFriend, or E.J. Thomas et al., *The effects of ICI 182780, a pure antioestrogen on reproductive endocrinology in normal pre-menopausal women*, J. Endocrinol. 137S, 183 (1993) (Ex. 2048). The latter, which is a published abstract, refers to a Phase I study in 16 pre-menopausal women, who received 12 mg of fulvestrant via the intramuscular route daily for 7 days prior to hysterectomy. The authors

measured specific hormones (LH and FSH) in the plasma, endometrial thickness, and evaluated ovarian hyperstimulation during fulvestrant once-daily dosing. They indicate that these effects are being evaluated when they state that "[p]harmacodynamic data are being analyzed. However, they do not indicate that plasma levels of fulvestrant were measured. The abstract contains no data regarding fulvestrant blood plasma levels, nor any details regarding the fulvestrant formulation used. The former article (DeFriend (Ex. 1038)) is discussed below.

B) McLeskey (Ex. 1008)

87. McLeskey et al., *Tamoxifen-resistant Fibroblast Growth Factor-transfected MCF-7 Cells Are Cross-Resistant* in Vivo *to the Antiestrogen ICI 182,780 and Two Aromatase Inhibitors*, 4 Clin. Cancer Res. 697 (1998) (Ex. 1008) ("McLeskey"), relates to preclinical work in mice. The authors utilized two different fulvestrant formulations, and two aromatase inhibitors, letrozole and 4-OHA. The two different fulvestrant formulations used for the study were a "powdered drug was first dissolved in 100% ethanol and spiked into warmed peanut oil . . . to give a final concentration of 50 mg/ml" and "50 mg/ml preformulated drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil," both of which were administered subcutaneously every week in 5 mg doses. Ex. 1008 at 698. No preference is expressed for one fulvestrant formulation over the other. McLeskey also provides

no solubility or other data for any of the formulations used.

88. McLeskey does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract." Further, McLeskey does not disclose "administering intramuscularly to a human in need of such treatment." Additionally, McLeskey does not disclose the limitations: "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (i.e., individual).

89. McLeskey is a basic science research paper designed to investigate an artificial hormone independent mouse tumor model related to growth factor signaling pathways.

90. McLeskey did not report plasma concentrations of fulvestrant in the mice, or even indicate that blood samples were drawn to assess such values. The authors do not allude to a target concentration for fulvestrant in animals or in humans, or suggest a time interval over which a target plasma concentration should be maintained.

91. An ordinary skilled pharmacokineticist would not have looked to the McLeskey publication as it is clearly only a publication relating to basic scientific research unrelated to human therapy with fulvestrant and contains no

pharmacokinetic data. Moreover, Dr. Bergstrom does not state why a person of ordinary skill in the art would have combined McLeskey with any of the other prior art references he discusses and I am not aware of any such motivation.[2] Indeed given how different the two publications are, in my opinion, a person of ordinary skill would not have combined Howell and McLeskey, let alone drawn any conclusions from such a "combination."

	Howell	McLeskey
Stage of research	Early clinical trial	Basic biological research
Study subjects	Patients with metastatic breast cancer	Mice implanted with FGF-transfected cells
Hormonal Dependence	Yes	No
Formulation excipients	Unknown	Ethanol, benzyl alcohol and benzyl benzoate
Dosing	100 or 250 mg, monthly	5 mg, weekly
Route of Administration	IM	SC
Serum fulvestrant levels	Measured	Not measured
Pharmacokinetic-pharmacodynamic link	Not found	Not applicable

C) O'Regan (Ex. 1009)

[2] Indeed it is unclear how or why Dr. Bergstrom selected McLeskey, which he states relates to "hormone-independent breast cancer" and "hormone-independent pathways" (Ex. 1013 ¶¶ 91-92) given that, by his own description, the ordinarily-skilled artisan in this regard is someone who has experience in "treating or researching ***hormone dependent*** diseases of the breast" (Ex. 1013 ¶ 64 (emphasis added)).

92. *Effects of the Antiestrogens Tamoxifen, Toremifene, and ICI 182,780 on Endometrial Cancer Growth*, 90 J. Nat'l Cancer Inst. 1552 (1998) (Ex. 1009) ("O'Regan") by O'Regan et al. describes a study in ovariectomized mice with implanted endometrial tumors, evaluating the risks of promoting endometrial cancer after treatment with toremifene or fulvestrant. The only fulvestrant formulation used in O'Regan was dissolved in ethanol and administered in peanut oil (following the evaporation of the ethanol under N_2) to mice by subcutaneous injection. Ex. 1009 at 2.

93. O'Regan does not disclose a "method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract" or "administering intramuscularly to a human in need of such treatment." O'Regan does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, O'Regan does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$" in a human (i.e., individual).

94. O'Regan cites to Howell as an early stage study and states that "there are not the same stringent requirements for a drug that is used as a palliative therapy in advanced disease compared with drugs that are used for long-term

adjuvant therapy." Ex. 1009 at 2. And, O'Regan observes that "[c]learly, a woman should not be led to believe that no risks exist because inadequate and early clinical studies are being reported." Ex. 1009 at 5.

95. O'Regan neither teaches nor discloses therapeutically significant blood fulvestrant concentrations or fulvestrant formulations (in fact, it does not disclose any information concerning blood plasma levels). Likewise, O'Regan does not relate to methods of treating hormonal dependent breast cancer (it is not even a study in humans). In my opinion, an ordinary skilled pharmacokineticist would not have looked to O'Regan as it is clearly only a publication relating to basic scientific research unrelated to treatment of breast cancer patients with fulvestrant and contains no pharmacokinetic data.

D) DeFriend (Ex. 1038)

96. *Investigation of a New Pure Antiestrogen (ICI 182780) in Women with Primary Breast Cancer*, 54 Cancer Res. 408 (1994) (Ex. 1038) ("DeFriend") discusses a small Phase I clinical study of a short-acting fulvestrant formulation in a propylene glycol-based vehicle. As in Phase I clinical studies generally, a major focus of this short-term trial was to determine if there were drug-related adverse events associated with fulvestrant administered daily for 7 days, and to obtain preliminary pharmacokinetic data concerning fulvestrant when given intramuscularly using a rapidly absorbed formulation in a once-a-day regimen. Ex.

1038 at 1.

97. DeFriend does not disclose "about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; about 15% w/v of benzyl benzoate; and a sufficient amount of castor oil vehicle." Further, DeFriend does not teach that "a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ [is achieved] for at least four weeks"; or "wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$."

98. Thirty-seven patients awaiting surgery for breast cancer received daily intramuscular injections of the short-acting, rapidly absorbed formulation, which contained fulvestrant (20 mg/mL) in doses of 6 mg (N = 21) or 18 mg (N = 16) for 7 days before surgery. Ex. 1038 at 2.

99. The authors observed that for this particular (propylene glycol-based) formulation, the plasma concentration of fulvestrant "was dose dependent but showed some variation between individual patients." Ex. 1038 at 3. Also, approximately a 3-fold drug accumulation of fulvestrant occurred in the serum during the short 7-day dosing period, but steady-state serum levels were not reached by the end of the study. Ex. 1038 at 3.

100. The article also states that daily intramuscular doses of 6 mg or 18 mg of fulvestrant were "well tolerated after short term administration and produced demonstrable antiestrogenic effects in human breast tumors *in vivo*, without

showing evidence of agonist activity" (Ex. 1038 at 1), and treatment "caused no serious drug-related adverse events, and no patients were withdrawn from the study because of drug toxicity." Ex. 1038 at 3.

101. Nowhere are the components or their proportions of the formulation used discussed, nor are target blood plasma concentrations of fulvestrant or the time course of such concentrations, mentioned.

102. DeFriend does disclose mean pre-dose serum levels of fulvestrant in Figure 1, but these data represent a small sample size, and vary substantially, as shown by the error bars representing 2 SEM. As such, person of ordinary skill would not have been able to reasonably predict mean daily pre-dose levels of fulvestrant upon administration of this formulation to a different cohort of patients, and certainly would have no basis to predict such values using a different formulation.

103. The study discussed in DeFriend was performed using a short-acting formulation of fulvestrant administered daily over a period of only seven days just before surgery. It was not designed to assess therapeutic levels of fulvestrant (and a person of ordinary skill in the art would have expected that the authors would have noted such a purpose, which they did not). Again, because this was a Phase I study that produced limited data over a period of only 7 days and therapeutic response was not assessed in these patients, a person of ordinary skill in the art

would also have understood that these data could not possibly establish the time course over which any target levels should be maintained.

104. Dr. Bergstrom states in his paragraph 98 that "DeFriend therefore teaches that the higher dose of 18 mg per day (or roughly 500 mg per 4 weeks) was more effective in reducing ER indices and thereby improved efficacy" without identifying how or why reduction in ER indices is related to efficacy or therapeutic effects. Ex. 1013 ¶ 98. Indeed, I do not believe Dr. Bergstrom is qualified to determine what a clinician treating breast cancer patients at the time would have deemed to be relevant therapeutic effects. And, whatever therapeutic effects were or were not achieved in the 7-day Phase I study described in the DeFriend paper, they apply to a very particular rapid-acting formulation that bears no resemblance (aside from the active ingredient) to the formulation used in the claimed therapeutic methods of the Patents-in-Suit. And, Dr. Bergstrom has not set forth any prior art or scientific rationale explaining why the results in DeFriend could, in turn, be predictive in any way of what would happen upon using the formulations in the challenged claims.

XI) THE CLAIM LIMITATIONS TO BLOOD PLASMA FULVESTRANT CONCENTRATIONS ARE NOVEL AND NOT OBVIOUS

A) Therapeutically Significant Blood Plasma Fulvestrant Concentrations Are Not Taught or Suggested in the Prior Art

1) Howell Does Not Disclose Therapeutically Significant Blood Plasma Fulvestrant Concentrations of at Least 2.5 ng/mL

for at Least 2 or 4 Weeks

105. For the reasons explained below, it was neither known nor obvious to a person of ordinary skill in the art as of the Invention Date what therapeutically significant blood plasma fulvestrant concentration to achieve, the period of time over which such therapeutically significant blood plasma fulvestrant concentration should be maintained, or how to achieve or maintain such therapeutically significant blood plasma fulvestrant concentration.

106. Dr. Bergstrom asserts that "Howell expressly teaches that 'therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$' is achieved for at least four weeks as claimed in claim 3 of the '680 patent" and that "Howell expressly teaches the limitations of claims 10 and 20 of the '139 patent, which require that the 'blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$' is achieved for at least four weeks. These levels also necessarily meet the limitations claim 2 of the '122 patent, which requires that the same blood plasma levels be achieved for only two weeks." Ex. 1013 ¶ 101. I disagree. To the contrary, nowhere does Howell "expressly teach" that "therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$" is achieved for at least four weeks or at least two weeks. For the reasons discussed below, Howell fails to teach or disclose any therapeutically significant blood plasma fulvestrant concentrations including at least 2.5 ng/ml for at least 2 or at

least 4 weeks.

107. It was not known, and Dr. Bergstrom has not demonstrated, that a concentration of 2.5 ng per ml of fulvestrant for at least four weeks was therapeutically significant. Rather, again, Howell and the data it reports make clear that there had not yet been established a linkage between measures of systemic exposure, e.g., C_{max} or AUC, and any clinical effect. And, there was absolutely no disclosure in Howell of the fulvestrant formulation used, and absolutely no data available regarding how changes in excipients in any given fulvestrant formulation would affect blood plasma concentrations—any predictions would amount to no more than pure speculation. In short, any assumption regarding the fulvestrant formulation used in Howell is unsupported, and is not an assumption a person of ordinary skill in the art would make—no responsible pharmacokineticist in my opinion would make such a bold guess.

108. For these reasons and those explained in more detail below, in my opinion, the references relied upon by Dr. Bergstrom would not teach or disclose to a person of ordinary skill in the art that a therapeutically significant blood plasma fulvestrant concentration of least 2.5 ng/mL could be achieved and maintained for at least 2 or at least 4 weeks.

a. Howell

109. Again, Howell does not disclose a therapeutically significant blood

plasma concentration, or the period of time over which such a level should be maintained. Although the maximum plasma levels of fulvestrant were tabulated for a subset of the patients in the first month and in month 6 of treatment (Howell, at Table II), their pre-dose fulvestrant concentrations were not reported and, as such, cannot be determined. In addition, because Howell does not set forth a therapeutically significant plasma concentration it also could not have provided information regarding the time course over which such levels should be maintained. And although Howell reports administering fulvestrant "as a long-acting formulation contained in a castor oil-based vehicle" (Ex. 1007 at 2), there is no disclosure of the composition of the formulation used or the proportion of excipients contained therein. A person of ordinary skill in the art would know and expect that even minor variations to formulation components or their specific proportions could significantly impact the rate of release of fulvestrant from the site of administration, the duration of the release of fulvestrant and ultimately, therefore, fulvestrant's blood plasma concentration-time profile.

110. Dr. Bergstrom ignores the full scope of the teachings in Howell. Specifically, he ignores the non-responders. About 1/3 of the patients had disease that progressed (i.e., were non-responders), about 1/3 showed no change in their condition, and about 1/3 responded partially (the latter two groups constituting "responders"). The authors did not ignore the non-responders (all 15 patients

receiving 250 mg dose in month 1 were included in mean serum concentration, Ex. 1007 at 3) and correctly concluded that they could not associate clinical outcomes with plasma levels of fulvestrant. Ex. 1007 at Table II. A person of ordinary skill in the art would have done the same. Accordingly, it is my opinion that Howell neither discloses nor teaches achieving or maintaining therapeutically significant blood plasma fulvestrant concentrations of at least 2.5 ng/mL for at least 2 or at least 4 weeks.

111. None of the other references upon which Dr. Bergstrom relies fill the gaps in the knowledge possessed by a person of ordinary skill in the art. O'Regan uses a peanut oil based formulation in animals and does not disclose blood plasma concentrations of fulvestrant let alone report on therapeutically significant levels; DeFriend involves a brief, pre-surgical study using a fast-acting propylene glycol-based formulation and provides a figure of mean serum fulvestrant level data for only 7 days (as such, it would have been considered separate and unrelated to the information presented in Howell); and McLeskey has nothing to do with pharmacokinetic data on fulvestrant—or ***any*** data on fulvestrant for that matter—and, as such, a person of ordinary skill in the art would not even have looked to it, let alone combined it with any of the above references reporting AstraZeneca's own work.

112. Again, since there was no known connection between any plasma

level of fulvestrant and therapeutic outcome disclosed in Howell (in fact, Howell reports just the opposite), a person of ordinary skill at the time was left to guess what, if any, target plasma fulvestrant concentration was relevant and certainly could not have been lead to at least 2.5 ng per ml, or ***any*** duration of time over which such concentration need be maintained, let alone for at least two weeks or at least four weeks. Accordingly, a person of ordinary skill in the art would not have been motivated to achieve and maintain a level of fulvestrant of at least 2.5 ng per ml for at least two weeks or at least four weeks, based on the results of Howell or upon the results of any publication cited by Dr. Bergstrom.[3]

113. I understand Dr. Bergstrom's opinion in paragraph 104 to be premised entirely on the opinions of and representations by another one of InnoPharma's experts, Dr. Burgess, who, according to Dr. Bergstrom, opines "that the fulvestrant formulation recited in the claims was fully disclosed in the art before the priority date."[4] Ex. 1013 ¶ 104. Dr. Bergstrom fails to identify any piece of prior art that purportedly "fully disclosed" "the fulvestrant formulation recited in the claims,"

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[3] Dr. Bergstrom (Ex.1013 ¶ 102) emphasizes the "predicted" serum levels of 2-3 ng ml^{-1} and results above those levels, but misses the conclusions regarding both—as discussed previously, the authors suggest lowering the dose used due to accumulation and explicitly conclude no pharmacokinetic-pharmacodynamic link was found.

[4] I understand that Dr. Illum will be responding to Dr. Burgess's declaration, which Dr. Bergstrom relies upon entirely for his opinions in paragraph 104. *See* Ex. 1013 ¶ 104. I defer to Dr. Illum's opinions on the issues raised by Dr. Burgess and adopted by Dr. Bergstrom.

and I am not aware of any such prior art. Certainly, as discussed in the Sawchuk Declaration, McLeskey does not. Thus, I understand Dr. Bergstrom has ***no basis*** other than the 2017 expert opinion of Dr. Burgess (which is not prior art), for his assertion that "the claimed 'therapeutically significant blood plasma fulvestrant concentrations' are an inherent property of the known formulation, which is additional evidence of obviousness." Ex. 1013 ¶ 104. As such, Dr. Bergstrom's opinions regarding the at least 2.5 ng/ml for at least two weeks or at least four weeks limitations must be disregarded.

114. Thus, for at least these reasons, Dr. Bergstrom's conclusion that "Howell fully discloses 'therapeutically significant blood plasma fulvestrant concentrations' and 'blood plasma fulvestrant concentrations' at or above 'at least 2.5 ng ml^{-1}' for at least four weeks after injection of the castor-oil based intramuscular formulation" (Ex. 1013 ¶ 105) is incorrect.

B) The Prior Art Does Not Disclose Therapeutically Significant Blood Plasma Fulvestrant Concentrations of at Least 8.5 ng/mL for at Least 4 Weeks

1) Howell Does Not Disclose Therapeutically Significant Blood Plasma Fulvestrant Concentrations of at Least 8.5 ng/mL for at Least 4 Weeks

115. Nowhere does Howell "expressly teach[] that a 'therapeutically significant blood plasma fulvestrant concentration of at least 8.5 $ngml^{-1}$' is attained for at least 4 weeks after injection.'" Ex. 1013 ¶ 106. Further, nowhere do the data

in Howell "reflect that at least some of the patients in the overall patient population would have had therapeutically significant blood serum fulvestrant concentration of at least 8.5 ng ml^{-1} for at least 4 weeks after injection." Ex. 1013 ¶ 106. For the reasons discussed below, Howell fails to teach or disclose therapeutically significant blood plasma fulvestrant concentrations of at least 8.5 ng/ml^{-1} for at least 4 weeks.

116. As an initial point, I note that it was not known or disclosed in the prior art that a blood plasma fulvestrant concentration of 8.5 ng per ml for at least four weeks was therapeutically significant. In fact, this limitation (***at least*** 8.5 ng/ml for at least four weeks)—assuming everything Dr. Bergstrom says is correct—is simply not disclosed in the prior art relied on by Dr. Bergstrom and appears to have been derived solely using hindsight.

117. Dr. Bergstrom's opinion, that attaining a therapeutically significant blood plasma fulvestrant concentration of at least 8.5 ng ml^{-1} for at least 4 weeks after injection is obvious, is premised entirely upon calculations he makes after the Invention Date (in 2017), from Figure 2 in Howell. Ex. 1013 ¶¶ 107-119. Dr. Bergstrom does not support his motivation for making such calculations with prior art citations. Moreover, he does not explain his basis for focusing on the data point at Month 6, "Day 0" in Figure 2 of Howell, or the bars that appear above and below the datum point. Nor does Dr. Bergstrom explain or justify the purpose for

his tabulating hypothetical standard error and standard deviation of the Month 6, "Day 0" datum point.

118. Without explanation, Dr. Bergstrom identifies a concentration of 8.5 ng per ml that should be produced. Ex. 1013 ¶ 114. I note that he ***does not assert*** that this concentration, even if produced, would necessarily be maintained for at least four weeks. It is unclear how he identified 8.5 ng per ml as a target concentration—seemingly Dr. Bergstrom looked at the therapeutically significant values set forth in the challenged claims and, using a retrospective analysis, attempts to find them in the data purportedly, but not actually, reported in Howell. But, even accepting all of Dr. Bergstrom's assertions, there is no disclosure of 8.5 ng/ml of fulvestrant in blood plasma being maintained over a 4-week period. Neither Figure 2 itself nor the text of the article support that assertion. Rather, Dr. Bergstrom tries to justify the number 8.5 ng/ml by asserting "at least 2 patients would be above 8.5 ng/ml four weeks after the month five injection" because "[i]n a normal distribution, 19.5% of a sample will be more than .86 standard deviations above the mean" (Ex. 1013 ¶ 116) and "***[a]ssuming*** a normal distribution, 2.28% of the overall patient population will be more than 2 standard deviations above the mean" (Ex. 1013 ¶ 118 (emphasis added)). In making these assertions concerning the serum concentrations at only one time point (Day 0 of Month 6), Dr. Bergstrom glosses over the "for at least 4 weeks" limitation in the challenged claims.

119. Moreover, simple inspection of the serum concentration data in Figure 2 from Howell shows that: (1) none of the mean values during the first month of treatment even reaches 8.5 ng/ml, let alone being maintained at that level for any period of time; (2) only three of the mean values during the sixth month of treatment are at least 8.5 ng/ml, and this represents a period of less than one week (i.e., from day 1 until day 7); (3) neither the figure legend nor the text indicates whether these error bars represent standard deviations, or standard errors of the mean, or something else. Thus one of skill in the art would not have been able to understand the distribution of these serum concentrations, or to estimate a range of serum concentrations at any of the time points in the figure; and (4) none of the values shown in this figure can be interpreted as therapeutically significant, because the authors conclude that "a direct pharmacokinetic – pharmacodynamic link is not proven with the few patients studied to date." Ex.1007 at 6.

120. There is no reason why a person of ordinary skill in the art would have been motivated to determine the standard error or the standard deviation of the data points in Figure 2 of Howell. That would have been irrelevant to him or her. The authors conclude that the data obtained are insufficient for purposes of drawing conclusions regarding pharmacodynamics. That would have ended the

inquiry—more data were needed.[5] Indeed, Dr. Bergstrom suggests no reason or motivation anywhere in his report. Thus, it seems clear, the only reason why Dr. Bergstrom does such calculations is to try to find some suggestion in Howell that therapeutically significant blood plasma fulvestrant concentrations of at least 8.5 $ngml^{-1}$ are achieved and maintained for at least 4 weeks, i.e., Dr. Bergstrom is searching for the therapeutically significant blood plasma fulvestrant concentration limitation recited in the claims. The sole motivation for Dr. Bergstrom's calculations seems to be hindsight.

121. In fact, Dr. Bergstrom does not even examine the most relevant time point: in order to make such an assertion, he would have had to have repeated his calculation using the mean concentration value at Day 28, Month 6 (i.e., the four week time point in question). He did not—***had*** he done so, using the same calculations he used for the SD (Ex. 1013 ¶ 114), he would have calculated that 7.26 ng/ml is within 1 standard deviation of the mean, a value much less than he calculates using the mean and his estimated standard deviation at Day 0, Month 6 (Ex. 1013 ¶ 115). Thus, Dr. Bergstrom would ***not have been able to assert, for Day 28, Month 6, that "8.5 ng/ml is within one standard deviation… of the mean".*** Therefore, Dr. Bergstrom ***would not*** have found the therapeutically

[5] In my opinion, a ordinarily-skilled artisan would have concluded that Dr. Bergstrom was motivated to make the calculations he does solely in order to find support for a statistical statement that there must be some portion of the sample in Howell that exhibited concentrations higher than 8.5 $ngml^{-1}$ at one point on time.

significant blood plasma fulvestrant concentration limitation recited in the claims that he is clearly searching for. And, even if he were able to suggest, for example, that statistically at least 2 patients exhibited levels above 8.5 ng/ml at all time points during Month 6 in Figure 2 of Howell, there is no evidence to suggest that ***any one particular patient*** in the group would have had all of their concentrations above 8.5 ng/ml during this 4-week period.

122. Regardless, even if a person of ordinary skill was motivated to make the calculations that Dr. Bergstrom does (which a skilled artisan would not have been), Dr. Bergstrom's opinion that "Howell teaches fulvestrant concentrations of at least 8.5 $ngml^{-1}$ after four weeks" is premised on at least three assumptions that a skilled artisan would not make. *First*, Dr. Bergstrom assumes that the data plotted in Figure 2 of Howell, and the bars above and below each data point, are accurately plotted, and that he has accurately determined their length from the Figure. Seemingly, these concentrations can only be inferred as being the top and bottom ends of error bars. In this case, if the data in Figure 2 were correctly plotted, the mean concentrations (i.e., the data points) should fall exactly at the midpoint between the bar above and below each data point—but in some instances they do not. The reason they should is because error bars, whether they represent standard deviations or standard errors of the mean, are symmetric about the mean.

123. *Second*, Dr. Bergstrom assumes, without support, that the serum

concentrations represented in Howell's Figure 2 are normally distributed. His assumption of a normal distribution of these serum concentrations is inconsistent with the usual distribution noted for measures of drug exposure. For example, a well-known treatise in the field of pharmacokinetics states: "Generally, distributions of pharmacokinetic parameters or observations are unimodal rather than polymodal, and they are often skewed rather than normal as seen . . . . A more symmetrical distribution is often obtained with a logarithmic transformation of the parameter; such distributions are said to be log-normal." *Variability, in Clinical Pharmacokinetics Concepts and Applications* 203, 207 (M. Rowland & T.N. Tozer, eds., 3d ed. 1995) (Ex. 2170) ("Rowland & Tozer").

124. Without support, Dr. Bergstrom asserts that "[b]ased on the data available at the priority date, nothing indicated that fulvestrant followed anything other than a normal distribution, so this is a reasonable assumption." Ex. 1013 ¶ 118. Dr. Bergstrom does not disclose what "data available at the priority date" form the basis for his assumed normal distribution. The authors of Howell do not state that fulvestrant serum concentrations follow a normal distribution. Indeed, the data in Howell Table II show that fulvestrant C_{max} values ***do not*** follow a normal distribution. Thus, his assertion that there is nothing that indicated that fulvestrant followed anything other than a normal distribution is incorrect—a normal distribution ***cannot*** be assumed.

125. As shown below, using two separate tests (the D'Agostino & Pearson omnibus normality test, and the Shapiro-Wilk normality test),[6] ***the month 1 C_{max} data in Howell, Table II are not normally distributed***:

Col. stats	A Month 1 Cmax
	Y
1 Number of values	15
2	
3 Minimum	4.400
4 25% Percentile	5.900
5 Median	9.100
6 75% Percentile	11.00
7 Maximum	29.90
8	
9 Mean	10.47
10 Std. Deviation	6.407
11 Std. Error	1.654
12	
13	
14 D'Agostino & Pearson omnibus normality test	
15 K2	19.70
16 P value	< 0.0001
17 Passed normality test (alpha=0.05)?	No
18 P value summary	****
19	
20 Shapiro-Wilk normality test	
21 W	0.7627
22 P value	0.0013
23 Passed normality test (alpha=0.05)?	No
24 P value summary	**
25	
26 Sum	157.0

126. The **D'Agostino-Pearson** normality test computes the skewness and kurtosis to determine how far the asymmetry and shape is from a normal (Gaussian) distribution. It then calculates a P value from the sum of these

[6] Results reported were generated using GraphPad Prism 5, Version 5.04.

discrepancies. *See* R.B. D'Agostino et al., *A Suggestion for Using Powerful and Informative Tests of Normality*, 44 American Statistician 316 (1990) (Ex. 2168). The **D'Agostino-Pearson** normality test used by Prism is the "omnibus K2" test. As shown in the table above, the P value calculated by this test for the Month 1 C_{max} values reported in Table II in Howell is less than 0.0001, meaning that the probability that this sample of concentrations was derived from a normal distribution is less than 0.0001 (1 in 10,000). Given this, a reasonable pharmacokineticist would assume the data in Howell were ***not normally distributed*** (or, at the very least, not made an assumption one way or the other).

127. An alternative test that is also used in this software application is the **Shapiro-Wilk** normality test. It works very well if every value is unique, as is true with these data. *See* S.S. Shapiro et al., *An analysis of variance test for normality (complete samples)*, 52 Biometrika 591 (1965) (Ex. 2171). The Month 1 C_{max} data were also found ***not to be normally distributed*** by this test. As shown in the table above, the P value calculated by this test for the Month 1 C_{max} values reported in Table II in Howell is 0.0013, meaning that the probability that this sample of concentrations came from a normal distribution is 0.0013 (1 in 770). Again, given this, a reasonable pharmacokineticist would assume the data in Howell were ***not normally distributed*** (or, at the very least, not made an assumption one way or the

other).[7]

128. Howell was a small study with highly variable data—attempts at drawing conclusions like those drawn by Dr. Bergstrom would not have been condoned by the ordinarily-skill artisan given this small and highly variable data set. Again, it bears repeating that the authors noted, for example, "a direct pharmacokinetic-pharmacodynamic link is not proven with the ***few*** patients studied to date." Ex. 1007 at 6 (emphasis added).

129. In statistics, if one incorrectly assumes that the distribution of observations is normal, the entire scaffolding for subsequent data analyses is violated and the related inferences are unreliable. Thus, this assumption must be tested and validated before any statistical analysis of data is performed. Given the non-normal distribution of month 1 C_{max} data, there is simply no way to know, and a person of ordinary skill would not assume, that the data describing the patients' blood plasma fulvestrant concentrations are distributed normally. And because Dr. Bergstrom's opinion, that attaining therapeutically significant blood plasma fulvestrant concentration of at least 8.5 ng ml^{-1} for at least 4 weeks after injection is obvious, is premised entirely on an unsupported assumption that fulvestrant concentration data are normally distributed, his entire opinion fails.

[7] The Month 6 C_{max} values were shown to pass both normality tests (P= 0.3513 and 0.4972, respectively). This serves to highlight an important point: there is serious ambiguity regarding normality.

130. *Third*, Dr. Bergstrom states that the month 6, Day 0 data point in Howell Figure 2 reflects mean serum concentrations at month 5, Day 28. Dr. Bergstrom asserts, "Turning now to Figure 2 of Howell, one can see that the mean serum concentrations are lowest on day 0 and day 28, which represent the C_{min} values before the next monthly dose." Ex. 1013 ¶ 111. In reality, there can be only one "lowest" mean serum concentration in the series of eight mean concentrations plotted for month 6 in Figure 2 in Howell, and that is the value of 5.6 ng/ml (Ex. 1007 at 3) that occurs at the end of month 6, at Day 28. Figure 2 in Howell, is shown below:

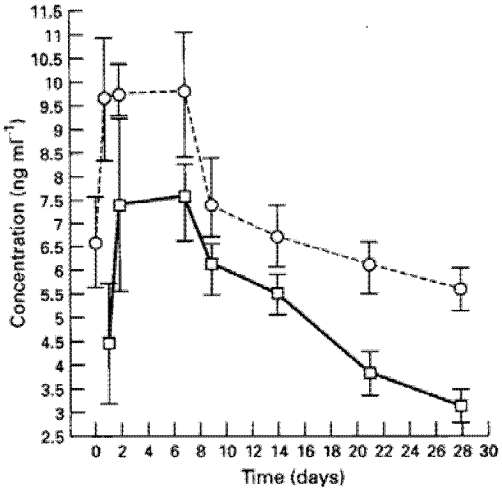

Figure 2 Mean serum concentrations of ICI 182780 during the first and sixth months of treatment. ——, Profile at entry; - - -, profile month 6.

131. In making these assertions, Dr. Bergstrom ignores the express disclosures of Howell. It is clear from Figure 2, that the ***only*** concentrations reported are mean serum concentrations "during ***the first and sixth months*** of treatment." Ex. 1007 at Figure 2 (emphasis added). Howell ***does not*** report,

discuss or provide ***any*** findings, let alone mean serum concentrations, ***during*** the fifth month of treatment—neither in Figure 2 nor anywhere else in the paper. Thus, there is no way to know, and ***one cannot assume***, the ***mean serum concentration at any time during month 5***.

132. It is clear "that the mean serum concentrations are lowest" (Ex. 1013 ¶ 111) on Day 28 of Month 6—not on Day 0 (*see* Ex. 1007 at Figure 2). Consistent with this, Howell reports, "the mean end-of-month concentration" for the sixth month was 5.6 ng ml^{-1}. Ex. 1007 at 3 ("Mean C_{max} (which occurred on day 7) increased from 10.5 ng $m1^{-1}$ to 12.8 ng $m1^{-1}$, accompanied by increases in mean end-of-month concentrations from 3.1 ng ml^{-1} to 5.6 ng ml^{-1} and AUC values from 140.5 ng day ml^{-1} to 206.8 ng day ml^{-1} for the first and sixth months respectively in the 11 patients studied.").

133. Indeed, Dr. Bergstrom entirely ignores the mean end-of-month concentration reported in Howell for month 6 (*see* Howell at 301 reporting 5.6 $ngml^{-1}$), using instead the mean concentration on Day 0, Month 6. *See* Ex. 1013 ¶ 112. Dr. Bergstrom attempts to justify his reliance on what he assumes to be end of month concentrations for month 5 as "appropriate because the claims do not specify any particular month, and only require that blood levels be achieved and maintained for one month." Ex. 1013.0051, n.5. To the contrary, it is unnecessary and inappropriate to rely on an assumption because Howell ***expressly taught*** the

mean end of month concentration—at month 6 (5.6 $ngml^{-1}$ (Ex. 1007 at 3)), but ***did not*** report any data during month 5.

134. Further, Dr. Bergstrom's assertion that "the mean serum concentrations are lowest on day 0 and day 28" (Ex. 1013 ¶ 111) is contradicted by his own assertion that "the mean serum concentration at day 0, month 6 is just above 6.5 ng/ml" (Ex. 1013 ¶ 115). It is clear that there cannot be two values in a series of 8 values during month 6 that are ***both*** the lowest (alleged by Dr. Bergstrom to occur on day 0 and day 28), unless they are equal. That is not the case here. A mean serum concentration of 5.6 ng ml^{-1} (Ex. 1007 at 3) is clearly lower than a mean serum concentration that is "just above 6.5 ng/ml" (Ex. 1013 ¶ 115). Moreover, although Dr. Bergstrom asserts that the patients in Howell did not reach steady state (*see* Ex. 1013 ¶ 153 ("Howell does not show that steady state was reached by month 6.")), that cannot be determined based on the very limited and variable data. Once again, Dr. Bergstrom applies no statistical analysis and cites to no prior art in support of his conclusions—ostensibly so that he is free to make whatever assertions he wants.

135. Howell describes mean "end of month" serum concentrations, i.e., mean serum concentrations on day 28, and even then, only for the first and sixth months of treatment. *See* Ex. 1007 at 3 ("Mean C_{max} (which occurred on day 7) increased from 10.5 ng $m1^{-1}$ to 12.8 ng $m1^{-1}$, accompanied by increases in ***mean***

end-of-month concentrations from 3.1 ng ml^{-1} to 5.6 ng ml^{-1} and AUC values from 140.5 ng day ml^{-1} to 206.8 ng day ml^{-1} for the first and sixth months respectively in the 11 patients studied.") (emphasis added)). Although Howell tabulates C_{max} values for individual patients during months 1 and 6, nowhere does Howell identify or refer to "C_{min}" serum concentrations. Accordingly, a person of ordinary skill in the art at the time of the invention would not draw any conclusions with respect to "C_{min}" serum concentrations based on Howell, and importantly, would not make the assumptions that Dr. Bergstrom makes today.

136. In any event, Dr. Bergstrom's assertion that some patients have blood plasma fulvestrant concentrations of at least 8.5 ng ml^{-1} for at least 4 weeks is a ***mathematical fiction***. A person of ordinary skill in the art at the time of the invention would not have been motivated to make the assumptions and calculations that Dr. Bergstrom does, i.e., to calculate the standard deviation for the month 6, Day 0 data point in Howell Figure 2, *and* to assume the data are normally distributed, *and* to consider values that are more than one standard deviation from the mean. Given the authors conclusions regarding their own data (no pharmacokinetic-pharmacodynamic link) such assumption would have been considered pointless. Moreover, Dr. Bergstrom's numbers "2.28% of the overall patient population will be more than 2 standard deviations above the mean" (Ex. 1013 ¶ 118) are nonsensical in the real world. A skilled artisan would appreciate

that 2.28% of 11 patients is ***one quarter of a patient***—i.e., less than one patient. This is pure mathematical fiction concocted with the challenged claims in mind.[8]

137. Also, Dr. Bergstrom's approach ignores the text of Howell itself. A person of ordinary skill in the art at the time of the invention, looking at Howell Figure 2, would not know whether the bars above and below each data point represent the standard error of the mean, two standard errors of the mean, one standard deviation, two standard deviations, or any other number of possible metrics. The skilled artisan examining the error bars would note that some of these, in both the month 1 and month 6 data, are not equal in length above and below the mean. Thus, he or she would simply have no way to know what the bars represent. ***And***, the skilled artisan would have had no way of knowing if the underlying serum concentrations are normally distributed. To this point, Howell reports the ***median*** of C_{max} values in Table II—***not the mean***. This would suggest that the ***data are not distributed normally,*** as the reported measure of central tendency for normally distributed data is usually the mean. The skilled artisan clearly has no way to know whether these serum fulvestrant values reported in Figure 2 of Howell are normally distributed. Accordingly, it was ***not known***—statistically or otherwise—that "at least some patients will fall more than 2

[8] In fact, Howell (Ex. 1007 at 3) discloses that the authors conducted a statistical analysis of their data—yet nowhere in the article are the statistical calculations and inferences Dr. Bergstrom asserts, found.

standard deviations above the mean." Ex. 1013 ¶ 119. Likewise, the data reported in Howell ***do not show***—in Figure 2 or otherwise—that "at least some patients in the overall patient population will have day 28 minimum serum concentrations above 8.5 ng ml^{-1}." Ex. 1013 ¶ 119. This assertion by Dr. Bergstrom concerning serum concentrations on Day 0 has no basis as discussed above. Moreover, Dr. Bergstrom did not try to calculate how many patients would have serum concentrations above 8.5 ng/ml bases on day 28 data for month 6. He apparently focused his attention on the Day 0 data because the mean serum concentration at Day 0 was about 1 ng/ml higher than that on Day 28 in Figure 2, and moreover because the error bar (undefined) at Day 0 was much larger than that at Day 28 (bringing Dr. Bergstrom closer to the 8.5 ng/ml value he was looking to support). The small error bar at Day 28 means a much narrower distribution of values (if one could properly assume that this was a normal distribution) and therefore the proportion of serum levels above 8.5 ng/ml would be very much less than what Dr. Bergstrom calculated at Day 0 (2.28%, or ¼ of a patient).

138. I understand Dr. Bergstrom's opinion in paragraph 120 to be premised entirely on the opinions of and representations by another one of InnoPharma's experts, Dr. Burgess, who, according to Dr. Bergstrom, opines "that the fulvestrant formulation recited in the claims was fully disclosed in the art before the priority date." Ex. 1013 ¶ 120. Dr. Bergstrom fails to identify any piece of prior art that

purportedly "fully disclosed" "the fulvestrant formulation recited in the claims," and I am not aware of any such prior art. Again, as set forth in the Sawchuk Declaration, certainly McLeskey does not. Thus, I understand Dr. Bergstrom has ***no basis*** other than the 2017 expert opinion of Dr. Burgess (which is not prior art), for his assertion that "the claimed 'therapeutically significant blood plasma fulvestrant concentrations' are an inherent property of the known formulation, which is additional evidence of obviousness." Ex. 1013 ¶ 120. As such, Dr. Bergstrom's opinions regarding the at least 8.5 ng/ml for at least four weeks limitation must be disregarded.

139. At the end of the day, Howell does not identify minimum concentrations achieved in the individual patients nor does it suggest having established a target concentration of fulvestrant during therapy, or a time period during which such levels should be maintained—just the opposite, the authors conclude that a pharmacokinetic-pharmacodynamic link had not been established. Ex. 1007 at 6. Moreover, had the results of this study demonstrated an "inherent" outcome of any kind, a person of ordinary skill in the art would have expected the authors to have noted it—but they do not, which is not surprising as the data are the first of their kind—meaning it would be premature to make any such conclusion. And, the data were extremely limited in their utility as evidenced by the very significant variability in maximum concentrations of fulvestrant and areas

under the curve reported in Howell. *See* Ex. 1007 at Table II. To the extent Dr. Bergstrom is attempting to suggest that the plasma levels are an inherent result for ***any*** 50 mg/ml fulvestrant formulation containing castor-oil that is given by intramuscular injection, again, Dr. Bergstrom offers no proof that this is the case and offers no scientific explanation in support. And to the contrary, Howell confirms this is not the case, as the patients (Patients 1-4), who received 100 mg of fulvestrant using the identical formulation during month 1 consistently had lower C_{max} during month 1 (range, 1.6 to 4.4 ng/ml) when compared with patients (Patients 5-19) who received 250 mg during month 1 (range, 4.4 to 29.9 ng/ml)." *See* Ex. 1007 at Table II.

140. Further, none of the other references upon which Dr. Bergstrom relies fill the gaps in the knowledge possessed by a person of ordinary skill in the art. O'Regan uses a peanut oil based formulation in animals and does not disclose blood plasma concentrations of fulvestrant let alone report on therapeutically significant levels; DeFriend involves a brief, pre-surgical study using a fast-acting propylene glycol-based formulation and provides a figure of mean serum fulvestrant level data for only 7 days (as such, it would have been considered separate and unrelated to the informative presented in Howell); and McLeskey has nothing to do with pharmacokinetic data on fulvestrant—or ***any*** data on fulvestrant for that matter—and, as such, a person of ordinary skill in the art would not even

have looked to it, let alone combined it with any of the above references reporting AstraZeneca's own work.

141. For these reasons alone I believe Dr. Bergstrom's opinions regarding the ***at least*** 8.5 ng/ml for at least four weeks limitation must be dismissed. Below I expand on some of the other points Dr. Bergstrom makes concerning this limitation.

2) Howell and DeFriend Do Not Disclose Therapeutically Significant Blood Plasma Fulvestrant Concentrations of at Least 8.5 ng/mL for at Least 4 Weeks

142. For the additional reasons explained below, it would not have been obvious to a person of ordinary skill in the art as of January 2000 what, if any, therapeutically significant blood plasma fulvestrant concentration(s) to achieve, the period of time over which such therapeutically significant blood plasma fulvestrant concentration(s) should be maintained, or how to achieve or maintain such a therapeutically significant blood plasma fulvestrant concentration.

143. As an initial point, I note that it was not known or disclosed in the prior art that a blood plasma fulvestrant concentration of 8.5 ng per ml for at least four weeks was therapeutically significant. In fact, this limitation (***at least*** 8.5 ng/ml for at least four weeks) is simply not disclosed in the prior art relied on by Dr. Bergstrom and appears to have been derived solely using hindsight and calculations designed by Dr. Bergstrom to get the result he desires.

144. As is clear from the four corners of the Howell and DeFriend publications, the limitation to "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 8.5 ng ml^{-1} for at least four weeks," as recited in claims 2 and 6, is not taught or disclosed by the Howell or DeFriend publications—neither separately nor in combination.

145. Further, Dr. Bergstrom does not even attempt to identify a prior art formulation that would allow for a therapeutically significant blood plasma fulvestrant concentration of at least 8.5 ng/mL to be achieved and maintained for at least four weeks. He simply cannot because the article his opinions rest on (Howell) does not discuss the components of the formulation used. And, a person of ordinary skill would not have ventured any guesses as to what the formulation was.

146. For these reasons alone I believe Dr. Bergstrom's opinions regarding the at least 8.5 ng/ml for at least four weeks limitation must be dismissed. Below I expand on some of the other points Dr. Bergstrom makes concerning this limitation.

147. As I explained above, DeFriend used a rapid release short-acting propylene glycol-based formulation of fulvestrant administered once a day for only seven days, and measured pre-dose levels on a daily basis. The plasma concentration-time profiles obtained with a ***short-acting*** formulation of fulvestrant

administered once a day for ***only seven days*** provides no insight regarding what the plasma concentrations of fulvestrant would be with a ***long-acting formulation***, designed to be administered once ***every four weeks***. This can be demonstrated by simply comparing the results of DeFriend to those in Howell, which in terms of blood plasma levels are completely different (*see, e.g.*, Fig. 1 of DeFriend (Ex. 1038) versus Fig. 2 in Howell (Ex. 1007)).

148. Furthermore, as mentioned earlier, the study discussed in DeFriend was not designed to assess therapeutic effects of fulvestrant, and it disclosed nothing regarding the time course over which any target levels should be maintained to provide efficacy. As such, from a reading of this publication one of skill in the art would not have understood what therapeutically significant blood plasma fulvestrant concentration(s) might be relevant, how they should be achieved or how long they should be maintained following the administration of one dose.

149. In paragraphs 123-124, Dr. Bergstrom asserts that "DeFriend would have motivated a person of skill in the art to increase the dose used in Howell based on" the teaching in DeFriend that "fulvestrant is dose-dependent and that a higher dose of 18 mg per day (or roughly 500 mg per 4 weeks for long-term use) was significantly more effective in reducing ER indices and thereby improved efficacy." Ex. 1013 ¶¶ 123-124. Here Dr. Bergstrom is considering doses ***higher***

than used in Howell, and appears to believe that any long-acting castor-oil formulation of fulvestrant would work. There is simply no basis or scientific support for Dr. Bergstrom's assertion that one of skill in the art would have been motivated by DeFriend to administer higher doses than in Howell—and no responsible clinician would administer a 500 mg dose, or a loading dose (two 250 mg doses) based on the combined teachings of Howell and DeFriend.

150. *First*, Dr. Bergstrom is forced to run to the DeFriend reference because Howell does ***not*** support his assertions. Specifically, Howell would have taught a skill artisan that there was ***no*** evidence that increased blood plasma levels of fulvestrant lead to improved outcomes in human patients; this is clear from the authors' conclusion no pharmacokinetic-pharmacodynamic link was found. *See, e.g.*, Ex. 1007 at 6; at 4, Table II. In fact, from Table II it is clear that the patient with the highest blood plasma levels of fulvestrant experienced disease progression. Ex. 1007 at 4, Table II.

151. *Second*, Dr. Bergstrom's suggestion that doses above 250 mg are required to obtain and maintain plasma levels in excess of 8.5 ng/ml also directly conflicts with Howell, which expressly teaches that ***doses lower than 250 mg should be pursued***. Ex. 1007 at 6 ("[D]ata suggest that ***lower*** doses of the drug may be effective in maintaining therapeutic serum drug levels, although further

clinical studies are required to confirm this hypothesis.") (emphasis added).[9] And, in fact, the next clinical study in line, which is discussed in a 1999 Abstract by Robertson et al., uses ***lower*** doses in direct contradiction to Dr. Bergstrom's opinions. *See* Robertson et al., *A Partially-Blind, Randomised, Multicentre Study Comparing the Anti-tumor Effects of Single Doses (50, 125, and 250 mg) of Long-Acting (LA) 'Faslodex' (ICI 182,780) with Tamoxifen in Postmenopausal Women with Primary Breast Cancer Prior to Surgery*, 57 Breast Cancer Res. & Treat. 31 (1999) (Ex. 1075) ("Robertson 1999"). Moreover, the suggestion to test lower doses makes sense given the authors' concern regarding potential long-term effects of fulvestrant on, among other things, bone. Ex.1007 at 7. *See also* Alan E. Wakeling, *The Future of New Pure Antiestrogens in Clinical Breast Cancer*, 25 Breast Cancer Res. & Treat. 1, 4 (1993) (Ex. 1058) ("Wakeling 1993") ("One predicted undesirable action of pure antiestrogens in therapeutic use may be a tendency to reduce bone density and hence to precipitate or exacerbate osteoporosis.").

152. *Third*, DeFriend was not designed to assess therapeutic effects of fulvestrant, and it disclosed nothing regarding the time course over which any

[9] Moreover, Dr. Bergstrom never explains how a person of ordinary skill would have reconciled a target in "excess of 8.5 ng/ml" given the express, and very narrow, predicted window of between 2 to 3 ng/ml referred to in the Howell reference itself. Ex.1007 at 6. Despite Drs. Howell and DeFriend authoring both the Howell and DeFriend references, they do not suggest any other range and nowhere in either publication even allude to higher doses.

target levels should be maintained to provide efficacy. DeFriend conducted a ***seven***-day dosing study with fulvestrant using a ***rapidly*** acting formulation administered once a day in patients who were scheduled to have breast tumors removed, this study teaches nothing about long acting formulations.

153. For these reasons and those discussed both above and below, Howell does not teach that serum concentrations of fulvestrant of at least 8.5 ng ml^{-1} are achieved and maintained for at least four weeks.

154. Accordingly, a person of ordinary skill in the art would not have been motivated to increase the dose used in Howell (who expressly teaches to go down) based on results of DeFriend (who did not assess, let alone discuss, therapeutic efficacy). Accordingly, there is no motivation for a skilled artisan to combine these two publications, let alone to combine these two publications and be motivated to increase the dose of fulvestrant above 250 mg. Likewise, there would be no reason why a skilled artisan would administer a 500 mg dose or a loading dose of two 250 mg doses, as Dr. Bergstrom suggests. Ex. 1013 ¶ 124.

155. Simply put, Howell does not set forth or establish as a goal achieving and maintaining the blood plasma concentrations set forth in the challenged claims and certainly does not teach or suggest how to achieve and maintain those concentrations given the absence of any formulation details.

156. Without basis or support, Dr. Bergstrom goes on to suggest that

"[r]egardless of whether a person of skill in the art administered a 500 mg dose or a loading dose, the person of skill in the art would reasonably expect that therapeutically significant blood concentrations of at least 8.5 ng ml^{-1} would be achieved for at least four weeks." Ex. 1013 ¶ 125. It is unclear how Dr. Bergstrom came up with this target concentration—seemingly Dr. Bergstrom looked at the therapeutically significant values set forth in the patent claims and, using a retrospective analysis, finds them in the data purportedly reported in Howell. For example, even accepting all of Dr. Bergstrom's assertions, there is no disclosure in Howell of 8.5 ng/ml of fulvestrant in blood plasma being *maintained* over a 4 week period. Rather, as discussed above, Dr. Bergstrom tries to justify the number 8.5 ng/ml by asserting it falls within some window above the mean concentration data point on Day 0, Month 6 as plotted in Howell Figure 2 (as would—mathematically speaking—countless other values both above and below that mean value) and glossing over the 4 week limitation in the challenged claims.

157. Simply put, one of skill in the art was not motivated to administer a "500 mg dose or a loading dose." And the skilled artisan ***would not have reasonably expected*** that, even if "blood concentrations of at least 8.5 ng ml^{-1} would be achieved for at least four weeks" (Ex. 1013 ¶ 125) that these levels would have been therapeutically significant. Again, nothing in the art teaches or suggests administering a 500 mg dose or a loading dose, nor does the art teach or

suggest that therapeutically significant blood concentrations or durations would be expected with either of these dosing regimens. Indeed, as of January 10, 2000, 250 mg was the highest dose taught in the art. *See* Howell (Ex. 1007) and Robertson 1999 (Ex. 1075). Moreover, even assuming a person of ordinary skill did predict a blood plasma fulvestrant level of 8.5 ng ml^{-1} the skilled artisan ***would not*** have known whether that level was therapeutically significant. There is simply nothing in the art supporting Dr. Bergstrom's assertions.

158. Despite the fact that Dr. Bergstrom cites to no prior art supporting his assertion that a person to ordinary skill would be motivated to increase the dose (or predicted range of serum levels) in Howell (because there is no such prior art), Dr. Bergstrom goes on at length in his paragraphs 126-131 about various pharmacokinetic principles, which are neither relevant nor appropriate here. I comment only to note that Dr. Bergstrom's primary assumption that one of ordinary skill would be motivated to increase the dose in Howell and would do so by administering a loading dose or doubling the dose, depends on a number of other assumptions that he makes in paragraphs 126-131. *First*, Dr. Bergstrom assumes that an increase in drug accumulation is desired, i.e., that it is safe and effective, among numerous other factors relevant to the goals of drug development. As explained above, Howell expresses concern regarding long-term effects of fulvestrant and expressly taught the levels were too high—***because of***

accumulation—which Howell teaches should be avoided. *See* Ex. 1007 at 7 ("At the dose used, there was accumulation of the drug over time and thus lower doses than those administered in this study may be as effective."). This express teaching in Howell that accumulation should be minimized, and in any event, accumulation was not related to efficacy, as reflected throughout the art. *See e.g.*, Dukes et al., *Antiuterotrophic effects of a pure antiestrogen, ICI 182,780: magnetic resonance imaging of the uterus in ovariectomized monkeys*, 135 J. Endocrinol. 239, 246 (1992) (Ex. 1036) ("Dukes 1992") ("Interestingly, in that study the increasing delay of the onset of uterine growth after the second and third doses indicated a cumulative biological effect. However, ***estimates of concentration of drug in the serum did not indicate that drug accumulation was responsible for this increased efficacy*** (F. Sutcliffe, unpublished studies)." (emphasis added)).

159. *Second*, Dr. Bergstrom asserts "[o]n the absorption side of the equation, doubling the dose of fulvestrant would be expected to double the amount of drug absorbed." Ex. 1013 ¶ 127. In making this assertion (Ex. 1013 ¶ 127), Dr. Bergstrom assumes that fulvestrant when administered in a long acting formulation exhibits linear kinetics. Dr. Bergstrom does not cite anything in support of this assertion, and I am not aware of anything in the art which supports that assumption. More, Dr. Bergstrom is assuming that fulvestrant exhibits linear kinetics in both immediate release (akin to the short-acting fulvestrant formulation

used in DeFriend) and sustained release (such as the fulvestrant formulation administered in Howell) dosage forms. Not all drugs exhibit the same linearity across all dosage forms. For example, propranolol immediate release dosage form exhibits different kinetics (greater bioavailability) than propranolol sustained release (Long Acting, LA) dosage form. This occurs because the drug is metabolized more efficiently by the liver during absorption of drug from the LA dosage form when the absorption rate is slowed. *See* Physician's Desk Reference, 53d ed., 3309 (1999) (Ex. 2169) ("PDR").

160. *Third*, Dr. Bergstrom asserts "one skilled in the art would expect the amount of fulvestrant absorption from a 500 mg dose to be double that of a 250 mg dose." Ex. 1013 ¶ 129. In making this assertion, Dr. Bergstrom assumes that only absorption—which is only part of a drug's kinetic profile—is relevant. In actuality, absorption is only a piece of the overall pharmacokinetics. Furthermore, absorption alone cannot inform whether any given drug exhibits linear kinetics. For example, many lipophilic drugs are highly bound to plasma proteins. As their plasma concentrations increase (for example, at higher doses), their binding to circulating proteins may become saturated and a greater fraction of the drug in plasma is free (unbound), allowing the drug to be more efficiently cleared (by metabolism and/or renal excretion) from the body. This results in nonlinear pharmacokinetics, and an increase in dose will produce a less than proportional

increase in plasma or serum drug concentrations.

161. *Fourth*, in paragraph 130 Dr. Bergstrom concludes, without support, that "on the elimination side of the equation, one of skill would conservatively expect that the elimination of fulvestrant to be first-order." Ex. 1013 ¶ 130. In so concluding, Dr. Bergstrom assumes (incorrectly) that one of ordinary skill would base his or her expectations—and ***conservative expectations*** at that—on a proposition that is completely lacking any scientific support or evidence that it is the case. There are several mechanisms related to drug elimination that may be responsible for nonlinear kinetic drug behavior, resulting in elimination kinetics that are not first-order. For example, in addition to the existence of capacity-limited protein binding mentioned above, the saturation of drug metabolizing enzymes within the range of blood plasma concentrations observed clinically may exist, causing metabolic clearance to ***decrease*** as plasma drug levels are ***increased***. When this occurs, drug elimination is not first-order, and drug concentrations and AUCs during a dosing interval are not proportional to the dosing rate, and the half-life is prolonged at higher serum concentrations. In addition, the degree of accumulation of serum or plasma levels cannot be predicted when this type of nonlinear behavior exists. It may be that the concern expressed in Howell that mean end of month drug levels and AUCs increased substantially during month 6 when compared with data from month 1 is related to this. *See* Ex. 1007 at 6-7.

That fulvestrant may be exhibiting nonlinear pharmacokinetics during multiple dosing with the long acting formulation employed in Howell is also suggested by the apparent prolongation of half-life observed in the mean serum concentration-time data during month 6 when compared with month 1 data. *See* Ex. 1007 at Figure 2.

162. *Fifth*, Dr. Bergstrom further assumes that "[b]ecause both absorption and elimination would be expected to behave in a first-order and dose-proportional manner, doubling the dose that was used in Howell, as taught by DeFriend, would be expected to approximately double the blood plasma concentrations of fulvestrant." Ex. 1013 ¶ 131. However, because the formulation used in DeFriend is different than the formulation used in Howell, it is scientifically improper to assume that any of the limited information taught by DeFriend (which does not include, for example, a 500 mg dose, as discussed above) could—in any way—inform what would be expected to happen assuming one was motivated to even consider doubling the dose taught by Howell.[10]

163. Dr. Bergstrom asserts, in paragraph 132, that "were one to double the

[10] Of course, Howell does not disclose the details of the formulation used. Moreover, there is no information in the prior art regarding the blood plasma levels produced by either fulvestrant formulation used in McLeskey; so any assumptions made with respect to the Howell formulation would be inapplicable to those formulations. More specifically, there are no pharmacokinetic data in the prior art indicating what influence ethanol, benzyl alcohol and/or benzyl benzoate has on the release of fulvestrant from a fulvestrant castor-oil based formulation. And no credible assumptions could therefore have been made by a person of ordinary skill.

dose of fulvestrant used in Howell (or use a loading dose), as taught by DeFriend, this would result in trough serum concentrations of fulvestrant that are far above 8.5 ng ml^{-1} (approximately 12-13 ng ml^{-1}) for at least 4 weeks after injection and the blood plasma concentrations of fulvestrant in a greater number of patients would have achieved at least 8.5 ngml-1 for an entire 4-week period." Ex. 1013 ¶ 132. Such a broad-based assumption—premised entirely upon equally-faulty assumptions and hypotheticals—would not be made or accepted by one of ordinary skill in the art (or a responsible pharmacokineticist). Given the utter absence of any scientific support, and for the other reasons described above, Dr. Bergstrom's assertions that one should pursue higher doses (and target levels) of fulvestrant, are contrary to the very text of Howell and, thus, what a person of ordinary skill in the art would believe. Howell express concerns related to higher serum levels (relating to both long-term effects and accumulation), and also suggests that lower doses may be effective in maintaining therapeutic serum levels of this drug—that is the direction (down) a person of ordinary skill would have followed . In contrast, Dr. Bergstrom seems to focus on a serum level of 8.5 ng/ml based upon his reading of the patent claim terms, and his assertion that higher doses of this drug are needed is in direct opposition to what is stated in the prior art. Likewise, Dr. Bergstrom's assumptions are contrary to what a person of ordinary skill in the art would do—namely, ***not*** make assumptions relating to complicated matters like linear versus

nonlinear kinetics.

164. For these reasons, Dr. Bergstrom's opinion that Howell and DeFriend teach therapeutically significant fulvestrant concentrations of at least 8.5 $ngml^{-1}$ for at least four weeks is incorrect.

C) There Was No Motivation to Combine the Prior Art Cited and in Any Event, There Would Have Been No Reasonable Expectation of Success in Doing So

1) A Person of Skill in the Art Would Not Have Been Motivated by the Results Reported in Howell

165. Dr. Bergstrom states: "a person of skill in the art would have been motivated to achieve these therapeutically significant blood plasma fulvestrant concentrations." Ex. 1013 ¶ 133. In support of this statement, Dr. Bergstrom states: "As Dr. Harris explains, a person of skill in the art would be motivated to achieve the positive results in Howell. In particular, Howell reported a 69% response rate for the patients in the study. Moreover, Howell reported that 'no serious drug-related adverse events occurred in any of the 19 patients treated with' fulvestrant. Based on these results, it is my opinion that a person of skill in the art would have been motivated to achieve and maintain these blood serum or plasma fulvestrant concentrations, which directly correlated with efficacious results with no drug-related adverse side effects" (Ex. 1013 ¶ 134 (citations omitted)) and that "Howell teaches that blood plasma concentrations as high as 8.5 ng ml^{-1} can be achieved and maintained for at least four weeks" (Ex. 1013 ¶ 135). Dr. Bergstrom

concludes that a "person of skill in the art would have been motivated to achieve the positive results reported in Howell." Ex. 1013 at p.56. This is incorrect.

166. As reported by Howell, approximately 1/3 of the patients studied had progressive disease despite fulvestrant treatment, 1/3 of the patients showed no change during treatment, and 1/3 of the patients showed a partial response. And, a person of ordinary skill in the art would have concluded—as did the authors—that ***no*** relationship had been established between any metric that associated plasma levels of fulvestrant with therapeutic response. *See* Ex. 1007 at 3, at Table II, at 6. In fact, a person of ordinary skill in the art would have recognized that there was much clinical work yet to be done with this drug. Even the authors state, "However, further studies are required to confirm the response rate and also to determine the long-term effects of this agent on bone." Ex. 1007 at 7.

167. Further, and as explained above, I do not understand Dr. Bergstrom's basis for asserting that the results of the study reported in Howell were "positive" or have been understood to have been as such. Although I note that in paragraph 134, Dr. Bergstrom cites to the expert opinion of Dr. Harris, which is not prior art. In any event I disagree with Dr. Bergstrom's otherwise unsupported characterization of Howell as "positive." As such, I believe a person of ordinary skill in the art would not have combined these references in the way Dr. Bergstrom has and certainly—in particular given the results in Howell—would not have had a

reasonable expectation of success.

2) A Person of Skill in the Art Would Not Have Been Motivated to Increase Dose and Concentration

168. In his paragraph 136, Dr. Bergstrom asserts: "a person would be motivated to use a 500 mg dose based on the teachings of Howell and DeFriend. In particular, a person of skill in the art would search the existing literature for information regarding how to increase the response rate shown in Howell and thereby be motivated to improve upon the efficacy of fulvestrant for the treatment of breast cancer. Such a person would have been led to DeFriend, which teaches that doses of 18 mg per day (or roughly 500 mg per 4 weeks) was highly effective in ER reduction." Ex. 1013 ¶ 136. Again, in coming to the opinions set forth in his paragraphs 136-147, Dr. Bergstrom relies solely on the present-day opinion of another expert, Dr. Harris, which I again note is not prior art. *See* Ex. 1013 ¶¶ 136-147. I understand that Dr. Robertson will be responding to Dr. Harris's declaration, which Dr. Bergstrom relies upon entirely for his opinions in paragraphs 136-147. I defer to Dr. Robertson's opinions on the issues raised by Dr. Harris and adopted by Dr. Bergstrom.

169. Regardless, for the reason discussed below, together with my discussion regarding Howell and DeFriend above, I disagree.

3) A Person of Skill in the Art Would Not Have Been Motivated to Combine Howell and DeFriend

170. In his paragraph 141, Dr. Bergstrom, citing Dr. Harris's present-day (i.e., non-prior art) expert opinion, asserts: "DeFriend in combination with Howell teach a person of skill in the art that increasing the dose above the 250 mg dose used in Howell would lead to an even more successful treatment result." Ex. 1013 ¶ 141. For the reason discussed below, together with my discussion regarding Howell and DeFriend above, I disagree.

171. Importantly, the authors of Howell do not draw the conclusions Dr. Bergstrom and Dr. Harris do now in retrospect. The authors do not conclude or even hypothesize that there is a target blood plasma concentration level that ***should*** be achieved in future studies based on their results. They certainly never, suggest a ***higher*** range then the one "predicted" (2-3 ng/ml) before they obtained the results they did. They do not discuss the period of time over which such levels should be maintained. And, the authors do not recommend a dosing regimen. A person of ordinary skill in the art would have recognized that Howell was a preliminary, early clinical study in which clinicians were only just beginning to gather relevant clinical data. Furthermore, unlike Dr. Bergstrom and Dr. Harris, the authors ***avoid*** drawing a conclusion regarding any correlation between blood plasma levels and efficacy. The authors conclude "a direct pharmacokinetic-pharmacodynamic link is ***not*** proven with the ***few*** patients studied to date." Ex. 1007 at 6 (emphasis added). And to the extent Howell et al., make any conclusions regarding dose or

blood fulvestrant levels, the authors conclude ***lower amounts of fulvestrant*** should be considered in future studies. I agree with the authors of Howell especially given potential long-term adverse effects that were mentioned as a concern by the authors.

172. In his paragraph 145, Dr. Bergstrom asserts that "Howell shows that the minimum toxic concentration of fulvestrant is quite high, as no toxicity was observed despite achieving and maintaining the higher fulvestrant concentrations." Ex. 1013 ¶ 145. I do not understand the basis for this assertion by Dr. Bergstrom given that nowhere does Howell mention or refer to a purported "minimum toxic concentration of fulvestrant" let alone that such a concentration is "quite high."

173. In his paragraph 200, Dr. Harris asserts, without basis or support, that the therapeutic window for fulvestrant is large. Ex. 1015 ¶ 200. But regardless, assuming Dr. Harris's calculation of a human dose and dosing interval is valid, Dr. Harris, without explanation, identifies intramuscular dosing regimens for fulvestrant in humans: "Thus, if a person of ordinary skill in the art wanted the dose to be administered monthly by IM injection, starting with a dose of 100 or 250 mg/month is quite predictable and a common step to take in my opinion." Ex. 1015 ¶ 200. Dr. Harris seems to have selected this range of monthly doses to be consistent with that described in Howell. Dr. Harris goes on to suggest that a person of ordinary skill would determine blood plasma concentrations in the

patient to see whether the dose would need to be increased. Importantly, however, Dr. Harris does not indicate what target plasma fulvestrant concentration he is trying to achieve with this increase in dose. Indeed, based upon prior art, one of skill in the art would not know what plasma levels of fulvestrant were therapeutically significant, so this proposed dosage adjustment would be done entirely without guidance.

174. Contrary to the assertions by Drs. Bergstrom and Harris, neither Howell nor DeFriend disclose target plasma levels known to correspond to efficacious treatment of patients. As I have already explained, Howell reported that approximately 1/3 of the patients studied had progressive disease despite fulvestrant treatment, 1/3 of the patients showed no change during treatment, and 1/3 of the patients showed a partial response (and that the response rate had to be confirmed in "further studies" (Ex. 1007 at 7)). And, a person of ordinary skill in the art would have concluded—as did the authors—no relationship had been established between any metric that associated plasma levels of fulvestrant with therapeutic response. *See* Ex. 1007 at 4, at Table II and at 6. As I have explained in detail above, as of the relevant date here no pharmacokinetic-pharmacodynamic link had been established. And, even if a link had been established, it is not a simple matter to develop a formulation for intramuscular use that could achieve and maintain the identified levels of fulvestrant over an extended period with

infrequent dosing, e.g., once every four weeks. Regarding DeFriend, again, what limited results are reported in DeFriend are limited to that study, including the dosing regimen and formulation used—i.e., a ***seven***-day dosing study with fulvestrant using a ***rapidly*** acting propylene glycol-based formulation administered once a day in patients who were scheduled to have breast tumors removed. In short, DeFriend teaches nothing about long acting fulvestrant formulations.

175. As I have explained in detail above, as of the relevant date here no pharmacokinetic-pharmacodynamic link had been established. And, even if a link had been established, it is not a simple matter to develop a formulation for intramuscular use that could achieve and maintain the identified levels of fulvestrant over an extended period with infrequent dosing, e.g., once every four weeks. The development of such a formulation would represent a major challenge and because the references relied on by Drs. Bergstrom and Harris do not set forth the details of the formulations used they are of no utility in predicting what any given formulation would do.

176. Furthermore, for the reasons previously discussed, neither O'Regan nor the McLeskey publication fill in the gaps in the knowledge possessed by a person of ordinary skill in the art after reviewing Howell and DeFriend—in fact, a pharmacokineticist would not even have looked to or referenced O'Regan or McLeskey, let alone combine either or both with Howell and/or DeFriend given

how disparate those references are. Also it makes no sense to combine studies that had very different objectives, used different designs, and very different formulations, as seen in DeFriend and Howell.

177. In paragraph 148, Dr. Bergstrom asserts: "DeFriend would have also motivated a skilled person to use a loading dose, which would have resulted in the maintenance of blood plasma fulvestrant concentrations of at least 8.5 ng ml-1 for at least four weeks." Ex.1013 ¶ 148. This is not correct.

178. Dr. Bergstrom's only support for his opinion, once again, appears to be limited to the present-day opinion of Dr. Harris. *See* Ex.1013 ¶ 149 (citing Ex.1015 ¶ 223 ("As Dr. Harris explains, a person of skill in the art administering long-acting IM injections would have appreciated that a 'loading dose' would be beneficial in administering fulvestrant because it would more quickly reach the desired steady state concentrations and would therefore promote a more prompt reduction of the ER.")).

179. As an initial matter, although a loading dose of a long-acting intramuscular injection may hasten the approach to steady state, Dr. Harris, in his paragraph 242, offers no evidence that this would "promote faster reduction of the ER." *See* Ex. 1015 ¶ 223. Furthermore, Dr. Harris does not offer support for any increase in efficacy, even if ER indices were to be reduced more rapidly.

180. Further, Drs. Howell and DeFriend did not utilize a loading dose in

the Howell study nor do they recommend one in the conclusions they drew from their own study. The only guidance they provide is to consider clinical trials with lower doses. Moreover, a person of ordinary skill in the art would have understood that steady-state levels of fulvestrant will not be affected by the use of a loading dose. So, the teaching to lower dose applies equally whether considering a loading dose nor not.

D) No Reasonable Expectation of Success

181. I understand that Dr. Robertson will be responding to Dr. Harris's declaration, which Dr. Bergstrom relies upon entirely for his opinions in paragraphs 167-171. I defer to Dr. Robertson's opinions on the issues raised by Dr. Harris and adopted by Dr. Bergstrom.[11]

182. Dr. Bergstrom states "Howell discloses that the claimed blood plasma concentrations can be achieved in the patient population and then observes a high response rate with the achievement of those concentrations." Ex.1013 ¶ 175. Dr. Bergstrom's statement, and his opinion that "a person of skill in the art would have at least a reasonable expectation of success based on the information disclosed in Howell" (Ex.1013 ¶ 175) is not correct.

183. Most importantly, there is nothing in Howell or any other prior art

[11] I further understand that Dr. Robertson will be responding to Dr. Bergstrom's paragraphs 156-163 and 172-176. I defer to Dr. Robertson's opinions on the issues raised by Dr. Bergstrom in those paragraphs.

publication that showed that the therapeutically significant concentration limitations were associated with therapeutic effects in female breast cancer patients. To the contrary, Howell concludes, as I have indicated before, that a relationship between plasma levels of fulvestrant and any therapeutic effects in the patient population studied had not been established, stating, "[t]here was no significant difference in the median C_{max} and AUC between responders and non-responders to treatment. (Table II)." Ex. 1007 at 3.

E) The Skilled Artisan Would Not Have Expected the Castor Oil-Based Formulation in McLeskey to Achieve the Claimed Therapeutically Significant Fulvestrant Concentration Limitations

184. In paragraph 177 Dr. Bergstrom states, "I have also been asked to consider whether a person of skill in the art—reviewing the 50 mg/ml castor oil-based formulation disclosed in McLeskey—would reasonably expect that intramuscular injection of the McLeskey castor oil-based formulation would produce the same or similar mean serum blood concentrations on day 28 as the 50 mg/ml castor oil-based formulation taught in Howell. In my opinion, a person of ordinary skill in the art would have such a reasonable expectation." Ex.1013 ¶ 177. Dr. Bergstrom's opinion is incorrect for the reasons below as well as for the reasons I have already explained above. In particular I incorporate by reference here my discussion regarding these points above, as well as my opinions set forth in the Sawchuk Declaration (Ex. 1019).

185. As an initial matter, I understand Dr. Bergstrom's opinions in paragraphs 177-189 to be premised entirely on the opinions of and representations by another expert, Dr. Burgess. Ex.1013 ¶¶ 177-178. I understand that Dr. Illum will be responding to Dr. Burgess's opinions, and I defer to Dr. Illum's opinions on the issues raised by Dr. Burgess and adopted by Dr. Bergstrom in his paragraphs 177-189. Further, I note that in paragraph 177, Dr. Bergstrom again ignores the limitations of the claims, which are directed to a method of treating ***a human*** with hormonal dependent breast cancer and ***achieving and maintaining*** therapeutically significant levels for at least 2 weeks or at least 4 weeks, and thus I do not understand Dr. Bergstrom's opinion, which is with regard to "***mean*** serum blood concentrations ***on day 28***" (Ex.1013 ¶ 177 (emphasis added)) to be relevant to the challenged claims.

186. In any event, contrary to Dr. Bergstrom's assertions, as discussed, there was nothing in the prior art that would have provided a person of skill in the art with a reasonable expectation that one could achieve and maintain therapeutically significant concentrations of fulvestrant of at least 2.5 ng/ml, and at least 8.5 ng/ml for at least 2 or 4 weeks as recited in the claims. Importantly, there was nothing in the prior art that associated these serum levels and time periods with therapeutic effects in breast cancer patients.

187. As I have explained above, as well as below in response to certain

arguments made by Dr. Harris, McLeskey contains no data regarding blood plasma concentrations of fulvestrant. As such, I do not believe a person of ordinary skill in the art would have combined this reference in the way Dr. Bergstrom has and certainly—in particular given the results in Howell—would not have had a reasonable expectation of success.

188. Furthermore, the use of McLeskey's mouse model to predict a human dose is inappropriate here because dissimilar modes of administration (subcutaneous vs. intramuscular) are involved; these dosing routes may exhibit major differences in rates and extent of absorption. Indeed, it is this latter issue that precludes one from knowing what would happen following intramuscular injection in humans based on information garnered following subcutaneous administration in mice. *See* Ex. 1019 (I adopt by reference my opinions on this issue as set forth in the Sawchuk Declaration). And in fact, in this case, McLeskey, provides ***no information*** regarding the rate and extent of absorption of fulvestrant in her mouse model since no plasma levels of fulvestrant are reported. Thus, I agree with Dr. Robertson that a skilled artisan would not reasonably expect the fulvestrant formulation that was used subcutaneously in McLeskey—***and failed***—would work when administered intramuscularly to breast cancer patients. Quite simply, it is not a reasonable assumption, nor one that a responsible pharmacokineticist or clinician, would make.

189. And Dr. Bergstrom has no evidence that the formulation used in the McLeskey publication is similar to the product used in Howell, and therefore no basis for asserting that the pharmacokinetics of fulvestrant would have been the same as that observed in Howell if given via the intramuscular route to a human. McLeskey does not disclose any pharmacokinetic data, nor does she disclose the formulation she used. And, Howell also does not disclose the details of the formulation utilized. As, such the data in Howell simply would not have been used by a person of ordinary skill to make any predictions regarding any formulation.

190. Dr. Bergstrom fails to identify any piece of prior art that purports to support his opinion that "a person of skill in the art would reasonably expect that the formulation disclosed in McLeskey would exhibit the same or very similar pharmacokinetics as Howell" (Ex.1013 page 70) and I am not aware of any such prior art. Certainly, as discussed in the Sawchuk Declaration, McLeskey does not. Thus, I understand Dr. Bergstrom has ***no basis*** other than the 2017 expert declaration of Dr. Burgess (which is not prior art), for his assertions that "at day 28, the anticipated pharmacokinetics from McLeskey would closely mirror the pharmacokinetics reported in Howell" (Ex.1013 ¶ 182); "a person of skill in the art would have a reasonable expectation of success in using the formulation from McLeskey to achieve the mean serum concentrations in Howell" (Ex.1013 ¶ 183); and "a person of skill in the art would reasonably expect that McLeskey would

have certain pharmacokinetic parameters if administered intramuscularly based on the chemical properties of the co-solvents and the fact that it is a castor oil-based vehicle at the exact same concentration as Howell" (Ex.1013 ¶ 186). Given that Dr. Bergstrom's assertions are not supported by the prior art, his opinion that "a person of skill in the art, looking at the McLeskey formulation—which is also a castor oil-based composition supplied by AstraZeneca with the same concentration (50 mg/ml) of fulvestrant—would have expected it to have the same or highly similar day 28 pharmacokinetics as Howell if given intramuscularly in humans" (Bergstrom ¶¶ 177-189) must be dismissed.

XII) THE GAPS IN DR. BERGSTROM'S ANALYSIS ARE NOT FILLED BY INNOPHARMA'S OTHER EXPERTS' OPINIONS

191. In his paragraph 189, Dr. Harris asserts: "One of skill in the art would also have had a reasonable expectation of success that combining Howell and McLeskey, or Howell, McLeskey and O'Regan, or Howell, McLeskey, O'Regan and DeFriend would achieve the claimed methods prior to 2000. In my opinion, a person of skill in the art, looking at the McLeskey formulation—which, like the product used in Howell, is also a castor-oil based composition supplied by AstraZeneca with the same concentration (50 mg/ml) of fulvestrant—would have expected to see the same pharmacokinetics as Howell if given intramuscularly in humans." Ex. 1015 ¶ 189. Dr. Harris has no evidence that the formulation used in the McLeskey publications is similar to the product used in Howell, and therefore

no basis for asserting that the pharmacokinetics of fulvestrant would have been the same as that observed in Howell if given via the intramuscular route. McLeskey does not disclose any pharmacokinetic data. And, Howell does not disclose the details of the formulation utilized. As, such the data in Howell simply would not have been used by a person of ordinary skill to make any predictions regarding any formulation.

192. In his paragraph 190, Dr. Harris asserts: "There were numerous studies reporting on successful results using fulvestrant both in animals and humans as a treatment of hormone-dependent cancer and a person of ordinary skill in the art would have known that formulations used in the various tests can be comparably effective used in humans." Ex. 1015 ¶ 190. Dr. Harris does not point to any specific prior art study which reports successful results, if success is defined in terms of efficacy in the treatment of breast cancer. In addition, there is no information regarding what serum concentrations of this drug would be therapeutic in humans in the prior art. To the contrary, Howell reports no pharmacokinetic-pharmacodynamic link had been established.

193. Further, as has already been established, there is great difficulty in using the results of animal studies to predict pharmacokinetics in humans (a matter I discussed in detail in the Sawchuk Declaration (Ex. 1019), which I incorporate here by reference). And, to predict therapeutic levels of a drug's

(pharmacodynamics) in humans from the results of animal studies requires numerous assumptions, which may be tenuous at best.

194. Without basis or support, Dr. Harris opines that "it is routine practice to look to early animal studies to determine formulations for new drugs. Thus, a person of skill in the art would know that he or she could apply teachings regarding the fulvestrant formulation used in animals, such as McLeskey, to that used in humans with a reasonable expectation of success." Ex. 1015 ¶ 192. I disagree. Animal studies ***may*** be useful in selecting formulations for new drugs. However it is difficult to predict the spectrum of parameters involved in human pharmacokinetics, even when carefully designed animal studies are conducted. Furthermore, the formulation used by McLeskey, in spite of Dr. Harris's contention, is not fully disclosed. Even McLeskey admits in her declaration that she thought the composition of the formulation was expressed in terms of volume by volume. *See* Ex. 2043 at ¶ 8.

195. Citing to the McLeskey publication and a patent by AstraZeneca scientist, Michael Dukes, EP No. 0 346 014 (1989) (Ex. 1055) (the "Dukes Patent"), Dr. Harris states: "Several prior art sources taught long-acting fulvestrant injections solubilized in castor oil formulations that were used in animals during early drug development." Ex. 1015 ¶ 193. To the contrary, none of the prior art publications referred to by Dr. Harris discloses the exact composition of the

formulation specified in the patents-in-suit.

196. Citing a 1994 publication by Nicholson et al., Dr. Harris asserts: "In addition, a report published in 1994 explained that the efficacy and toxicity results shown in vitro can be predictive of and compared to results shown in vivo to achieve successful results." Ex. 1015 ¶ 194 (citing Nicholson et al., *Pure Antioestrogens in Breast Cancer: Experimental and Clinical Observations, in Sex Hormones & Antihormones in Endocrine Dependent Pathology: Basic & Clinical Aspects*, Proceedings of an International Symposium, Milano 347 (1994) (Ex. 1053) ("Nicholson")). I note that in Nicholson, the authors outline the cellular and antitumor properties of antiestrogens on human breast cancer cells *in vitro*, and then compare those properties with data derived from DeFriend. *See* Ex. 1053 at 3-4 ("Since pure antioestrogens are now entering clinical development, the current paper seeks to outline some of their basic cellular and antitumour properties on human breast cancer cells *in vitro* primarily using the lead compound ICI 164,384, and to compare this information with data derived from a phase I study of ICI 182,780 in primary breast cancer patients."). Indeed neither the Nicholson publication, nor DeFriend, examines the clinical efficacy of any compounds, including fulvestrant in patients. Based on effects observed in the cell studies, Nicholson concludes by expressing hope for the future, stating "Only when the maximum reduction in oestrogen-regulated genes and ER has been established will

the full potential of pure antioestrogens have been met in clinical breast cancer and the role of oestrogens delineated. Having achieved this goal, their actions should be compared to other treatments designed to interfere with the production of oestrogens or their cellular activity. Such studies would establish whether pure antioestrogens pass existing thresholds of response to antihormonal measures and the importance of partial vs. complete oestrogen withdrawal." Ex. 1053 at 15. This pragmatic view of the current knowledge of antiestrogen pharmacology makes it clear that Nicholson et al. do not take the position that "efficacy and toxicity results shown in vitro can be predictive of and compared to results shown in vivo to achieve successful results" as Dr. Harris suggests (Ex. 1015 ¶ 194). Indeed, earlier in the paper Nicholson et al. explicitly state that "clinical trials with pure antioestrogens are in their infancy" and "consequently little is known about their clinical properties." Ex. 1053 at 12. And, in a later publication about ICI 164,384 and fulvestrant, by the same authors, Nicholson et al. conclude that "[i]n clinical breast cancer it is ***too early to judge*** the final value of these compounds." (Nicholson et al., *Responses to Pure Antiestrogens (ICI 164834, ICI 182780) In Estrogen-Sensitive And -Resistant Experimental And Clinical Breast Cancer*, 61 Annals N.Y. Acad. Sci. 148 (1995) (Ex. 1032) ("Nicholson 1995") at 12 (emphasis added)).

197. In his paragraph 195, Dr. Harris, without basis or support, asserts: "a

skilled artisan would have had a reasonable expectation that the formulation in McLeskey would be therapeutically effective in IM injections in humans even though it was used subcutaneously on mice in that case." Ex. 1015 ¶ 195. First of all, the formulation is not defined in McLeskey, and Dr. Harris has ***no evidence*** to suggest that it would be therapeutically effective when given intramuscularly in humans. McLeskey did not even show it to be effective in her mouse model. Indeed, McLeskey reports fulvestrant's inability to affect the estrogen-independent *in vivo* growth of FGF-transfected MCF-7 cells made it a "treatment failure." Ex. 1008 at 10; *see also* Ex. 1008 at 11 ("[T]he insensitivity of the estrogen-independent *in vivo* growth of the FGF transfectants to [fulvestrant] or the aromatase inhibitors implies that clinical tamoxifen resistance due to FGF receptor-mediated signaling ***may not respond*** to a second hormonal therapy.") (emphasis added)).

198. In his paragraph 196, Dr. Harris disagrees with statements made by Dr. Robertson regarding why one skilled in the art would not expect that the fulvestrant formulation used in McLeskey could be or would be effective if used in humans, and asserts, without basis or support, that "a person of ordinary skill in the art would have known (1) that there are well-established formulas for calculating the appropriate dose for humans compared to a mouse; and (2) how to account the differences between administering a drug subcutaneously in mice versus by IM injection in humans." Ex. 1015 ¶ 196. As an initial matter the calculation of an

appropriate dose in humans compared to a mouse is fraught with uncertainty, and therefore often involves the further application of an empirical safety factor. Indeed, a mouse would be the wrong animal to select for the calculation of human doses. Rather, one would select a much closer animal to man, such as the monkey.[12]

199. Furthermore, the use of McLeskey's mouse model to predict a human dose is inappropriate here because dissimilar modes of administration (subcutaneous vs. intramuscular) are involved; these dosing routes may exhibit major differences in rates and extent of absorption. Indeed, it is this latter issue that precludes one from knowing what would happen following intramuscular injection in humans based on information garnered following subcutaneous administration in mice. *See* Ex. 1019 (I adopt by reference my opinions on this issue as set forth in the Sawchuk Declaration). And in fact, in this case, McLeskey, provides ***no information*** regarding the rate and extent of absorption of fulvestrant in her mouse model since no plasma levels of fulvestrant are reported. Thus, I agree with Dr. Robertson that a skilled artisan would not reasonably expect

[12] Assuming *arguendo* that the approach and calculations conducted by Dr. Harris are applicable the following could be said of Wakeling 1993 (Ex. 1058). Under the heading "Clinical application," the authors cite to Dukes 1992 as "measuring the duration of anti-estrongenic action of oil depots of ICI 182,780 in monkeys" with respect to "the likely dose and frequency of treatment of breast cancer patients." Ex. 1058 at 10. Assuming a 60 kg human patient, the dose used in monkeys translates to 74.4 mg for a human patient—consistent with the teaching in Howell to go down in dose.

the fulvestrant formulation that was used subcutaneously in McLeskey—***and failed***—would work when administered intramuscularly to breast cancer patients. Quite simply, it is not a reasonable assumption, nor one that a responsible pharmacokineticist or clinician, would make.

200. In his paragraph 197, Dr. Harris asserts that allometric scaling might be used to determine the human dose based upon information obtained in the mouse. While this may be true as a general principle, allometric scaling is not appropriate in the case of the McLeskey publication. Allometric scaling requires the measurement of pharmacokinetic parameters, such as clearance and volume of distribution, in two or three animal species (e.g., rat, dog, monkey) to predict those parameters in a human. Allometric scaling is not done using only one species. Using allometry, pharmacokinetic parameters are determined using the same route of administration, because different routes may result in significant differences in the extent of absorption (bioavailability). The drug is typically given intravenously to avoid complications related to bioavailability (which may differ markedly from one species to another), and measurement of blood plasma levels of the drug is required in order to calculate the pharmacokinetic parameters in that particular species. The pharmacokinetic parameters of the drug in the different species are regressed against body weight on a log-log scale to predict the corresponding parameter in a human. Since McLeskey, who administered the drug

subcutaneously in mice, does not measure any plasma levels of fulvestrant in her mouse model, and reports no pharmacologic effects (toxicity or efficacy) related to subcutaneous administration of fulvestrant, it would be impossible to predict an intramuscular human dose using "formulas based upon known metabolic rates," as Dr. Harris suggests, from the McLeskey publication, or from any prior art preclinical publication. *See* Ex. 1019 (I adopt by reference my opinions on this issue as set forth in the Sawchuk Declaration).

201. The use of a scaling factor of 12.3 that Dr. Harris introduces here comes fundamentally from the work of Freireich et al. (Ex. 1062) who reported that doses that were lethal to 10% of rodents (an LD_{10} dose) were correlated with human maximum tolerated doses when the doses were normalized to the same administration schedule and expressed in terms of milligrams per meter squared of body surface area. Because McLeskey did not report any fulvestrant toxicity in her mice (the dose of 5 mg administered by McLeskey was not an LD_{10}), Dr. Harris has no basis for using this approach for calculating a human equivalent dose, whether or not it is modified by a safety factor. *See* Ex. 1015 ¶ 198. In addition, Dr. Harris ignores the fact that McLeskey used subcutaneous administration in her mice, whereas fulvestrant is administered intramuscularly to humans. These different routes of administration invalidate the calculation of human equivalent doses, simply because one has no information regarding the relative bioavailability

of fulvestrant ***in different species***, given by ***different routes of administration***. Certainly, McLeskey provided no plasma concentration-time data in her report, and therefore discloses nothing regarding the extent of absorption of fulvestrant or the plasma concentration time course of this drug following subcutaneous administration.

202. It is unclear how a person of skill in the art, recognizing that McLeskey administered her oil-based fulvestrant formulations subcutaneously "would know that mice have a much higher and faster metabolism and rate of clearance than humans, ***further supporting that a monthly IM injection would work***." Ex. 1015 ¶ 199 (emphasis added). McLeskey reports no pharmacokinetic data for fulvestrant, and therefore offers no basis upon which to conclude anything regarding the selection of a dosing regimen in mice, let alone in humans. Dr. Harris does acknowledge that there may be differences in the absorption of fulvestrant given subcutaneously vs. intramuscularly, but assumes, without any evidence to support his view, that absorption following a subcutaneous dose would occur more rapidly. Ex. 1015 ¶ 199. Dr. Harris then apparently confuses rate of absorption with extent, stating, without any support "[a] person of skill in the art would consider that a weekly subcutaneous injection in a mouse would be released more rapidly and thus would not start initially with administering four times that dose monthly in a human by IM injection, but rather would start with a lower

dose." Ex. 1015 ¶ 199.

203. Assuming his calculation of a human dose and dosing interval is valid, Dr. Harris goes on and identifies, without explanation, intramuscular dosing regimens for fulvestrant in humans: "Thus, if a person of ordinary skill in the art wanted the dose to be administered monthly by IM injection, starting with a dose of 100 or 250 mg/month is quite predictable and a common step to take in my opinion." Ex. 1015 ¶ 200. Here, Dr. Harris seems to have selected this range of monthly doses to be consistent with that described in Howell. Dr. Harris then goes on to suggest that a person of ordinary skill would determine blood plasma concentrations in the patient to see whether the dose would need to be increased. Ex. 1015 ¶ 200. Importantly, however, Dr. Harris does not indicate what target plasma fulvestrant concentration he is trying to achieve with this increase in dose. Indeed, as discussed extensively above, based upon prior art, ***one of skill in the art would not know what plasma levels of fulvestrant were therapeutically significant and, in fact, the prior art taught lowering the 250 mg dose used in Howell***, so this proposed dosage adjustment would be done entirely without guidance.

204. In his paragraph 207, Dr. Harris, citing only the present-day opinion of another expert, asserts: "one of skill in the art would expect that the 50 mg/ml, castor oil-based formulation disclosed in McLeskey would produce the same or

very similar pharmacokinetics at day 28 if administered in a 5 ml intramuscular injection (as disclosed in Howell) in humans." Ex. 1015 ¶ 207. Since the compositions of the McLeskey formulation and the Howell formulation are not disclosed, the expectation of "the same or very similar pharmacokinetics at day 28" is ***completely unfounded***.

205. Again, citing only the present-day opinion of another expert, Dr. Harris asserts: "a person of skill in the art would have appreciated that both Howell and McLeskey were oil solutions. Thus, at day 28, the anticipated pharmacokinetics from McLeskey would closely mirror the pharmacokinetics reported in Howell." Ex. 1015 ¶ 208. I disagree. To the contrary, a person of skill in the art would not conclude that two different formulations would exhibit similar pharmacokinetics simply because they were both oil-based. Contrary to what Dr. Harris is asserting, a person of skill in the art would have recognized that the exact composition of an oil-based formulation for intramuscular injection, both with respect to the identity of the components and their percent content, can play a significant role in the rates and extent of release of the active drug. *See* Sawchuk Declaration (I adopt by reference my opinions on this issue as set forth in the Sawchuk Declaration (Ex. 1019)). A person of skill in the art recognizes, therefore, that the development of pharmaceutical formulations, whether they be oil-based or aqueous, requires a great deal of testing and evaluation.

206. In his paragraph 209, Dr. Harris asserts that the "difference in route of administration between Howell and McLeskey is among the reasons why one would have a reasonable expectation that the McLeskey formulation would have the therapeutic effect disclosed in Howell" because subcutaneous injections of fulvestrant would be more rapidly absorbed then intramuscular injections. Ex. 1015 ¶ 209. However, Dr. Harris fails to recognize that subcutaneous administration of a drug does not always result in more rapid absorption. There are examples of this in the pharmaceutical literature.

207. For example, a study in sheep using probenecid demonstrated significant differences in the rate of absorption following intramuscular and subcutaneous injections. *See* V.H. Guerrini et al., *Pharmacokinetics of probenecid in sheep*, 8 J. Vet. Pharmacol. Therap. 128 (1985) (Ex. 1042) at 549-556. The absorption of probenecid was found to be ***more rapid following intramuscular injection***, compared to subcutaneous injection. Ex. 1042 at 551-553. The subcutaneous dose was absorbed more slowly, with average plasma levels of the drug peaking at 1.5 hr, compared to 0.67 hr for the intramuscular dose. Consistent with these observations, the rate constant for absorption for the intramuscular dose was 41% greater than for the subcutaneous dose. Ex. 1042 at 554.

208. This example clearly demonstrates that the rate and extent of absorption of a given drug administered by different routes of dosing (e.g.,

subcutaneous vs. intramuscular), and therefore the predictability of pharmacologic effects (even if there were a recognized association between plasma drug levels and efficacy) cannot be known until comparative studies are performed in a suitable animal model.

209. In his paragraph ¶ 210, Dr. Harris refers to the Bergstrom report but does not specify where it is in the Bergstrom report that he is reading. I comment only to note that, as discussed throughout my report, Dr. Bergstrom presents no credible evidence for plasma levels of at least 8.5 ng per ml either at the beginning or the end of any fulvestrant dosing interval, leave alone for at least four weeks, and even if he did, he would have no indication that these levels were therapeutically significant or that a person of ordinary skill would have looked for those values or been motivated to achieve them.

210. Contrary to what Dr. Harris asserts (Ex. 1015 ¶ 211), I see nothing in Dr. Bergstrom's report at paragraph 191 that discusses "the 50 mg/ml castor-oil based formulation of Howell", specific blood plasma concentrations achieved by monthly intramuscular injection, or durations. Further, nothing in Dr. Bergstrom's paragraph 108 addresses "a 69% response rate reported by Howell" (Ex. 1015 ¶ 211). To the contrary, Dr. Bergstrom, in his paragraph 108, is discussing the Burgess Report and the McLeskey formulation. In any event, as discussed above, even the authors of Howell cautioned that the reported response rate had to be

confirmed by further clinical trials and it takes a complete rewrite of Howell to suggest increasing dose or target range—the article itself teaches the opposite (and, in fact, in this regard, also teaches that the "predicted" range could not be confirmed).

211. In general, elsewhere in Dr. Bergstrom's report where he suggests that 8.5 ng per ml serum concentrations of fulvestrant would be therapeutic, Dr. Bergstrom appears to have adopted the definition of "therapeutically significant" levels from the patent. As I have explained above, Dr. Bergstrom has no evidence that these levels were achieved and maintained over the four week period by any patient in the Howell study. In addition, there is nothing in Dr. Bergstrom's report that shows that Howell determined serum concentrations as high as 8.5 ng per ml, either at the beginning or the end of the fulvestrant dosing interval. Furthermore, Howell states that he has ***not found*** a link between pharmacokinetics and pharmacodynamics. *See* Ex. 1007 at 4, at 6. Thus, based on this preliminary study reported in the Howell publication, ***Howell does not—and cannot—disclose what therapeutically significant levels of fulvestrant are***.

212. Although Howell does identify castor oil as the vehicle for the formulation used in this study, Howell does not disclose other components or the composition of the fulvestrant formulation used in his study. Contrary to Dr. Harris's contention (Ex. 1015 ¶ 212), Dr. Bergstrom in his paragraph 109 does not

"explain[] that a person of skill in the art would appreciate that the rate-limiting aspect of the injection in Howell is castor oil."

213. I do not understand how the injection of the castor oil-based fulvestrant vehicle used in Howell could possibly produce blood plasma levels "at ***or above*** the levels specifically reported in Howell." Ex. 1015 ¶ 213 (emphasis added). It is not clear what levels Dr. Harris is referring to, although he appears to have misread Dr. Bergstrom's report. Dr. Harris attributes this statement to paragraph 109 in Dr. Bergstrom's report. In fact, Dr. Bergstrom draws no such conclusion here. Rather, in his paragraph 109, Dr. Bergstrom is discussing why, in his opinion, the bars in Howell Figure 2 do not represent "the range of blood plasma concentration of fulvestrant in patients." Bergstrom ¶ 109.

214. Apparently Dr. Harris (Ex. 1015 ¶ 214) does not recognize that Dr. Gellert, an experienced formulator employed by Astra Zeneca, not only would have had internal knowledge of the inventors' confidential research on the physicochemical properties of fulvestrant and other related molecules, but would also have had access to all of the internal, confidential research results related to fulvestrant and its analogues that had been generated by the inventors. This puts Dr. Gellert in an entirely different position than a person of skill in the art who would be starting from square one to develop a formulation of fulvestrant for use in patients with breast cancer. Indeed, in his declaration, which is not prior art, Dr.

Gellert starts from a very different point than where one of ordinary skill would have started. While the person of ordinary skill would have been starting from scratch, Dr. Gellert, as he explained in his declaration, began with the invention in mind. *See* Ex. 1020 at ¶ 11 ("In about early 2000, ***a person responsible for developing a sustained release injectable formulation suitable for administration to humans for a new steroidal compound such as fulvestrant***, would have had specialized training and experience in developing pharmaceutical formulations and methods for their administration. ***In developing such a formulation for fulvestrant***, the objective would have been to formulate an intramuscular (IM) injection that would provide for the satisfactory sustained release of fulvestrant over a period of at least two weeks and preferably over a period of at least four weeks to reduce the frequency of administration, and would have a target fulvestrant content of at least 45 mg/mL so as to provide a fulvestrant dose of at least 250 mg in a single 5-6 mL injection. ***From my personal experience*** and knowledge of the literature at about that time, I believe that such an experienced formulator would likely have approached the task of developing a formulation for fulvestrant in about the following manner.") (emphasis added)).

215. Without explanation, Dr. Harris opines that "a person of skill in the art would have a reasonable expectation of success in combining the teachings of Howell, McLeskey, O'Regan and DeFriend to achieve therapeutically significant

blood plasma fulvestrant concentrations of its least 8.5 ng per ml for at least four weeks." Ex. 1015 ¶ 216. This is not correct. As an initial matter, none of these four publications cited by Dr. Harris had identified what therapeutically significant blood plasma fulvestrant concentrations were, nor was there any indication in these publications, or in any of the prior art, what the durations were over which these levels should be maintained.

216. Howell showed no association between plasma levels and efficacy in his preliminary study, so there was no indication here that any given concentration, let alone at least 8.5 ng per ml, should be achieved and/or maintained for any amount of time including at least four weeks. In fact Howell expressed concern about the relatively high plasma concentrations he observed in his study resulting from accumulation and potential negative long-term effects, and suggested that lower doses should be used in future studies (Ex. 1007 at 6-7), which AstraZeneca did in subsequent clinical trials (*see* Ex. 1075). Furthermore, Howell did not specifically identify the formulation used in his study.

217. McLeskey used two different oil-based formulations of fulvestrant, which she administered subcutaneously to mice, and which she considered to be interchangeable. She did not fully disclose the composition of the castor oil-based formulation she used, and in her declaration, she indicated that she thought the composition was expressed in terms of % volume by volume. In addition

McLeskey's publication did not report any plasma levels of fulvestrant in her mouse model, so there was no information regarding the rate and/or extent of absorption of fulvestrant in her studies (assuming that fulvestrant was absorbed in the mouse model at all). Furthermore, fulvestrant did not work to slow tumor growth in her mice, perhaps because this model was a hormone-independent model of cancer, or perhaps because fulvestrant was not actually absorbed sufficiently by the subcutaneous route, if at all.

218. O'Regan, using a different model than that employed by McLeskey, studied mice implanted with tamoxifen-stimulated/estrogen-responsive endometrial tumors. O'Regan et al. did not use a castor oil-based formulation of fulvestrant. Rather, she dissolved fulvestrant in ethanol and then administered it to the mice (after evaporating the ethanol) in peanut oil subcutaneously weekly, using the same dosing regimen as McLeskey. O'Regan et al. did not measure serum or plasma levels of fulvestrant in the mice. Thus, O'Regan offers no data regarding a potential kinetic-dynamic link for fulvestrant in mice, let alone in humans.

219. DeFriend conducted a one-week phase 1 study in patients scheduled for breast cancer surgery. The purpose of this study was to assess short-term tolerance, pharmacokinetics, and biological effects in women with primary breast cancer. DeFriend did not attempt to assess efficacy because this was a short term study. The authors used a water-soluble, rapidly acting propylene glycol-based

intramuscular injection of fulvestrant. Patients were dosed at either 6 mg or 18 mg of fulvestrant daily. Serum concentrations of fulvestrant were measured prior to dosing on days 2-7.

220. In summary, because these publications are so diverse in terms of their objectives, methods, and findings, it is my opinion that the teachings of these publications cannot be combined in any meaningful way, let alone to conclude that levels of fulvestrant of 8.5 ng per ml, maintained over a period of four weeks, would provide a person of skill in the art with any reasonable expectation of success of treating patients with breast cancer. The diversity of these publications is summarized below. I also incorporate my earlier discussion of these points above in sections X) and XI) here.

221. Howell and DeFriend are the only publications that involved humans. However Howell's study was several months in length, but DeFriend's study was very short term, only seven days.

222. Howell's study was the only one that involved fulvestrant in an oil-based sustained release formulation in breast cancer patients. And, he failed to find any pharmacokinetic–pharmacodynamic link. DeFriend was assessing short-term tolerability and biological activity (not efficacy) and measured pre-dose serum fulvestrant concentrations following daily dosing with a completely unrelated, rapidly-absorbed formulation.

223. Three of the four studies (Howell, O'Regan and McLeskey) used an oil-based formulation of fulvestrant (either castor-oil based, peanut-oil based or both), but only disclosed the exact formulation employed for the peanut oil formulation.

224. Two of the four studies (McLeskey and Howell) used a castor oil-based formulation of fulvestrant, but neither of these studies disclosed the exact formulation employed.

225. Two of the studies (DeFriend and Howell) used intramuscular dosing of fulvestrant, but DeFriend used an aqueous propylene glycol-based rapidly absorbed formulation, given once a day whereas Howell used a castor oil-based formulation administered monthly.

226. Two of the studies (McLeskey and O'Regan) administered fulvestrant subcutaneously in (very different) mouse models, but neither investigator reported serum concentrations of fulvestrant in their mice.

227. One of the mouse studies (McLeskey) used a peanut oil and a castor-oil based formulation, treating them interchangeably (McLeskey Declaration, para 6), but the other (O'Regan) used a peanut oil-based formulation.

228. One of the mouse studies (McLeskey) used a hormone-independent breast cancer mouse model, but the other (O'Regan) used an endometrial cancer mouse model.

229. Not one of the four studies listed identified therapeutically significant serum or plasma levels or durations, and Howell was the only one that even alluded to this concept—referring to a pre-study "predicted" range. However, Howell failed to identify therapeutically significant serum or plasma levels or durations because this was a preliminary study with too few patients enrolled, and at the 250 mg monthly dose used in Howell resulted in serum concentrations that Howell concluded were too high.

230. In his paragraph 217, Dr. Harris uses the phrase "dose-dependent nature of fulvestrant" without explaining its meaning. Ex. 1015 ¶ 217. Although the phrase "dose-dependent pharmacokinetics" has often been used to suggest that the pharmacokinetics of a drug are nonlinear, it is not clear what Dr. Harris implies with this wording. If he is suggesting that as the dose is increased, so will plasma concentrations increase, this is a qualitative statement that would provide no guidance to one of skill in the art engaged in therapeutic drug monitoring. If, on the other hand, Dr. Harris is suggesting that there is a linear relationship between plasma concentrations and dosing rate as suggested by the data in DeFriend, it does not necessarily mean that employing an extended-release oil-based formulation (rather than a rapid-release propylene glycol-based formulation as used in DeFriend) would result in a similar finding. And, there are simply no data in the prior art that would allow for even considering or analyzing this issue. To suggest

that any biological effects observed with a three-fold increase in dose using a rapid-release formulation would result in a similar outcome, either qualitatively or quantitatively, when doses were increased using an entirely different formulation (e.g., an extended release castor-oil based formulation) is completely speculative and without foundation. Howell does not disclose data analogous to those found in DeFriend and relied on by Dr. Harris. And, in any event, DeFriend provides no firm insight as to the mechanism of the effects of fulvestrant on ER expression in ER-positive tumors. DeFriend does not show how this biological activity is related to efficacy, or how ER expression might be affected by the very different serum concentration-time profiles expected when using extended-release formulations of fulvestrant, or whether ER expression has a significant bearing on therapeutic outcome, if at all.

231. In his paragraph 218, Dr. Harris indicates that a person of skill in the art would want to use higher doses than 250 mg per month (Ex. 1015 ¶ 218)—without recognizing, or perhaps in spite of, the concern that Howell et al. express for the high plasma levels of fulvestrant observed because of accumulation and potential negative long-term effects of fulvestrant during multiple dosing (Ex. 1007 at 6-7). Dr. Harris contends that higher fulvestrant steady state plasma concentrations "would enhance ER downregulation and lead to a more successful treatment because the evidence at the time correlated greater ER downregulation

with superior efficacy." Ex. 1015 ¶ 218. It is not clear to me what evidence Dr. Harris is relying upon to make this statement, as he does not cite any source. Furthermore, Dr. Harris apparently ignores Howell's statement that the plasma levels may be too high, and disregards the caution that Howell expresses regarding the "long-term effects of this agent on bone, plasma lipids and the endometrium." *See* Howell at 306. In this same concluding paragraph, Howell states that "[a]t the dose used, there was accumulation of the drug over time and thus lower doses than those administered in this study may be as effective." Howell at 306. In fact, consistent with this recommendation, the next study performed by Robertson et al. included ***lower doses*** of fulvestrant than those used by Howell, i.e., 50, 125, and 250 milligrams per month. *See* Ex. 1075.[13]

232. Dr. Harris asserts that "as of the year 2000, a person of skill in the art would have expected he or she could successfully increase steady state blood plasma concentrations in several ways." Ex. 1015 ¶ 219. Dr. Harris then suggests this could be done by increasing the monthly dose or by using a loading dose, or a combination of the two. Ex. 1015 ¶ 219. Dr. Harris cites nothing in support of

[13] Dr. Harris also does not account for the fact that 1) no data related to ER activity are presented in Howell, and 2) even if such data were reported in Howell, there is nothing in the prior art to suggest that maximum ER downregulation or even saturation of the ERs was advantageous in any way, or linked to therapeutic efficacy. Absent both 1) and 2), a person of ordinary skill in the art would not have been motivated to take any action on the basis of ER downregulation (or saturation of ER) as that would have amounted to pure speculation.

these assertions.

233. Apparently, Dr. Harris does not understand fundamental pharmacokinetic principles. The use of a loading dose will not have any effect on steady-state plasma levels, although a loading dose, if appropriately chosen, ***may*** hasten the approach to steady state. Implicit in Dr. Harris's statement here (Ex. 1015 ¶ 219) is his contention that one would ***want*** to increase steady-state levels, ***in direct opposition*** to what Howell states, and ***in contrast*** with the lower dose fulvestrant regimens used in the subsequent study by Robertson, as referred to above.

234. Turning to paragraph 220, here, Dr. Harris suggests that doubling the dose of fulvestrant would double the amount of drug absorbed intramuscularly, leading to a proportional increase in the steady-state levels in the blood plasma. Ex. 1015 ¶ 220. Dr. Harris assumes that only absorption—which is only one component of a drug's kinetic profile—is relevant. Clearly, absorption kinetics alone cannot inform whether any given drug exhibits linear kinetics. For example, it is known that many lipophilic drugs are highly bound to plasma proteins. As their plasma concentrations increase (for example, at higher doses), their binding to circulating plasma proteins (e.g., albumin) may become saturated and a greater fraction of the drug in plasma is free (unbound), allowing the drug to be more efficiently cleared (by metabolism and/or renal excretion) from the body. This

results in nonlinear pharmacokinetics, causing an increase in dose to produce a less than a proportional increase in plasma or serum drug concentrations.

235. The higher concentrations of fulvestrant noted by Dr. Harris (Ex. 1015 ¶ 221) at month 6 than at month 1 as observed in Howell is simply a consequence of drug accumulation during multiple dosing. The more important issue, which Dr. Harris fails to recognize, is that under steady-state conditions, the amount of drug absorbed over a dosing interval is essentially equal to, and balanced by, the amount of drug eliminated during that same interval. Therefore, under steady-state conditions, contrary to what Dr. Harris contends, the amount of drug eliminated from the body during a dosing interval is the *same* as that replenished by the next monthly dose. That is why this condition is referred to as a "steady state."

236. Dr. Harris's statements here (Ex. 1015 ¶ 222) further underscore his lack of knowledge of pharmacokinetic principles. He states "[a] person of skill in the art would therefore have expected that, if one were to double the dose of fulvestrant, ***at least double the blood plasma concentrations*** could be achieved . . . ." Ex. 1015 ¶ 222 (emphasis added). Here, Dr. Harris suggests that nonlinear kinetics would be observed, since more than a doubling of the plasma levels would be achieved by doubling the dose. This would imply that either the intramuscular bioavailability of fulvestrant is increased at the higher dose, or the clearance of fulvestrant is decreased as plasma levels are elevated. He then goes on to state that

if the dose were doubled to 500 mg per month, "the C_{min} reflected in FIG 2 of Howell would likewise increase roughly two-fold." Ex. 1015 ¶ 222. Here Dr. Harris is contradicting his assertion of nonlinear pharmacokinetics, indicating that the serum levels produced by doubling the dose would be approximately doubled, not ***more than*** doubled. Dr. Harris's additional assertion that doubling the blood plasma concentrations "would lead to improved efficacy in reducing ER indices" (Ex. 1015 ¶ 222) is entirely speculative, as he provides no evidence to support his contention that ER indices would be reduced with higher steady-state levels of fulvestrant, and furthermore no evidence that this would lead to improved efficacy.

237. Although, as a general principle, a loading dose of a long-acting intramuscular injection may hasten the approach to steady state, Dr. Harris offers no evidence that this would "promote faster reduction of the ER" (Ex. 1015 ¶ 223). Furthermore, Dr. Harris does offer support for any increase in efficacy, even if ER indices were to be reduced more rapidly, or, for that matter support for any connection between efficacy and ER indices reduction. And again, it should be noted that steady-state serum or plasma levels of fulvestrant will not be affected by the use of a loading dose.

238. It is also possible to hasten the approach to steady-state plasma levels of drug by administering the same maintenance dose more frequently during the early phase of multiple dosing, rather than using a loading dose (an initial higher

dose of a drug) as defined by Dr. Harris. *See* Ex. 1015 ¶ 224. However, Dr. Harris offers no evidence to support his assertion that a more rapid approach to steady state would be beneficial in the therapy of patients with fulvestrant (Ex. 1015 ¶ 224) and certainly that suggestion is not found in Howell or any prior art.

239. Dr. Harris points to prior art publications that he asserts indicate that loading doses of aminoglutethamide and tamoxifen allow the attainment of steady state sooner. Ex. 1015 ¶ 226. However, whether or not a more rapid attainment of steady-state levels of fulvestrant would be beneficial in the therapy of patients was not known in January of 2000, and Dr. Harris provides no evidence to that effect. In fact, H.K. Adam, the author of Chapter 10 cited here by Harris (Ex. 1015 ¶ 226, citing H.K. Adam, *Pharmacokinetics of Agents in Relation to Response*, *in Endocrine Management of Cancer: Biological Bases* 112 (Stoll ed., 1988) (Ex. 1082) ("Adam")), focuses on this dilemma. At the end of his chapter, Adam underscores the complexity in the relationship between drug levels and clinical response in endocrine therapy by stating ". . . the present state of knowledge in the field of endocrine agents is such that the clinical pharmacologist can provide input on frequency of dosing, ***time to steady state*** and activity of metabolites, ***but not the sort of detailed information possible, for example, in the cardiovascular field***. Here, good correlations between heart rate or blood pressure and drug concentrations have been established, and precise titration of drugs on individual

subjects is achievable." Ex. 1082 at 21-22 (emphasis added).

240. Regarding the publication by Wilkinson et al. (*see* Ex. 1015 ¶ 226, citing P.M. Wilkinson et al., *Tamoxifen (Nolvadex*) Therapy—Rationale for Loading Dose Followed by Maintenance Dose for Patients with Metastatic Breast Cancer*, 10 Cancer Chemother. Pharmacol. 33 (1982) (Ex. 1086) ("Wilkinson")), these authors observed that, in view of an observed delay in reaching steady-state serum concentrations using the dose of 10 mg of tamoxifen twice daily, "[i]t was suggested that a loading dose followed by a maintenance dose could overcome this delay in reaching steady state and might induce more rapid clinical response." Ex. 1086 at 1. The authors compared three loading dose regimens over a period of approximately four weeks, noting the time course of serum levels of tamoxifen and its active metabolite, and observed that some of these levels were actually in excess of the final steady-state values. However they reached no conclusions regarding whether or not these loading dose regimens induced a more rapid clinical response. Rather, they suggested that one of the regimens studied "could be used in the context of a clinical trial." Ex. 1086 at 3.

241. With regard to Dr. Harris's citation of the paper by Robertson, I note that this was published in 2007, and therefore would not have been available to a person of skill in the art as of January 2000. Ex. 1015 ¶ 226 (citing Robertson, *Fulvestrant (Faslodex®)—How to Make a Good Drug Better*, 12 Oncologist 774

(2007) (Ex. 1090)).

242. The paper by Goldenberg cited by Dr. Harris (Ex. 1015 ¶ 227 (citing Goldenberg, *Trastuzumab, a Recombinant DNA- Derived Humanized Monoclonal Antibody, a Novel Agent for the Treatment of Metastatic Breast Cancer*, 21 Clin. Ther. 309 (1999) (Ex. 1085)) describes the use of trastuzumab, a monoclonal antibody, in the treatment of patients with breast cancer in a phase 2 trial. This drug, unlike fulvestrant, does not interact with the estrogen receptor. It specifically targets the human epidermal growth factor receptor 2 (HER2). Ex. 1085 at 1. In one study described by Goldenberg, patients received an intravenous loading dose of trastuzumab, followed by weekly intravenous doses of the drug. Ex. 1085 at 5. The patient response rate was 14%, with a 2% complete response rate and a 12% partial response rate. Ex. 1085 at 6. Because there was no treatment group that received only the weekly maintenance doses without a loading dose, it is not possible to assess the effect of a loading dose on clinical response from this study.

243. The publication by Baselga (*see* Ex. 1015 ¶ 227 (citing Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14 J. Clin. Onc. 737 (1996) (Ex. 1083)) referred to by Harris describes the use of a monoclonal antibody that interacts with a growth factor receptor, not the estrogen receptor. In this study, 46 patients received this antibody

as a loading dose (250 mg) followed by 10 weekly doses of 100 mg, intravenously. Ex. 1083 at 1-2. Once more, there was no control arm in which patients received only the weekly doses, with no loading dose. Ex. 1083 at 2. From the results of this prior art publication, it is therefore not possible to assess the role of the loading dose in affecting clinical response of the study patients. However, the authors did note that, shortly after the administration of the loading dose, three patients experienced chest pain, and one of these required an overnight hospital admission for pain control. Ex. 1083 at 3. Dr. Harris does acknowledge that in certain cases a loading dose or increased dose may not be advantageous because it may produce severe side effects. Ex. 1015 ¶ 227. However, without explanation, he contends that "such was not the case with fulvestrant." Ex. 1015 ¶ 227. I do not know the foundation for Dr. Harris's assertion in this regard, as I am unfamiliar with any prior art publication in which the clinical effect of a loading dose or an increased dosing rate for fulvestrant was assessed clinically.

244. I disagree with Dr. Harris's contentions in his paragraph 228. DeFriend ***did not show*** any "successful result" in patients, nor did DeFriend's study have this as an objective. In fact, DeFriend did not teach "increasing each monthly dose" nor did DeFriend teach "using a loading dose" as Dr. Harris suggests. Ex. 1015 ¶ 228. Those words are simply not even stated in the text of DeFriend. Again, the study reported in DeFriend used daily doses of a rapid-

release formulation of fulvestrant, administered for only one week. There was no dosage adjustment in individual patients. This was a short-term, parallel group, study in which patients were assigned to receive *either* 6 mg *or* 18 mg daily, without a dosage adjustment, and without a loading dose. Since DeFriend administered daily doses using a water-soluble, rapidly absorbed, propylene glycol-based formulation of fulvestrant, one would be unable to use the results of the study in DeFriend to predict serum levels of fulvestrant in patients dosed intramuscularly every four weeks with an entirely different dosage form—an extended-release, oil-based formulation of this drug. And furthermore, because there was no relationship between serum levels of this drug and clinical outcome, one of skill in the art would be unable to know that "higher blood plasma levels of fulvestrant"—***if produced***—"would increase reduction of the ER indices" as Dr. Harris suggests. Ex. 1015 ¶ 228, or, whether, most importantly, that they would result in enhanced therapy of breast cancer patients, as Dr. Harris implies.

245. Again, in his paragraph 230, Dr. Harris asserts, without support, that "if either a higher dose or a loading dose were used, the blood plasma concentrations of fulvestrant would be significantly higher than what was reported in Howell Figure 2." Ex. 1015 ¶ 230. If Dr. Harris is referring to the data in month 6 in figure 2 of Howell, he again demonstrates that he does not understand that the loading dose would have no impact on plasma levels of fulvestrant under

steady-state conditions. With regard to Dr. Harris's unsupported contention that Figure 2 in Howell includes data from patients who received only 100 mg during month 1, he appears to suggest that this would have an impact on the mean plasma levels during month 6 following conversion after the first month to a 250 mg per month regimen, I disagree. Dr. Harris completes his thought by mistakenly asserting "[w]ith a loading dose, the blood plasma concentrations of fulvestrant in a greater number of patients would have achieved at least 8.5 $ngml^{-1}$ for an entire 4-week period." Ex. 1015 ¶ 230. Dr. Harris's statement indicates that he assumes that ***some patients*** in Howell exhibited plasma levels of at least 8.5 ng/ml, and yet he offers ***no evidence*** to support this contention (certainly the text of Howell does not state that and in fact indicates just the opposite, for example in Figure 2 (Ex. 1007)). Furthermore, as indicated previously, one of skill in the art would recognize that a loading dose administered at the beginning of treatment would not have any significant effect on levels measured during month 6, or during steady state.[14]

246. Accordingly, for these reasons, I do not agree with Dr. Harris's opinion that "a person of ordinary skill in the art would have been both motivated to apply the teachings of McLeskey to Howell, or McLeskey and O'Regan to

[14] I also note that a person of ordinary skill in the art would have assumed steady state was reached by month six given that the authors use the data from month six to make suggestions regarding future clinical studies including those involving lower doses.

Howell, or McLeskey, O'Regan and DeFreind [sic] to Howell and further would have had a reasonable expectation of success that the combination could be used for using the claimed formulation in the claimed amounts as taught in the asserted claims to treat hormone dependent breast cancer in humans." Ex. 1015 ¶ 231.

247. In her paragraph 187, Dr. Burgess asserts: "[h]ere, Howell 1996 confirms that an adequate minimum serum concentration of fulvestrant can be maintained by once-monthly injection of a castor oil-based fulvestrant solution with a fulvestrant concentration of 50 mg/ml." Ex. 1012 ¶ 187. I do not understand what Dr. Burgess means by "adequate." This is not defined, and there is no way of knowing what levels are therapeutic. Howell makes it clear that there is ***no kinetic-dynamic link*** that he was able to identify, and that raises the question as to what adequate levels of fulvestrant are. *See* Howell at 305. Howell discusses previous data from a phase 1 study and from a monkey study indicating that concentrations of 2 to 3 ng per ml ***may be*** therapeutic, but he clearly represents this as a prediction, and in any event, Howell acknowledges that the 250 mg dose used in his study was too high and then suggests going down in dose because of accumulation and safety concerns. Howell at 305. Clearly, at this stage of development of the drug, there was ***no*** indication as to what plasma levels of fulvestrant were "adequate."

248. Dr. Burgess, citing the present-day expert opinions of Dr. Bergstrom

and Dr. Harris, that "based on the results in Howell 1996, a POSA would know that fulvestrant has a large therapeutic window and would target the upper end of this window." Ex. 1012 ¶ 187. Regarding Dr. Bergstrom, as an initial matter, I note that he does not state in his paragraph 87 that "fulvestrant has a large therapeutic window and that therefore one would target the upper end of this window" as Dr. Burgess appears to suggest. On the contrary, Dr. Bergstrom, in his paragraph 87, cites a passage from Howell who expresses concern about untoward accumulation of drug levels, and suggests that lower doses may be effective.

249. But in any event, there was nothing in Howell, or in the prior art, that defined a "therapeutic window" for fulvestrant. Therefore one would not know how to "target the upper end of this window" as Dr. Burgess suggests. Ex. 1012 ¶ 187. In addition, neither Dr. Harris nor Dr. Bergstrom refers to a "therapeutic window" for fulvestrant.

250. Dr. Burgess contends that the high concentrations observed during the early part of a dosing interval are of no concern to a skilled formulator. Ex. 1012 ¶ 187. It is not clear how she reaches this conclusion, but it is inconsistent with Howell's final cautioning statement regarding potential long-term adverse effects related to high serum concentrations of fulvestrant. *See* Ex. 1007 at 7.

251. Finally, Dr. Burgess's reference to Howell as indicating that there was "no toxicity" observed (Ex. 1012 ¶ 187) is, to the extent her statement is accurate,

merely a reflection of the relatively short-term nature of the preliminary study reported in Howell. But again, Howell's concern about long-term exposure and potential adverse effects related to bone, plasma lipids, and the endometrium ***is stated clearly*** in the last paragraph of the publication. *See* Ex. 1007 at 7. Thus, Howell states that lower doses than those administered in his study may be as effective, and may avoid exposure to higher than necessary fulvestrant levels. Ex. 1007 at 7.

XIII) CONCLUSION

252. For the foregoing reasons, it is my opinion that InnoPharma has not shown a reasonable likelihood that claims 1-3 and 6 of the '680 Patent are unpatentable.

* * *

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Dated: June 7, 2017

Ronald J. Sawchuk

Ronald J. Sawchuk, Ph.D.

EXHIBIT A

RONALD J. SAWCHUK, Ph.D.

PERSONAL DATA

Home Address:	14934 Pixie Point Circle SE
	Prior Lake, MN 55372
	Telephone: (952) 226-6507
	E-mail: sawch001@umn.edu
Born:	May 29, 1940, Toronto, Ontario, Canada
Marital Status:	Married, three children
Citizenship:	Dual: U.S. and Canadian

EDUCATION

1959	(High School)	Oakwood Collegiate Institute, Toronto
		Secondary School Grade XIII)
1963	B.Sc. Phm.	University of Toronto, Toronto
		Ontario College of Pharmacy Licentiate No. 10748
1966	M. Sc. Phm.	University of Toronto, Toronto
1972	Ph.D.	University of California, San Francisco
		Pharmaceutical Chemistry (Pharmacokinetics)

PROFESSIONAL AND ACADEMIC EXPERIENCE

1963 - 1965	Teaching Assistant, University of Toronto
1966	Community Pharmacist (part-time), Toronto
1966 - 1968	Teaching Assistant, University of California
1971 - 1972	Instructor in Pharmaceutics, University of Minnesota
1972 - 1977	Assistant Professor of Pharmaceutics, University of Minnesota
1977 -1983	Associate Professor of Pharmaceutics, University of Minnesota
1974 - 1982	Associate Director, Clinical Pharmacokinetics Laboratory, U of Minnesota
1982 - 1995	Director, Clinical Pharmacokinetics Laboratory, College of Pharmacy, U of Minnesota
1983 - 2010	Professor of Pharmaceutics, University of Minnesota
1983 - 1989	Director of Graduate Studies in Pharmaceutics, University of Minnesota
1983 - 1986	Acting Head, Department of Pharmaceutics, University of Minnesota
1984 (summer)	Quarter Leave, Sandoz Pharma, Pharmacokinetics and Drug Metabolism Dept., Basel, Switzerland (M. Lemaire)
1991 - 1994	Director of Graduate Studies in Pharmaceutics, University of Minnesota
1992 (Summer)	Quarter Leave, Sandoz Pharma, Drug Safety, Basel, Switzerland (W. Niederberger)
1996 - 1999	Member, Board of Directors, Century Mortar Club
1997 (Spring)	Semi-Quarter Leave, Toyama Medical and Pharmaceutical University, Japan (H. Sato)
1997 (Summer)	Semi-Quarter Leave, Novartis AG, PKDM, Basel, Switzerland (J. Vonderscher)
1998 - 1999	Head, Department of Pharmaceutics, University of Minnesota
2001 (Summer)	Faculty Development Leave, Novartis AG, PKDM, Basel, Switzerland (M. Lemaire)
2010 - present	Professor Emeritus of Pharmaceutics, University of Minnesota
2010 - 2014	Research Professor, Part-time, Pharmaceutics, University of Minnesota
2015- present	Adjunct Professor of Pharmaceutics

APPOINTMENTS AND PROFESSIONAL RESPONSIBILITIES

1972 - present	Member, Graduate Program in Pharmaceutics, University of Minnesota
1982 - present	Consultant to the pharmaceutical industry
1995 - present	Director, Bioanalytic and Pharmacokinetic Services, University of Minnesota
1995 - present	Editorial Board, *Saudi Pharmaceutical Journal*
1996 - 2007	Editorial Board, *Journal of Pharmaceutical Sciences*
1996 - present	Member, Graduate Program in Neurosciences, University of Minnesota
2001 - present	Member, Graduate Program in Experimental and Clinical Pharmacology, U of M
2002 - present	Member, Graduate Program in Social, Administrative and Clinical Pharmacy, U of M
2008 - present	Editorial Advisory Board, *AAPS Journal*
2009 - present	Editorial Board, *Xenobiotica*

OTHER PROFESSIONAL ACTIVITIES

Prepared two videotapes on "Pharmacokinetics" for undergraduate instruction, 1974
Co-editor of a book with James Blanchard, Ph.D. and B.B. Brodie, Ph.D., entitled "Principles and Perspectives in Drug Bioavailability." S. Karger, Publisher, 1979
Assistant Director, Clinical Pharmacokinetics Laboratory, 1974-82
Consultant in the Establishment and Implementation of the Drug Quality Assurance Program, United Hospitals, St. Luke's Division, St. Paul, 1975
Participant in Critical Incidents Workshop, PDI - College of Pharmacy, 1977
Assessor in the Pharmacy Assessment Exercises, 1978
Coordinator for Continuing Education in Pharmacy, TV Series 1978, 1980
Expert, Bureau of Drugs and Biologics, Food and Drug Administration, 1982-84
Screening Committee, Abstracts, Basic Pharmaceutics Section, APS, APhA, 1981
Review of Grants, Medical Research Council (Canada) 1980-86
Review of Grants, British Columbia Health Care Foundation, 1981-84
Advisory Consultant, Site Visit Team NIH (NINCDS) Yale University School of Medicine, October 1979
Member, Site Visit Team NIH (NINCDS) University of Utah School of Medicine, January 1983
Member, Special Pharmacology Study Section NIH, April-June 1988
Review of Grants, Idaho State Board of Education, 1989-91
Review of Grants, Greater Minnesota Corporation, 1990-91
Organizer and Symposium Co-Chair, "Microdialysis in Drug Metabolism and Disposition Studies", for the Annual AAPS Meeting, San Antonio TX, 1992
Symposium Co-Chair, "Kinetic and Dynamic Challenges of the 90's", for the Annual AAPS Meeting, San Diego, CA, 1994
Organizing Committee Member for the NATO Advanced Study Institute, "Pharmacokinetics: From Theory to Practice", Erice, Italy, April 5-16, 1994
Co-organizer and Participating Instructor, "Pharmacokinetics for the Pharmacist and Pharmaceutical Scientist" University of Milan, Varese, September 10 -15, 1995.
Member, Board of Directors, Century Mortar Club, 1996-present.
National Advisory Committee, FAMU RCMI Program, Tallahasse, FL 1996-present
Co-organizer and Participating Instructor, "Pharmacokinetics for the Biomedical and Pharmaceutical Scientist", University of Milan, Varese, September 7 -12, 1997.
Scientific Advisory Committee, 1st Symposium on Microdialysis and Pharmacokinetics, Leiden, The Netherlands April 1998
Organizer and Participating Instructor, "Pharmacokinetics for the Biomedical and Pharmaceutical Scientist", University of Malta, Msida, September 6 -15, 1998.
Founder, Microdialysis Focus Group, American Association of Pharmaceutical Scientists, 1998.
Scientific Advisory Committee, 2nd International Symposium on Microdialysis in Drug Research and Development, Stockholm, Sweden, June 2000
Chair, Microdialysis Focus Group, American Association of Pharmaceutical Scientists, 1998-2000.
Co-Chair, Organizing Committee, 3rd International Symposium on Microdialysis in Drug Research and Development, Minneapolis, MN, USA, June 2002
Visiting Professor, Guilin Medical College, Guilin PRC (2002-2007)
Scientific Advisory Committee, 4th International Symposium on Microdialysis in Drug Research and Development, Vienna, Austria, June 2004

Scientific Advisory Committee, Abbott Laboratories, for the FDA Critical Path Initiative, September 2004
Scientific Advisory Committee, 5th International Symposium on Microdialysis in Drug Research and Development, Leiden, The Netherlands, June 2006
GLP-1 Scientific Advisory Panel, Medtronic, Minneapolis, MN, April 2009-present

CURRENT AND PAST MEMBERSHIP IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

American Association of Pharmaceutical Scientists (Fellow)
American Association for the Advancement of Sciences (Fellow)
American Pharmacists Association (APhA)
American Society for Pharmacology and Experimental Therapeutics
International Society of Anti-Infective Pharmacology
International Society for the Study of Xenobiotics
Technology Park, Heidelberg, Germany
Century Mortar Club (Board of Directors, 1996-98)
Rho Chi Honor Society

SCHOLARSHIPS, HONORS AND AWARDS

1964	Scholarship, Canadian Foundation for the Advancement of Pharmacy
1965-66	National Research Council of Canada
1965	Warner-Lambert Research Fellowship
1968-70	National Institute of Health (NIH) Training Grant
1981-82	Teacher of the Year, College of Pharmacy, University of Minnesota
1986	Recipient of Horace T. Morse-Amoco Foundation Award
1988	Fellow, American Association of Pharmaceutical Scientists
1990	Fellow, American Association for the Advancement of Sciences
1996	Hallie Bruce Memorial Lecture Award
1997	Fellowship, Japanese Society for the Promotion of Science
1999	Meritorious Manuscript Award, American Association of Pharmaceutical Scientists
2001	Weaver Medal of Honor
2004	Distinguished Lecture, Creighton University School of Pharmacy and Health Professions
2005	Academy of Distinguished Teachers, University of Minnesota
2006	Distinguished Lecture, Temple University School of Pharmacy
2007	APhA Research Achievement Award in the Basic Pharmaceutical Sciences

COMMITTEE APPOINTMENTS

COLLEGE OF PHARMACY

1972-73, 1973-74	Student American Pharmaceutical Association Minnesota Chapter (Faculty Advisor)
1972-75	Student Admissions and Academic Standing Committee, College of Pharmacy
1972-73	Task Force on College of Pharmacy Organization
1973-74	Continuing Education Committee
1972-78	Admissions Committee for Pharm.D. Program, College of Pharmacy (Chair 1973-74; 1977-78)
1974-75	University of Minnesota Health Sciences B/C Implementation Committee
1974-77	Constitution and By-laws Committee
1974-75	Unit K Committee, Graduate School
1975-76	Task Force on Pharm.D. Admissions
1976-78	Professional Education Committee
1977-78	Task Force on Travel
1977-78	Anatomy, Physiology, Pathology Study Group
1977-78	Drug Product Design and Evaluation Study Group
1976-78	Search Committee for Biopharmaceutics Faculty Member
1977-78	Search Committee for Assistant Director HCMC
1977-78	Search Committee for Research Associate, CEP Project D-1 (Chairman)
1978-79	Pharm.D. Program Planning Committee (Chairman)
1978-79, 1979-80	Computer Systems Committee (Chairman)
1979-80	Professional Education Committee (Chairman)

1980-81	Educational Policy Committee (Chairman)
1980-82	Externship Committee
1981-82	Academic Standing Committee
1981-83	Health Sciences Policy and Review Council
1981-82	Graduate Faculty Nominations and Course Proposals Committee
1982-83	Academic Standing Committee (Chairman)
1982-83	Advisory Committee on Animal Care Facilities
1983-85	Council of Directors of Graduate Studies
1982-83	Task Force on Computers
1983	Search Committee for Department Chairman (Chairman)
1983	Search Committee for Clinical Faculty at HCMC
1984	Ad Hoc Committee on External Pharm.D. Program
1984	Executive Committee (Chairman)
1984	Search Committee for Dean of College of Pharmacy
1984	Search Committee for Psychiatry Position, St. Paul-Ramsey Medical Center
1984	Search Committee for Clinical Faculty at Hennepin County Medical Center
1985	Endowed Chair in Pharmaceutics Search Committee (Chair)
1985	Assistant Professor in Pharmaceutics Search Committee (Chair)
1985	Appointments, Promotion and Tenure Committee
1985	Space Committee
1985	Clinical Assistant Professor (MMC) Search Committee
1985-89	Executive Committee
1986-87	Appointments, Promotion and Tenure Committee (Chair)
1986-90	Educational Policy Committee
1986-87	Subcommittee of Educational Policy Committee
1986	Search Committee for Endowed Chair (Chair)
1986-87	College of Pharmacy Strategic Planning Committee
1986-87	Subcommittee of Strategic Planning Committee to Develop College Goals and Objectives
1987-90	Continuing Pharmacy Education Advisory Committee (Chair)
1987-88	Admissions Committee
1988-89	Admissions Committee (Chair)
1989-91	Promotion and Tenure Committee
1991-92	Promotion and Tenure Committee (Chair-Elect)
1991-92	General Research Support Committee
1992-93	Promotion and Tenure Committee (Chair)
1992-93	General Research Support Committee
1993-94	Academic Standing Committee (Chair-Elect)
1994-95	Academic Standing Committee (Chair)
1994-98	College Computer Committee
1995-96	Promotion and Tenure Committee
1995-96	Internal Organization and Leadership Task Force
1996-97	Non-traditional Pharm.D. Task Force
1997-98	Search Committee for Endowed Chair in Geriatric Pharmacotherapy
1997-98	Admissions Committee
1997-98	Search Committee for Immunotherapy Faculty Position (Chair)
1998-2000	Search Committee for Pharmaceutics Faculty Position
2000-2001	Educational Policy Committee
2001-2002	Search Committee for ECP Faculty Position
2001-2002	Educational Policy Committee (Chair)
2001-2002	Search Committee for Pharmaceutics Faculty Position
2001-2002	College of Pharmacy Phar. Sci. 2020 Committee, Capital Campaign (Co-Chair)
2001-2004	College of Pharmacy Faculty Consultative Committee
2002-2003	Educational Policy Committee (Past Chair)
2002-2003	College of Pharmacy Collegiate Review Committee (Chair)
2002-2003	College of Pharmacy Central Council (Faculty Representative)
2002-2003	College of Pharmacy Instructional Development Working Group for the Duluth Expansion
2003-2005	Search Committee for Pharmaceutics Faculty Position at UMD (Chair)
2004-2007	College of Pharmacy Assessment Committee
2005-2006	Search Committee for Endowed Chair in Geriatric Pharmacotherapy

2006-2007 Search Committee for Pharmaceutics Faculty Position

UNIVERSITY COMMITTEE APPOINTMENTS

1974-78	Subcommittee on Academic-Industrial Interface, Academic Relations Committee, 3M Technical Forum
1975-76	Health Sciences Primary Health Care Program Committee (Alternate), Solicitor for the University of Minnesota Consolidated Fund Drive
1977-78	Alternate Senator (U. of Minnesota)
1978-81	Senator (U. of Minnesota)
1984-85	Health Sciences Learning Resources Committee
1986	College Delegate to All-University Single Quarter Leave Working Group, Academic Affairs
1989	Health Sciences Policy and Review Council, Graduate School
1989-91; 1991-93	Biological Sciences (formerly Plant and Animal Sciences) Policy and Review Council, Graduate School
1991-93	Graduate Faculty Nominations Subcommittee, Biological Sciences Policy and Review Council, Graduate School
1992-93	Graduate Faculty Nominations Subcommittee (Chair), Biological Sciences Policy and Review Council, Graduate School
1995-1998	Biological Sciences Policy and Review Council, Graduate School
1997-98	Faculty Research Development Proposal Review Committee for the Academic Health Center
2001-2004	Academic Health Center Faculty Consultative Committee
2001-2002	SCFP Subcommittee on Twin Cities Facilities and Support Services (STCFSS)
2003	AHC Seed Grant Review Committee
2003	AHC FCC Internal Screening Committee for Academy of Excellence Nominees
2004-2007	All-University Honors Committee, University of Minnesota

STATE, NATIONAL, AND INTERNATIONAL COMMITTEE APPOINTMENTS

1974-76	Representative to AACP Council of Faculties
1977-78	AACP Task Force on Guidelines for Pharm.D. Accreditation
1980-82	Academic Advisory Committee, Kellogg Pharmaceutical Scientist Program
1981	Screening Committee for Academy of Pharmaceutical Sciences, Basic Pharmaceutics Section
1989-present	Member, Scientific Committee, International Pharmaceutical Technology Symposium (FIP)
1990	Academic Affairs Committee, AACP (Member)
1990	Program Committee, Controlled Release Society Annual Meeting (Member)
1989-91	Continuing Education Committee, State Board of Pharmacy (Member)
1990-95	USP Committee of Revision (Member)
1991-93	NIH/NINDS Antiepileptic Drug Development Program (Consultant)
1995	Fellows Nominations Committee for AAPS, PPDM Section
1995	Screening Committee for AAPS PPDM Section Abstracts
1997-2000	Fellows Nominations Committee for AAPS, PPDM Section
1999-2000	Committee on AAPS Section Structure and Procedure Guideline
2000-2001	PPDM Vice Chair, American Association of Pharmaceutical Scientists
2000-2002	Co-Chair, Organizing Committee, 3rd International Symposium on Microdialysis in Drug Research and Development
2001-2002	PPDM Chair Elect, American Association of Pharmaceutical Scientists
2001-2002	Annual Program Planning Committee, American Association of Pharmaceutical Scientists
2001-2002	Program Coordinating Committee, American Association of Pharmaceutical Scientists
2002-2003	PPDM Section Chair, American Association of Pharmaceutical Scientists
2002-2003	PPDM Committee for Graduate Student Symposium Awardees, American Association of Pharmaceutical Scientists
2002-2003	Short Course Program Review Team, American Association of Pharmaceutical Scientists
2003-2004	PPDM Section Past-Chair, American Association of Pharmaceutical Scientists
2004-2007	Member-at-Large, American Association of Pharmaceutical Scientists Executive Council
2004-2006	Clinical and Operational Working Group (CORWG), NASA
2004-2005	AAPS Executive Council Liaison to the Clinical Sciences section of AAPS
2005-2006	AAPS Executive Council Liaison to the DDD section of AAPS
2005-2006	AAPS Executive Council Liaison to the PDD section of AAPS

2005-2006	AAPS Executive Council Liaison to the 2006 Annual Meeting Program Committee
2005-2006	AAPS Executive Council Liaison to the 2006 Annual Meeting Screeners
2005-2006	AAPS Executive Council Liaison to the 2006 Program Coordination Committee
2006	AAPS Reference Resources Task Force
2006-2007	AAPS Executive Council Liaison to the APQ section of AAPS
2006-2007	AAPS Executive Council Liaison to the PT section of AAPS
2006-2007	AAPS Executive Council Liaison to the International Affairs Committee
2009-2011	Epilepsy NINDS Steering Committee
2009-2011	NINDS Consortium to Study Bioequivalence of AED Products

INVITED PRESENTATIONS

Continuing Education Program (6 hours) Minneapolis, MN, 1973.
Upper Midwest Hospital Conference, 1974.
Continuing Education Program (6 hours) Rochester, MN, 1974.
University of Illinois, Chicago, IL, 1974.
Department of Clinical Pharmacology, University of Minnesota, 1974.
AACP Annual Meeting and Teachers' Seminar (Workshop Leader), Lake Kiamesha, NY, 1975.
Debate Symposium, "Drug Product Selection," St. Paul, MN, 1977.
Continuing Education for Minneapolis Veteran Pharmacists (2 hours), Minneapolis, MN, 1978.
Continuing Education in Pharmacy (2 hours), Mankato, MN, 1978
Continuing Education in Pharmacy "Seminar at Sea" (4 hours of instruction), 1978.
HPLC Workshop, Invited Lecturer, Bloomington, MN, 1978.
University of Kentucky, Lexington, KY, 1979.
American Association of Clinical Chemists, Midwest Section, Minneapolis, MN, 1979.
University of Illinois, Chicago, IL, 1979.
Smith Kline Corp., Philadelphia, PA, 1979.
Department of Pathology, St. Cloud Hospital, St. Cloud, MN, 1979.
Comprehensive Epilepsy Program, Minneapolis, MN, 1979.
University of North Carolina, Chapel Hill, NC, 1979.
Burroughs Wellcome Co., Research Triangle Park, NC, 1979.
St. Paul-Ramsey Medical Center, St. Paul, MN, 1989.
Continuing Education in Pharmacy (4 hours) Minneapolis, MN, September-October, 1981.
Medical Research Council of Canada, Visiting Professor, University of British Columbia, Vancouver, 1982.
Invited Lecturer, National Institutes of Health, Epilepsy Branch, Bethesda, MD, 1982.
Geriatric Research, Education and Clinical Center, Bloomington, MN, September, 1982.
Continuing Education in Pharmacy (6 hours), Duluth, MN, September, 1982.
Ciba-Geigy, Pharmaceuticals Division, Ardsley, December 2, 1982.
Swiss Federal Institute of Technology, Zurich, Switzerland, June 19, 1984.
Biopharmacy Division, Sandoz AG, Basel, Switzerland, June 22, 1984.
Biopharmacy Division, Sandoz AG, Basel, Switzerland, July 24, 1984.
"Cyclosporine Pharmacokinetics in the Rabbit: In Vivo Disposition and In Situ Absorption Studies," Rhone-Poulenc Visiting Professor, University of Toronto, Ontario, February 5, 1985.
"Pharmacokinetics and Pharmacodynamics," Drug Therapy Symposium VI, St. Paul, MN, February 27, 1985.
"Absorption and Disposition Studies with Cyclosporine," Sandoz, AG, Basel, Switzerland, July 15, 1985.
"Absorption of Cyclosporine from Rabbit Small Intestine Using an In Situ Perfusion Model," Vorstand des Instituts fur Pharmazie U. Lebensmittlechemie der Ludwig-Maximilians-Universitat, Munich, West Germany, July 17, 1985.
"Analytic considerations in the Investigation of the Pharmacokinetics of Cyclosporine," Medizinischen Hochschule, Hanover, West Germany, September 11, 1985.
"Mixed-Order Absorption of a Sustained Release Carbamazepine Tablet in Humans," Institut fur Pharmazeutische Technologie der Johann Wolfgang Goethe-Universitat, Frankfurt am Main, West Germany, May 15, 1986.
"Simultaneous First- and Zero-order Absorption of Commercial Carbamazepine Tablets," 5th Symposium on Biopharmaceutics and Pharmacokinetics, Piestany, Czechoslovakia, May 22, 1986.
"Simultaneous First- and Zero-order Absorption of Tegretol in Human Volunteers," National Institutes of Health, Epilepsy Branch, NINCDS, Bethesda, MD, November 6, 1986.
"Comparison of Plasma AUCs using the Traditional Point-by-Point and Pooled Sample Methods: Application in the Analysis of Human Pharmacokinetics of Carbamazepine and its metabolites," Food and Drug Administration, Rockville, MD, July 20, 1987.

"Pharmacokinetics in Contemporary Pharmacy Practice," Minneapolis Veteran Pharmacists Association, Richfield, MN, September 15, 1987.

"The Absorption and Disposition Kinetics of Carbamazepine and its Metabolites in Humans," Ciba-Geigy, Summit, NJ, July 23, 1987.

The following four lectures were given in Beijing, Chengdu, and Guilin, China during a visit sponsored by the Chinese Academy of Medical Sciences in late October/early November 1987:

1. "Theory and Application of a Pharmacokinetic Model in Individualizing Dosing Regimens for the Aminoglycosides."
2. "First- and Zero-order Absorption of Carbamazepine from Commercial Tablets in Epileptic Patients and Normal Volunteers."
3. "Significance of Nonlinear Disposition Kinetics in the Adjustment of Dosing Regimens."
4. "Relative Bioavailability of Phenytoin Formulations: Problems in Assessment Due to Michaelis-Menten Elimination Kinetics."

"Does Tegretol need to be Dosed TID?" Comprehensive Epilepsy Program, Minneapolis, MN, March 21, 1988.

"The Kinetics of Absorption of Carbamazepine (Tegretol) and its Metabolism in Humans," Vorstand des Instituts der Pharmazie, Ludwig-Maximilians Universitat, Munich FRG, June 8, 1988.

"Pharmacokinetic and Physiologic Considerations in Oral Controlled Drug Delivery," Novel Drug Delivery Symposium, Minneapolis, MN, September 20, 1988.

"Clinical Applications of the Two-Compartment Open Model," Regional Kidney Disease Program, Hennepin County Medical Center, Minneapolis, MN, November 16, 1988.

The following five lectures were presented in a Continuing Education in Pharmacy Program: "Concepts and Applications in Pharmacokinetics, Parts I and II"; "Therapeutic Response and Toxicity"; "Monitoring Drug Therapy"; and "Bioavailability and Bioequivalence", St. Thomas, Virgin Islands, March 8-13, 1989.

"The Pharmacokinetics of Zidovudine (AZT) with Some Observations on the Interaction with Probenecid," Queen's University of Belfast, Belfast, North Ireland, June 15, 1989.

"Pharmacokinetic and Analytical Considerations in Monitoring Zidovudine (AZT) Levels in Children with Aids," Fourth International Congress on Pediatric Laboratory Medicine, Washington, DC, August 23, 1989.

"Inhibition of Zidovudine Metabolism and Excretory Transport," Department of Pharmacodynamics, Semmelweis University of Medicine, Budapest, Hungary, September 13, 1989.

"Evaluating Bioequivalence," Western Michigan Society of Hospital Pharmacists, Grand Rapids, MI, March 2, 1990.

"Effect of Temperature and Medium of Analysis on Cyclosporine Concentration," Canadian Consensus Meeting on Cyclosporine Monitoring, Minaki Lodge, Canada, May 11, 1990.

"Studies of the Interaction between Zidovudine (AZT) and Probenecid in Animals and Humans." Pharmaceutics and Process R & D, Ayerst Laboratories Inc., Rouse's Point, NY, August 17, 1990.

"Mechanistic Studies to Examine the Effect of Probenecid on the Brain Uptake of Zidovudine," Shanghai Medical University, Shanghai, P.R.C., October 13, 1990.

A lecture series (16 hrs) on the topic of "Clinical Pharmacokinetics and Therapeutic Drug Monitoring" was given to staff members of the Chinese Academy of Medical Sciences and Hospital Pharmacists, Beijing, P.R.C., October 15-20, 1990.

"Comparative Intestinal Absorption of Compounds of Varying Lipophilicity, and the Effect of Absorptive Water Flux." Lederle Laboratories, Pearl River, NY, September 12, 1991.

"Analysis of Zidovudine Distribution into Specific Brain Regions Utilizing Microdialysis," Bristol Myers-Squibb Research Institute, Princeton, NJ, September 17, 1991.

"Distribution of AZT Into Specific Brain Regions in the Rabbit Utilizing Microdialysis," University of Illinois College of Medicine, Peoria, IL, October 9, 1991.

"Studies on the Transport of Nucleosides into Specific Brain Regions Using Microdialysis with *In Vivo* Calibration." University of Florida, College of Pharmacy, Gainesville, FL, December 6, 1991.

"Analysis of Zidovudine Distribution into Specific Brain Regions Utilizing Microdialysis," University of Arizona College of Pharmacy, Tucson, AZ, February 17, 1992.

"Regional Considerations in the In Situ Intestinal Absorption of Glycylcycline and Minocycline, and the Effect of Solvent Drag," Lederle Laboratories, Pearl River, NY, May 11, 1992.

"Comparative Absorption of Fluorothymidine and Related Nucleosides in Different Anatomic Intestinal Regions," Lederle Laboratories, Pearl River, NY, May 11, 1992.

"Microdialysis Techniques for the Study of Drug Distribution, and the Problem of Recovery *In Vivo*," Europhor Toulouse, France, June 19, 1992.

"The Use of Microdialysis in Studying the Distribution of Exogenous Substances in Biological Tissues," Sandoz Pharma, Basel Switzerland, June 24, 1992.

"Inhibition of Brain Distribution and Systemic Clearance of AZT by Probenecid," Sandoz Pharma, Basel Switzerland, June 30, 1992.

"Uptake of Zidovudine (AZT) into Rabbit Brain Using Microdialysis with *In Vivo* Calibration," Knoll AG, Ludwigshafen, Germany, July 1, 1992.

"Microdialysis in the Study of the Distribution and Metabolism of Exogenous Substances," Pharmaceutical Chemical Institute, University of Heidelberg, Heidelberg, Germany, July 2, 1992.

"The Relationship Between Urine and Plasma Concentrations of Lipophilic Drugs: Implications for Therapeutic Drug Monitoring," Sandoz Pharma, Basel Switzerland, July 8, 1992.

"Estimation of the Elimination Rate Constant for Metabolites which Exhibit Formation-Rate Limited Disappearance," Sandoz Pharma, Basel Switzerland, July 23, 1992.

"Experimental Determination of Free Tissue Levels Using Microdialysis," 4th Biennial Conference on Chemotherapy of Infectious Diseases and Malignancies, Prague, Czechoslovakia, August 31, 1992.

"*In Situ* Intestinal Absorption of Tetracycline Derivatives and the Effect of Absorptive Water Flux," Lederle Laboratories, Pearl River, NY, November 13, 1992.

"Reversibility of Carbamazepine Autoinduction upon Dose Termination in Normal Volunteers," Abbott Laboratories, Abbott Park, IL, December 2, 1992.

"Barriers to the Oral Delivery of Drugs," Wyeth-Ayerst Research, Radnor, PA, February 23, 1993.

"Preliminary Results of Studies which Examine the Distribution of the NMDA Antagonist, EAB 515, to Rat Brain," Sandoz Pharma, Basel Switzerland, April 26, 1993.

"Microdialysis Calibration Using the Zero-Net Flux Method and Retrodialysis in Studying the Distribution of Exogenous Substances to Rat Brain," Sandoz Pharma, Basel Switzerland, April 26, 1993.

"Investigation of the Pharmacodynamics of the NMDA Antagonist, EAB 515, in the Rat During Intravenous and Intracerebroventricular Administration." Sandoz Research Institute, Berne, Switzerland, April 28, 1993.

"Comparative Distribution of AZT to Brain Tissue Extracellular Fluid During Intravenous and Intracerebroventricular Infusion." Food and Drug Administration, Rockville, MD, May 21, 1993.

"Interspecies Scaling of Pharmacokinetics in the Evaluation and Development of New Antiepileptic Drugs." Natural Resources Research Institute, University of Minnesota—Duluth, Duluth, MN, August 11, 1993.

"Application of Pharmacokinetic Principles in Practice." Minneapolis Veteran Pharmacists Association, St. Louis Park, MN, September 21, 1993.

"Microdialysis as a Tool to Study Drug Delivery to the Brain." North Jersey American Chemical Society Drug Metabolism Discussion Group, Somerset, NJ, October 7, 1993.

"Graduate Studies and Research Careers in Pharmaceutics." University of Minnesota—Duluth Department of Chemistry, Duluth, MN, December 3, 1993.

"Microdialysis in Pharmacokinetic and Drug Metabolism Studies." 95th Annual Meeting, American Society for Clinical Pharmacology and Therapeutics, New Orleans, LA, April 1, 1994.

"Modeling and Simulation of Complex Pharmacokinetic Systems." NATO Advanced Study Institute, Erice, Italy, April 12, 1994.

"Microdialysis in the Study of Drug Distribution." NATO Advanced Study Institute, Erice, Italy, April 13, 1994.

"Pharmacokinetic Studies Utilizing Microdialysis." Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS, May 2, 1994.

"Pharmacokinetic Studies Utilizing Microdialysis and On-Line HPLC." 4th International Workshop in Bioanalysis, Lawrence, KS, July 12, 1994.

"Application of Microdialysis in Pharmacokinetic Studies." Gordon Research Conference in Drug Metabolism, Holderness School, Plymouth, NH, July 20, 1994.

"Microdialysis and its Application in Pharmacokinetic Studies." Ciba-Geigy, Pharmacokinetics and Bioanalytics Division, Ardsley, NY, July 25, 1994.

"Assessing Drug Transport in the Brain with Microdialysis." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

"Applications of Microdialysis in Preclinical Pharmacokinetic Studies." 3M Pharmaceuticals, 3M Center, St. Paul, MN, November 29, 1994.

"Problems in Assessing the Absorption of Carbamazepine from Sustained Release Dosage Forms in Epileptic Patients." Pharmavene, Inc., Gaithersburg, MD, February 23, 1995.

"Selected Preclinical Pharmacokinetic Studies with Tacrine." Parke-Davis Pharmaceuticals, Ann Arbor, MI, May 5, 1995.

"Brain Distribution and Metabolism Studies with Tacrine and Two Hydroxylated Metabolites." Department of Pharmaceutics and Pharmacodynamics, University of Illinois, Chicago, IL, July 28, 1995.

"Microdialysis and its Application in Preclinical Drug Distribution and Absorption Studies." Chiron Corporation, Emeryville, CA, August 18, 1995.

"The Principle of Quantitative Microdialysis and its Application in Preclinical Drug Distribution Studies." Genentech, Inc., South San Francisco, CA, October 9, 1995.

"Graduate Programs and Research Opportunities in Pharmaceutics." 13th Annual Symposium on Pharmaceutical Sciences Graduate Programs, Merrillville, IN, October 21, 1995.

"Principles of Microdialysis and Applications in Preclinical Drug Distribution and Absorption Studies," Wyeth-Ayerst, Pearl River, NY, December 6, 1995.

"Microdialysis in Preclinical Drug Distribution Studies." Dupont Merck, Newark ,DE, December 8, 1995.

"Microdialysis and its Application to the Study of Drug/Metabolite Distribution in the Central Nervous System," University of Pittsburgh, Pittsburgh, PA, January 25, 1996.

"Therapeutic Drug Monitoring: A Fodor's Guide." Hallie Bruce Memorial Lecture Award, Minnesota Society of Health-Services Pharmacists, Minneapolis, MN, April 13, 1996"

"Preclinical Studies of Drug Distribution to the Brain using Microdialysis." Pharmaceutical Peptides Inc, Cambridge, MA, May 2, 1996.

"Microdialysis and its Application in Nonclinical Studies of Drug Distribution and Absorption." Bristol-Myers Squibb, Pinceton, NJ, June 24, 1996.

"Continuous Monitoring by Microdialysis in Neuropharmacokinetic Investigations." Faculty of Pharmacy, University of Tanta, Tanta, Egypt, March 5, 1997.

"Preclinical Studies of Drug Distribution to the Brain using Microdialysis," Toyama Medical and Pharmaceutical University, Toyama, Japan, April 11, 1997.

"Application of Pharmacokinetic Principles in Individualizing Aminoglycoside Dosing," Toyama Medical and Pharmaceutical University, Toyama, Japan, April 11, 1997.

"Preclinical Studies of Drug Distribution to the Brain using Microdialysis," Meiji College of Pharmacy, Japan, April 18, 1997.

"Individualizing Aminoglycoside Dosing and Once-a-Day Aminoglyocosides," Meiji College of Pharmacy, Japan, April 18, 1997.

"Education of Pharmacists and Pharmaceutical Scientists at the University of Minnesota," 260th Meeting on Continuing Education of Pharmacists, Okuda-Shinmachi, Toyama, Japan, April 26, 1997.

"Pharmacokinetic Basis of Drug-drug Interactions," Novartis Workshop on Metabolic Drug-Drug Interactions, Schluchsee, Germany, October 14, 1997.

"Microdialysis and its Application in Preclinical Pharmacokinetic Studies," Merck Research Laboratories, West Point PA, December 16, 1997.

"Microdialysis and its Application in Preclinical Pharmacokinetic Studies," Merck and Co, Inc. Rahway NJ, December 17, 1997.

"Brain Distribution Studies employing Microdialysis and Crossover Designs," *1st International Symposium in Drug Research and Development*, Noorwijkerhout, Netherlands, April 3, 1998.

"Application of Sample Pooling in the Time Domain to Estimate CL, Vss and MRT in the Search for Lead Compounds." Chiron Corporation, Emeryville, CA, May 5, 1998.

"Microdialysis as a Sampling Technique in Preclinical Pharmacokinetic Studies." Pfizer Inc, Groton CT, June 18,1998

"Assessing Drug Delivery to the CNS Using Microdialysis Sampling." School of Medicine, University of Minnesota, Duluth, October 19,1998.

"Pharmacokinetic Studies Using Microdialysis Sampling." American Association of Pharmaceutical Scientists Annual Meeting, San Francisco CA, November 18, 1998.

"Applications of Microdialysis in Pharmacokinetics: Brain, Blood, and Middle Ear Fluid." Bristol-Myers Squibb, Wallingford CT, May 14, 1999.

"Applications of Microdialysis in Preclinical Pharmacokinetics: Brain, Blood and Middle Ear Fluid." Parke-Davis, Ann Arbor, MI, May 21, 1999.

"Blood Sample Pooling and the Determination of Mean Residence Times in High-Throughput Pharmacokinetic Screening"." Parke-Davis, Ann Arbor, MI, May 21, 1999.

"Role of controlled release formulations in the steady-state pharmacokinetics and pharmacodynamics of anticonvulsants" Impax Pharmaceuticals, Inc, Hayward CA, June 9, 1999.

"Investigating Neuropharmacokinetics and Drug Delivery to the CNS using Microdialysis." *8th International Conference on In Vivo Methods: Monitoring Molecules in Neuroscience.* Stony Brook NY, June 19-23, 1999.

"Use of Microdialysis in Pharmacokinetics" at the 8th BMSR Workshop on *Advanced Methods of Pharmacokinetic and Pharmacodynamic System Analysis,* Marina del Rey, CA June 25-26, 1999.

"Applications of Microdialysis in Preclinical Pharmacokinetics." Amgen, Inc., Thousand Oaks, CA, June 28, 1999.

"Pharmacokinetic –Pharmacodynamic Principles in Drug Development." Chiron Corporation, Emeryville, CA, August 20, 1999.

"Microdialysis and its Application in Pharmacokinetics: Brain, Blood, and Middle Ear Fluid." Abbott Labs, Abbott Park IL Aug 27, 1999.

"Distribution kinetics of antibiotics to the chinchilla middle ear" Department of Biopharmaceutical Sciences, Uppsala University, Uppsala, Sweden, March 16, 2000.

"In Vivo Microdialysis as a Tool to Study Site Specific Drug Delivery" *Millennial World Congress of Pharmaceutical Sciences.* San Francisco CA, April 17, 2000.

"In Vivo Microdialysis as a Tool to Study Site Specific Drug Delivery" *Engebretson Symposium on Drug Discovery and Development.* Minneapolis, MN. May 18, 2000.

"In Vivo Microdialysis as a Tool to Study Drug Delivery". *19th Annual Robert S. Rozman Memorial Symposium,* Langhorne PA , May 25, 2000.

"Basic Principles of Microdialysis, Experimental Setup". *Course on Basic and Advanced Aspects of In Vivo Microdialysis*", Stockholm, Sweden, June14, 2000.

"Recovery: Basic Idea and Practical Methods". *Course on Basic and Advanced Aspects of In Vivo Microdialysis*", Stockholm, Sweden, June14, 2000.

"Studies of Distribution of Antibiotics to the Middle Ear by Microdialysis" *2nd International Symposium on Microdialysis in Drug Research and Development*, Stockholm, Sweden, June15, 2000.

"Basic Concepts in Clinical Pharmacokinetics" A 2-Day Course. Abbott Laboratories, Abbott Park IL and Victory Hospital, Waukegan, IL, July 18-19, 2000

"Microdialysis and its Application in Preclinical Pharmacokinetics: Brain, Blood, and Middle Ear Fluid." Dupont Pharmaceuticals, Wilmington, DE July12, 2000.

"Pharmacokinetic –Pharmacodynamic Principles in Drug Development." Abbott Labs, Abbott Park IL Jan 9, 2001

"Biopharmaceutical and Pharmacokinetic Considerations in Delivering Drug to the CNS" Medtronic Neuro Division, Minneapolis. January 25, 2001

"Clinical Pharmacokinetic Principles in Drug Development." Novartis Pharma, Tokyo, April 12, 2001

"In Vivo Microdialysis as a Tool to Study Site Specific Drug Delivery" Showa University, Tokyo, Japan, April 13, 2001

"In Vivo Microdialysis as a Tool to Study Drug Delivery in Preclinical Studies". Xi'an Medical College, Xi'an, PRC. April 25, 2001

"Principles of Pharmacokinetics and their Application in Drug Development" Novartis Pharma, Basel, Switzerland, July 3, 2001.

"Microdialysis and its Application in Preclinical Studies of Drug Delivery to Target Tissues" Boehringer-Ingelheim Pharma KG, Dept. of Pharmacokinetics & Drug Metabolism, Biberach, Germany, July 5, 2001.

"Estimation of Intrinsic Clearances and Organ Partition Coefficients in an Organ Perfusion Model" Novartis Pharma, Basel, Switzerland, July 26, 2001.

"Pharmacodynamic Modeling of the Sigmoid Emax Model" Novartis Pharma, Basel, Switzerland, July 31, 2001.

"Prediction of the Pharmacokinetics of Cefdinir in Children from the Results of Animal Studies. Omnicef® Clinical Advisory Meeting, Dallas, TX, February 9, 2002.

"Applications of Microdialysis in Studying Drug Delivery to Specific Targets". Guilin Medical School, Guilin PRC, March 28, 2002

"Microdialysis: A Tool to Study Brain Uptake?" Gordon Research Conference on the Barriers of the CNS, Tilton School, Tilton NH, June 25, 2002

"A Model for the Distribution of Drugs between Plasma, CSF and Parenchyma", Workshop on Microdialysis Techniques in the CNS, Gordon Research Conference on the Barriers of the CNS, Tilton School, Tilton NH, June 26, 2002

"Microdialysis in the Study of Drug Delivery to the Central Nervous System", Department of Pharmaceutics, Seoul National University, Seoul, South Korea, November 25, 2002.

"Investigating Antibiotic Delivery to the Middle Ear". Chong Kun Dang Pharma, Cheonan, South Korea, November 27, 2002.

"Microdialysis and its Application in Preclinical Pharmacokinetic and Drug Delivery Investigations", 32nd Annual Meeting of the Korean Pharmaceutical Society, Seoul, South Korea, November 28, 2002.

"Applications of Pharmacokinetic Principles in Drug Development". Schering-Plough Research Institute. Kenilworth, NJ. December 19, 2002

"A Course in Pharmacokinetics in Pharmaceutical Development". Abbott Laboratories. Harrison Conference Center, Lake Bluff, IL. May 15-16, 2003

"Characterizing Antibiotic Delivery to the Middle Ear for the Treatment of Otitis Media. Biomedical Simulations Resource Workshop: Advanced Methods of PK/PD Systems Analysis. Marina del Rey, CA. June 20-21, 2003.

"Cerebrospinal Fluid Distribution of Intrathecally Administered Antiviral Nucleosides". Monitoring Molecules in Neuroscience. 10th International Conference on In Vivo Methods. Department of Neuroscience, Karolinska Institutet Stockholm, Sweden. June 24-27, 2003

"Microdialysis Sampling in Drug Development: Applications in Preclinical Research." Sunrise School, American Association of Pharmaceutical Scientists Annual Meeting, Salt Lake City, UT, October 26, 2003.

"Clinical Pharmacokinetics in Pharmaceutical Development." Abbott Laboratories. Harrison Conference Center, Lake Bluff, IL. July 23-24, 2003.

"Microdialysis Sampling in Drug Development: Applications in Preclinical Research." Sunrise School, American Association of Pharmaceutical Scientists Annual Meeting, Salt Lake City, UT. October 26, 2003.

"The Role of Pharmacokinetics in Drug Discovery." Abbott Laboratories. Harrison Conference Center, Lake Bluff, IL. March 18, 2004.

"Microdialysis and its Application in Preclinical Pharmacokinetic and Drug Delivery Investigations." CDER, Food and Drug Administration, Rockville, MD. March 29, 2004.

"Interspecies Scaling, PB-PK modeling and Microdialysis in Antibiotic Drug Development." Novartis Institute for Biomedical Research, Cambridge, MA. April 9, 2004.

"Does it get to the Target Site? Microdialysis as a Tool to Study Preclinical Drug Distribution and Delivery" Amgen Inc., Thousand Oaks, CA. April 30, 2004.

"Microdialysis of Antibiotics." 4th International Symposium on Microdialysis in Drug Research and Development, Vienna, Austria, June 19, 2004.

"The Chinchilla Microdialysis AOM Model" Pfizer Global Pharmaceuticals, New York, NY. June 25, 2004.

"Advantages of the Chinchilla Microdialysis Model" Scientific Basis for Tissue-Directed Antimicrobial Therapy Symposium, Boston MA, July 21-22, 2004.

"Evaluating Drug Distribution to the Target Site and Predicting Tissue Exposure in Humans from Animal Data" Scientific Advisory Committee, Abbott Laboratories. The FDA Critical Path Initiative and the Role of Modeling/Simulation in Improving the Efficiency of Drug Development. Lake Forest, IL. September 8-9, 2004.

"Assessing Drug Delivery to the Target Site: The Role of Microdialysis in Measuring Tissue Exposure in Animals and Humans." Distinguished Lecture, Creighton University School of Pharmacy and Health Professions, Omaha NE, November 30, 2004.

"Microdialysis—Introduction to Basic Principles and Applications". AAPS Workshop on Microdialysis Principles, Application, and Regulatory Perspectives, Nashville TN, November 4, 2005.

"A Phase I Open-Label, Dose-Ranging Study to Investigate the Safety and Tolerability of Gabapentin Injection Administered Intrathecally in Individuals with Chronic, Intractable Pain: A Pharmacokinetic Report". Medtronic WHQ, Fridley, MN, February 16, 2006.

"Public Outreach and AAPS: Students are the Future of Our Association". Temple University School of Pharmacy, Philadelphia, PA. February 20, 2006.

"Assessing Drug Delivery: Using Microdialysis to Measure Target Site Exposure in Animals and Humans". Wyeth Distinguished Lecture Series, Temple University School of Pharmacy, Philadelphia, PA. February 20, 2006.

"Pharmacokinetics for Scientists Engaged in Drug Discovery". Lundbeck Research, USA. Paramus NJ. February 24, 2006.

"Pharmacokinetic Issues related to Intrathecal Drug Dosing". Medtronic WHQ, Fridley, MN, March 15, 2006.

"TTM Technology: Antibiotic Distribution to Middle Ear Fluid" Abbott Laboratories, Abbott Park, IL. May 16, 2006.

"Trans-tympanic Membrane (TTM) Drug Delivery to the Middle Ear" Alcon Laboratories, Fort Worth TX. Feb 2, 2007.

"Bugs and Drugs: Does the Anti-infective Agent get to the Target Site?". Science Luncheon Presentation. APhA Annual Meeting. Atlanta, GA. March 18, 2007

"Future Perspectives on the Contributions of Microdialysis in Drug Research and Development" Keynote Address. Fifth International Symposium on Microdialysis in Drug Research and Development. Leiden, NE. April 25, 2007.

"Drug Delivery to the Middle Ear across the Tympanic Membrane for Therapy of Acute Otitis Media". Global Gators 6th Symposium on Clinical Pharmacy and Clinical Pharmacology. Munich, Germany. June 9, 2007.

"The Pharmacokinetics of Hydrophilic Drugs during Intrathecal Infusion: the Concept of a Targeted Delivery Advantage". Novartis Pharma AG, Basel, Switzerland. June 13, 2007.

"Trans-tympanic Membrane Delivery of an Antibiotic into Chinchilla Middle Ear" Alcon Laboratories, Fort Worth TX. October 15, 2008.

"A Phase I Study to Investigate the Safety and Pharmacokinetics of Intrathecal Gabapentin Injection in Individuals with Chronic Pain". University of Poitiers, Poitiers, France, April 29, 2009.

"Cerebrospinal fluid flow, and the convective/diffusive transport of drugs in the CSF" Abbott GmbH and Co., Ludwigshafen, Germany. Oct 15, 2010.

"The Neuropharmacokinetics of Hydrophilic Drugs during Intrathecal Infusion: the Concept of a Targeted Brain Delivery Advantage" Abbott GmbH and Co., Ludwigshafen, Germany. Oct 15, 2010.

"A Brief Introduction to Pharmacokinetics" Upsher-Smith Laboratories, Inc., Maple Grove, MN. December 2, 2010.

"CSF flow, and convective/diffusive transport of drugs" Upsher-Smith Laboratories, Inc., Maple Grove, MN. December 2, 2010.

"Modeling the delivery of drugs to target sites in the CNS" Upsher-Smith Laboratories, Inc., Maple Grove, MN. December 2, 2010.

TEACHING AT THE UNIVERSITY OF MINNESOTA

Undergraduate

1971 - 1972	Co-instructor in Phar 5680 "Pharmacokinetics"
1971 - 1975	Discussant in Pharm.D. Conferences
1972 - 1973	Participating instructor in Phar 5670
1972 - 1978	Discussion leader in Pharm.D. I conferences
1972 - 1985	Course director, Phar 5680 "Pharmacokinetics"
1975 - 1995	Course director, Phar 5685 "Clinical Pharmacokinetics"
1991 - 1999	Course director, Phar 5681 "Basic Pharmacokinetic Modeling"
1996 - 1998	Course director and Participating instructor, Phmc 5460 "Pharmacokinetics"
1998 - 2003	Course director and instructor, Phar 6216 "Pharmacokinetic Simulation and Data Analysis using SAAM"
1999 - 2004	Course director and Participating instructor, Phar 6163 "Pharmacokinetics"
1998 - 2004	Participating instructor in Phar 6164 "Biopharmaceutics"
2004 - 2010	Participating instructor, Phar 6163 "Pharmacokinetics"

Graduate

1972 - 1999	Course director in Phm 8420 "Modeling Approaches in Pharmacokinetics" Participating instructor in Phm 8421, Phm 8425
1972 - 2005	Participating instructor in Phm 8100 (Seminar) and Phm 8101 (Pharmaceutics Readings)
1984 - 1999	Participating instructor in Phm 8425 "Advanced Topics in Pharmacokinetics"
1986 - 1999	Course co-director in Phm 8105 "Pharmacokinetics Research Seminar"
2000 - 2006	Course co-director in Phm 8150 "Pharmacokinetics Research Seminar"
2000 - 2006	Course Co-director and Participating instructor in Phm 8421 "Advanced Pharmacokinetics"
2004 - 2010	Participating instructor in Phm 8481 "Advanced Neuropharmaceutics"
2006 - 2010	Participating instructor in Phm 8421 "Advanced Pharmacokinetics"
2016-present	Participating instructor in Phm 8421 "Advanced Pharmacokinetics"
2017	Course director and instructor, "Pharmacokinetic Simulation and Data Analysis using SAAM"

TEACHING AT OTHER SITES

"An Introduction to Clinical Pharmacokinetics" Abbott Laboratories. Abbott Park, IL. January 9-10, 2001.
"An Introduction to Clinical Pharmacokinetics" Abbott Laboratories. Abbott Park, IL. March 29-30, 2001.
"An Introduction to Clinical Pharmacokinetics" Abbott Laboratories. Abbott Park, IL. May 17-18, 2001.
"An Introduction to Clinical Pharmacokinetics" Abbott Laboratories. Harrison Conference Center, Lake Bluff, IL. November 8-9, 2001.
"An Introduction to Pharmacokinetics" Abbott Laboratories. Harrison Conference Center, Lake Bluff, IL. March 14-15, 2002.
"An Introduction to Pharmacokinetics" Abbott Laboratories. Abbott Park, IL. July 22-23, 2002.
"An Introduction to Pharmacokinetics" Abbott Laboratories. Parsippany, NJ. Aug 26-27, 2002.
"An Introduction to Pharmacokinetics" Bristol-Myers Squibb. Wilmington, DE. September 19-20, 2002.
"Applications of Pharmacokinetic Principles in Drug Development". Schering-Plough Research Institute. Kenilworth, NJ. December 19-20, 2002
"A Course in Pharmacokinetics in Pharmaceutical Development". Abbott Laboratories. Harrison Conference Center, Lake Bluff, IL. May 15-16, 2003
"An Introduction to Pharmacokinetics" Abbott Laboratories. Harrison Conference Center, Lake Bluff, IL. July 23-24, 2003.
"Short Course in Pharmacokinetics for Drug Discovery" Abbott Laboratories. Lake Bluff, IL. March 17-18, 2004.
"Preclinical Pharmacokinetics in Pharmaceutical Discovery." Bristol-Myers Squibb, Princeton, NJ. May 6-7, 2004.
"Introduction to Pharmacokinetics" Abbott Laboratories. Abbott Park, IL, July 27-28, 2004.
"Introduction to Clinical Pharmacokinetics" Millennium Pharmaceuticals, Inc. Cambridge, MA, December 2-3, 2004.
"Introduction to Clinical Pharmacokinetics" Gilead Sciences, Foster City, CA. December 8-9, 2005.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist" Co-instructor. Boehringer-Ingelheim Pharmaceuticals, Inc., USA. Ridgefield, CT, April 13-14, 2006
"An Introduction to Pharmacokinetics" Lundbeck Research, USA, Inc. Paramus, NJ, February 24, 2006.

"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist" Co-instructor. Abbott Laboratories. Abbott Park, IL. June 4-5, 2007.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist" Co-instructor. Theravance, Inc. South San Francisco, CA. August 20-21, 2007.
"Basic Pharmacokinetic Concepts" Co-instructor. US Patent and Trademark Office. Alexandria, VA. October 4, 2007.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist" Co-instructor. Allergan, Inc. Irvine, CA. July 24-25, 2008.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Abbott Laboratories, Abbott Park, IL. August 19-20, 2008.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Gilead Sciences, Foster City, CA. October 9-10, 2008.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Genentech, South San Francisco, CA. July 23-24, 2009.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Abbott Laboratories. Abbott Park, IL. July 30-31, 2009.
"Neuropharmacokinetic Concepts for CNS Drug Delivery". Co-instructor. Abbott Laboratories. Abbott Park, IL. January 8, 2010.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Abbott Laboratories. Abbott Park, IL. August 4-5, 2010.
"Basic Pharmacokinetic Concepts for the Upsher-Smith Pharmaceutical Scientist". Co-instructor. Upsher-Smith Laboratories, Maple Grove, MN. September 21-23, 2011.
"Basic Pharmacokinetic Short Course for Pharmaceutical Scientists". Co-instructor. Novartis Pharma, Florham Park, NJ. November 17-18, 2011.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Abbott Laboratories. Independence Grove, IL. April 12-13, 2012.
"Basic Pharmacokinetic Short Course for Pharmaceutical Scientists". Co-instructor. Novartis Institutes for Biomedical Research, Emeryville, CA. September 16 -17, 2013.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Genentech, South San Francisco, CA. May 7-8, 2014.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Abbvie. Independence Grove, IL. July 16-17, 2014.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Genentech, South San Francisco, CA. May 27-28, 2015.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Abbvie. Independence Grove, IL. June 17-18, 2015.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". For non-pharmacokineticists . Co-instructor. Abbvie. Independence Grove, IL. June 1, 2016.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". For pharmacometricians. Co-instructor. Abbvie. Independence Grove, IL. June 2, 2016.
"Basic Pharmacokinetic Concepts for the Pharmaceutical Scientist". Co-instructor. Vertex Pharmaceuticals Inc. Boston, MA. Oct 11-12, 2016.
"Pharmacokinetic Short Course for Genentech Pharmaceutical Scientists". Co-instructor. Genentech, South San Francisco, CA. May 11-12, 2017.

GRADUATE STUDENTS SUPERVISED AS PRIMARY ADVISOR

Graduate Students supervised as Primary Advisor and Year of Degree Award

1978	Wargin, W.A.	Ph.D.
1978	El-Yazigi, A.	Ph.D.
1980	Mugure Pyron	M.S.
1981	Sue-Chi Wu	M.S.
1983	Hsuehling Su	M.S.
1984	Dale Yu	Ph.D.
1984	Walid Awni	Ph.D.
1985	Lillian Riad	M.S.
1985	Rose Eggerth	Ph.D.
1987	Hisham Abou-Auda	Ph.D.
1989	Mohsen Hedaya	Ph.D.
1989	Ajit K. Shah	Ph.D.
1989	Lillian Riad	Ph.D.
1991	Helen Chan	Ph.D.
1992	William Elmquist	Ph.D.
1992	Shekman Wong	Ph.D.
1994	Yanfeng Wang	Ph.D.
1994	Bimal Malhotra	Ph.D.
1996	Richard Brundage	Ph.D.
1997	Zheng Yang	Ph.D
1998	Belinda Cheung	Ph.D.
2001	Yue Huang	Ph.D
2001	Guanfa Gan	Ph.D.
2002	Joanna Peng	Ph.D
2002	Tong Zhu	Ph.D.
2004	Ji Ping	Ph.D
2004	Wei Liu	Ph.D.
2005	Yan Song	Ph.D.
2007	Nael Mostafa	Ph.D.
2007	Zhihong Li	Ph.D.

GRANTS , CONTRACTS, and OTHER SUPPORT

1972-73	University of Minnesota Graduate School
1973-74	University of Minnesota Media Production Fund
1975-78; 1978-80	NIH/NINCDS Comprehensive Epilepsy Program Contract (Principal Investigator, Project D-1)
1976; 1977	Medical Education and Research Foundation Grant (Co-investigator with John W. McBride, M.D.)
1976-78	FDA Contract to Study the Pharmacokinetics and Toxicology of Phenytoin Sodium Products in Clinical Patients
1980-81; 1981-83	Grant to Support Research Involving the Analysis of Cyclosporin A in Biological Fluids (Sandoz, Inc.)
1982-83; 1983-84	"Pharmacokinetics and Biopharmaceutic Studies of Cyclosporin A in Selected Animal and *In Vitro* Systems" (NIH; Principal Investigator; Co-investigator, R.P. Enever)
1984	Comparative Bioavailability of Sodium Phenytoin in Normal Volunteers (Zenith Labs)
1984	Relative Bioavailability of Carbamazepine in Chewable and Conventional Tablets (Ciba-Geigy)
1984	Transdermal Delivery of Propranolol (Medtronics)
11/84 - 1/85	Absorption and Metabolism of Carbamazepine in Normal Volunteers (Ciba-Geigy)
1/85 - 4/85	Transdermal Absorption of β-Blockers (Medtronics, Inc.)
11/85 - 4/86	Relative Bioavailability of Sustained Release Oral Dosage Forms of Carbamazepine (Ciba-Geigy)
1/86 - 6/86	Analysis of Analgesics in Receptor Media (Medtronics)

8/86 - 12/86	Bioequivalence of Carbamazepine Oral Dosage Forms (Ciba-Geigy)
1/86 - 12/88	Pharmacokinetics of Diltiazem in the Rabbit (Marion)
2/87 - 9/87	Bioequivalence of Carbamazepine Dosage Forms Demonstrating Varying Dissolution Rates (Ciba-Geigy)
6/1/87 - 10/15/87	Effect of Urine Flow on the Renal Clearance of Carbamazepine and its Metabolites in Humans (Ciba-Geigy)
1/88 - 6/88	Effect of Fasting on the Absorption of Diclofenac Sodium in Normal Human Volunteers (Ciba-Geigy)
4/1/89 - 3/31/92	Enhancing Brain Uptake of AZT by Transport Inhibition, (NINCDS / NIH)
7/1/89 - 6/30/90	Induction of Carbamazepine Metabolism as a Function of Dosing Rate in Normal Volunteers (Ciba-Geigy)
9/91 - 6/92	Brain Distribution of EAB-515 in the Rabbit (Sandoz, Ltd.)
11/91 - 5/92	*In Situ* Absorption from Rabbit Intestine (Lederle Laboratories)
3/92 - 8/92	Clinical Studies of the Absorption of an Oral Immunosuppressant (Apotex Laboratories)
11/92 - 10/93	Brain Distribution of an NMDA-Receptor Antagonist in the Rat (Sandoz, Ltd).
10/92 - 5/93	Brain Uptake of a CNS-Active Agent (Warner-Lambert)
11/92 - 3/93	*In Situ* Absorption from Rabbit Intestine (Lederle Laboratories)
9/94 - 5/95	Population Pharmacokinetic Analysis of A General Anesthetic in Man (Abbott Laboratories)
7/94 - 5/95	Brain Uptake of a Cholinesterase Inhibitor and its Metabolites (Warner-Lambert)
10/94 - 9/95	Distribution of Antiviral Nucleosides into Rat Cortex (Bristol-Myers Squibb)
9/95 - 8/96	Bioanalytical Methods Development of Selected Drugs and Metabolites (MedTox)
1/96 - 9/96	Pharmacokinetic Analysis of IL-2 in the Pig (Chiron)
1/96 - 6/98	Analysis of Selected Macrolides by High-pressure Liquid Chromatography (TAP)
4/96 - 10/97	Brain Penetration of Fosphenytoin and Phenytoin in the Rabbit (Warner-Lambert)
4/96 - 9/96	Analysis and Brain Uptake of PPI-457 (Pharmaceutical Peptides, Inc)
7/97 - 3/98	Regional Intestinal Absorption of Anti-CMV agents (Bristol-Myers Squibb)
8/97 - 6/98	EM574 Absorption in the Rabbit in situ (TAP)
7/97 - 9/97	Pharmacokinetics of Macrolides in Protocol EM-97-006 (TAP)
11/97 - 12/97	Drug Interaction Pharmacokinetic Analysis (McNeil)
8/97 - 3/98	Analysis and Pharmacokinetics of Macrolides in EM-97-008 (TAP)
10/97 - 12/97	Pharmacokinetics of Slow Release Agents in the CNS (Chiron)
1/98	LC/MS/MS Equipment Grant (TAP)
2/98 - 12/99	Analysis of Macrolides and Metabolites in EM-97-013 (TAP)
3/98 - 12/99	Chemical Stability of Selected Agents (Medtronic)
5/98	Validation of Analysis of Macrolides in Dog Plasma (TAP)
8/98	Validation of Analysis of Macrolides in Rabbit Plasma (TAP)
8/98	Stability of Anticancer Drugs in Solution (Medtronic)
8/98	EM574 Toxicokinetics in the Dog (TAP)
12/98	EM574 Toxicokinetics in the Rabbit (TAP)
1/99	Pharmacodynamics of EM574 on LES Pressure (protocol 004) (TAP)
3/99	Effect of Time of Dosing on Absorption of EM574 (protocol 007(TAP)
4/99	Effect of Gastric Emptying on the Pharmacokinetics of EM574 and its Metabolites (protocol 002) (TAP)
2/99	Stability of FUDR and Heparin in Solution (Medtronic)
2/99	Pharmacodynamics and PKs of EM574 and its Metabolites During Chronic Dosing (protocol 029) (TAP)
3/00 - 8/01	Pharmacokinetics of CDTR and Distribution to Middle Ear Fluid (TAP)
8/00 - 6-01	Distribution of Ketolides to Middle Ear Fluid (Abbott)
10/01 - 09/03	Pharmacokinetics of Ketolides (Abbott)
12/01 - 11/03	Pharmacokinetics and Distribution of cefdinir (Abbott)
12/02 – 12/03	Effect of a P-Glycoprotein Inhibitor on the Middle Ear Distribution of Clarithromycin (Abbott)
12/02 – 6/04	Distribution a Cephalosporin into Middle Ear Fluid in Children with Otitis Media (H LaRoche)
12/02 – 12/04	Development and Testing of Formulations for Delivery of Antibiotics to the Middle Ear (Abbott)
5/03 - 4/05	A New Approach for the Therapy of Otitis Media (Abbott)
8/04 - 7/05	Distribution of Macrolide Antibiotics to tissue sites (Pfizer)
5/05 - 11/05	Testing the Distribution of Amoxicillin into Middle Ear Fluid in the Chinchilla following Pulsatile Dose Administration (Advancis)
1/06 – 9/06	Distribution of Macrolide antibiotics to Pulmonary Tissue and Skeletal Muscle (Pfizer)
9/07 – 10/08	Transtympanic Membrane Delivery of an Antibiotic to the Middle Ear (Alcon)
11/07 – 12/08	Development of an Acute Otitis Media Middle Ear Microdialysis Model in the Chinchilla with

	Implanted Tympanostomy Tube (Alcon)
1/10 – 12/10	Testing the Penetration of an Antibiotic into Chinchilla Middle Ear using Transtympanic Membrane Delivery Formulations – Phase II (Alcon)
1/11 – 12/11	Testing the Penetration of an Antibiotic into Chinchilla Middle Ear using Transtympanic Membrane Delivery Formulations – Phase II B (Alcon)
1/12 – 6/12	Testing the Penetration of Moxifloxacin into Chinchilla Middle Ear– Phase II, Supplement II (Alcon)
7/12 – 12/12	Testing the Penetration of Moxifloxacin into Chinchilla Middle Ear– Phase III (Alcon)
1/13 – 8/14	Testing the Penetration of Fluoroquinolones into Chinchilla Middle Ear– Phase IV (Alcon)

PATENTS

United States Patent. Number 7,220,431 "METHODS AND COMPOSITIONS FOR APPLYING PHARMACOLOGIC AGENTS TO THE EAR." UMN Docket # Z01159. RJ Sawchuk and BW Cheung. Issue Date: May 22, 2007. Filing Date: November 27, 2002: #06,306,517

PUBLICATIONS

BOOKS AND CHAPTERS

J. Blanchard, R.J. Sawchuk and B.B. Brodie, Editors. Principles and Perspectives in Drug Bioavailability. S. Karger, Basel, 1979.

J. Blanchard and R.J. Sawchuk, "Drug Bioavailability: An Overview" in Principles and Perspectives of Drug Bioavailability, J. Blanchard, R.J. Sawchuk and B.B. Brodie (Editors), S. Karger, Basel, 1979.

I.E. Leppik, J. Shope, R.J. Sawchuk, W.A. Hauser and B. Van Dyne, "Variability of Antiepileptic Drug Levels During Chronic Therapy" in Epileptology, M. Dam, L. Gram and K. Penry (Editors), Raven Press, NY, 1981.

R.J. Sawchuk, "Drug Absorption and Disposition in Burn Patients" in The Pharmacokinetic Basis of Drug Treatment, N. Massoud, L.Z. Benet, and J.G. Gambertoglio (Editors), Raven Press, NY, 1984.

"Use of Microdialysis in Drug Delivery Studies." Theme Issue. W.F. Elmquist and R.J. Sawchuk (Editors) *Advanced Drug Delivery Reviews* 45, Nos. 2-3 (2000).

R. J. Sawchuk and B.W.Y. Cheung, "Application of Microdialysis in Pharmacokinetic Studies." in Handbook of Microdialysis: Methods, Applications and Clinical Aspects , B.H.C. Westerink and T.I.F.H. Cremers (Editors), Academic Press, Amsterdam, 2007.

PROFESSIONAL PUBLICATIONS

R.J. Sawchuk, "The Plateau Principle in Drug Therapy. Part 1: The Principle and Its Application." *Minn. Pharmacist* 27(6): 19 (1973).

R.J. Sawchuk, "The Plateau Principle in Drug Therapy. Part 2: Factors Governing Plateau Levels During Chronic Drug Therapy." *Minn. Pharmacist* 27(7): 8 (1973).

M.C. Meyer, A.B. Straughn, L.J. Leeson, R.H. Levy and R.J. Sawchuk, "Meprobamate Bioavailability Monograph." *JAPhA* NS17, 173 (1977).

R.J. Sawchuk and T.S. Rector, "Burn-Induced Alterations in Drug Absorption and Disposition." *Minn. Pharmacist* 35: 6-9 (1981).

SCIENTIFIC PUBLICATIONS (NON-REFEREED)

I.E. Leppik, J. Cloyd and R.J. Sawchuk, "Coefficient of Variation as a Measure of Compliance" Letter. *Lancet*, October 14, 1978.

SCIENTIFIC PUBLICATIONS (REFEREED)

1. R.J. Sawchuk, J.M. Anderson and J.G. Nairn. "Stirring apparatus for the investigation of unstable strongly adsorbing chemicals." *J. Pharm. Sci.* 55: 1463 (1966).

2. R.J. Sawchuk and J.G. Nairn. "Rate studies on the binding of bilirubin by ion-exchange resins." *J. Pharm. Sci.* 57: 1896 (1968).

3. R.J. Sawchuk, J. Robayo and K.W. Miller. "The distribution of propranolol between blood and plasma in hypertensive patients." *Br. J. Clin. Pharmacol.* 1: 440 (1974).

4. R.J. Sawchuk and D.E. Zaske. "Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients." *J. Pharmacokin. Biopharm.* 4: 183 (1976).

5. D.E. Zaske, R.J. Sawchuk, D.N. Gerding and R.G. Strate. "Increased dosage requirements of gentamicin in burn patients." *J. Trauma* 16: (1976).

6. R.J. Sawchuk, D.E. Zaske, R.J. Cipolle, W.A. Wargin and R.G. Strate. "Kinetic model for gentamicin dosing with the use of individual patient parameters." *Clin. Pharmacol. Therap.* 21: 362 (1977).

7. J.C. Cloyd, D.E. Bosch and R.J. Sawchuk. "Concentration-time profile of phenytoin after admixture with small volumes of intravenous fluids." *Am. J. Hosp. Pharm.* 35: 45-48 (1978).

8. J.D. Wirtschafter, C.R. Volk and R.J. Sawchuk. "Trans-aqueous diffusion of acetylcholine to denervated iris sphincter muscle: A hypothetical mechanism for the tonic pupil syndrome (Adie's Syndrome). *Annals of Neurology* 4: 1-5 (1978).

9. D.E. Zaske, R.J. Sawchuk and R.G. Strate. "The necessity of increased doses of amikacin in burn patients." *Surgery* 84: 603-608 (1978).

10. S.M. Ehlers, D.E. Zaske and R.J. Sawchuk. "Massive theophylline overdose: rapid removal by charcoal memoperfusion. *JAMA* 240: 474 (1978).

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14. R.J. Sawchuk and T.S. Rector. "Steady-state plasma concentrations as a function of the absorption rate and dosing interval for drugs exhibiting concentration-dependent clearance: consequences for phenytoin therapy." *J. Pharmacokin. Biopharm.* 7: 543-555 (1979).

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22. R.J. Sawchuk* and T.S. Rector. "Drug kinetics in burn patients." *Clin. Pharmacokinetics* 5: 548-556 (1980).

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28. R.J. Sawchuk, S.M. Pepin, I.E. Leppik and R.J. Gumnit. "Rapid and slow release phenytoin in epileptic patients at steady state: comparative plasma levels and toxicity." *J. Pharmacokin. Biopharm.* 10: 365-382 (1982).

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39. W. Awni and R.J. Sawchuk. "The pharmacokinetics of cyclosporine. II. Blood-plasma distribution and binding studies." *Drug Metab. Disposition* 13(2): 133-138 (1984).

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43. R.J. Sawchuk and W. Awni. "Absorption of cyclosporine from rabbit small intestine *in situ*." *J. Pharm. Sci.* 75(12): 1151-1156 (1986).

44. G.R. Matzke, R.C. Brundage and R.J. Sawchuk. "Protein binding of phenytoin, p-hydroxyphenytoin, and p-hydroxy phenytoin glucuronide." *J. Clin. Pharmacol.* 26: 677-679 (1986).

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48. D.K. Yu and R.J. Sawchuk. "Pharmacokinetics of propylene glycol in the rabbit." *J. Pharmacok. Biopharm.* 15: 1-8 (1987).

49. A.K. Shah and R.J. Sawchuk. "Liquid chromatographic determination of cyclosporine and its metabolites in blood." *Clinical Chemistry* 34: 1467-1471 (1988).

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51. L.E. Riad and R.J. Sawchuk. "A sensitive method for the simultaneous determination of carbamazepine, its epoxide and transdiol metabolites in plasma by microbore liquid chromatography." *Clinical Chemistry* 34: 1863-1866 (1988).

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70. A.J. Shah and R.J. Sawchuk. "The effect of altering blood lipids on the pharmacokinetics of cyclosporine in the rabbit." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

71. M.A. Hedaya, W.F. Elmquist and R.J. Sawchuk. "Mechanism of zidovudine (AZT) dose-sparing by probenecid in humans." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

72. W.F. Elmquist and R.J. Sawchuk. "Tissue mean transit time determination from steady-state partition coefficients and tissue/plasma concentration ratios in the post-distributive phase." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

73. L.E. Riad and R.J. Sawchuk. "Relative bioavailability and effects of food on plasma levels of diclofenac sodium following a single oral dose of Voltaren 100-mg SR tablet." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

74. O.H. Chan and R.J. Sawchuk. "Intestinal absorption of diltiazem in the rabbit." Fourth Annual Meeting, AAPS, Atlanta, GA, October 21-26, 1989.

75. R.J. Sawchuk. "Pharmacokinetic and analytical considerations in monitoring zidovudine (AZT) levels in children with AIDS." The Fourth International Congress on Pediatric Laboratory Medicine, Washington, DC, August 23, 1989.

76. K.D. Lake, A.K. Shah, R.W. Emery, D.R. Holder and R.J. Sawchuk. "The effect of urine flow rate on the renal clearance of cyclosporine in heart transplant recipients." International Society for Heart Transplantation, Tenth Annual Meeting, Fort Lauderdale, FL, April 4-6, 1990.

77. R.J. Sawchuk. "Effect of temperature and medium of analysis on CsA concentration." Canadian Consensus Meeting on Cyclosporine Monitoring, Minaki Lodge, Ontario, May 10-13, 1990.

78. H. Das, S.W. Wong, K. Chan, R.J. Sawchuk and R.L. Oberle. "Pharmacokinetics and metabolism of diclofenac sodium (Voltaren) after IV and oral administration to Yucatan miniswine." Eastern Regional AAPS meeting, New Brunswick, NJ, June 3-5, 1990.

79. S.M. Wong and R.J. Sawchuk. "Interaction of zidovudine and probenecid at steady state." NATO Advanced Study Institute Symposium "New Trends in Pharmacokinetics." Erice, Sicily, September 4-15, 1990.

80. W.F. Elmquist and R.J. Sawchuk. "Tissue mean transit time determination from steady-state partition coefficients and tissue/plasma concentration ratios in the postdistributive phase." NATO Advanced Study Institute Symposium "New Trends in Pharmacokinetics," Erice, Sicily, September 4-15, 1990.

81. A.K. Shah, R.J. Sawchuk, A. Gratwohl and R.C. Brundage. "Modeling subcutaneous absorption of cyclosporine A in rabbits." NATO Advanced Study Institute Symposium "New Trends in Pharmacokinetics," Erice, Sicily, September 4-15, 1990.

82. L.E. Riad, K.K.H. Chan and R.J. Sawchuk. "Effects of dosing rate on carbamazepine enzymatic induction in normal volunteers." NATO Advanced Study Institute Symposium "New Trends in Pharmacokinetics," Erice, Sicily, September 4-15, 1990.

83. W.F. Elmquist, L.E. Riad, I.E. Leppik and R.J. Sawchuk. "The relationship between carbamazepine urine and plasma concentrations: implications for therapeutic drug monitoring." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

84. S.M. Wong, L.E. Riad, P. Degen, V. John, K. Chan and R.J. Sawchuk. "Comparison of plasma concentrations of diclofenac sodium and its metabolites during single and multiple dosing of Voltaren SR tablet in humans." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

85. O.H. Chan and R.J. Sawchuk. "Saturable first-pass elimination of diltiazem during intestinal absorption in the rabbit." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

86. L.E. Riad and R.J. Sawchuk. "Carbamazepine enzymatic induction: extent and effects of dosing rate in normal volunteers." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

87. Y.-F. Wang, M.A. Hedaya and R.J. Sawchuk. "Comparative absorption and disposition pharmacokinetics of AZT and AZddU in rabbits." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

88. S.L. Wong and R.J. Sawchuk. "Investigation of distribution of zidovudine into the brain by microdialysis." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

89. S.L. Wong and R.J. Sawchuk. "Interaction of zidovudine and probenecid at steady state." AAPS Fifth Annual Meeting, Las Vegas, NV, November 4-8, 1990.

90. S.L. Wong, Y.-F. Wang and R.J. Sawchuk. "Brain/plasma distribution kinetics of zidovudine (AZT) in the rabbit using microdialysis." 1991 Symposium on Microdialysis and Allied Analytical Techniques, Indianapolis, IN, May 16-17, 1991.

91. K. Van Belle, S.L. Wong, Y.-F. Wang and R.J. Sawchuk. "Comparative delivery and distribution kinetics of zidovudine (AZT) and AZddU into the rabbit brain by microdialysis." 1991 Symposium on Microdialysis and Allied Analytical Techniques, Indianapolis, IN, May 16-17, 1991.

92. Y.-F. Wang, S.L. Wong and R.J. Sawchuk "*In vitro* and *in vivo* calibration of microdialysis probes using retrodialysis." 1991 Symposium on Microdialysis and Allied Analytical Techniques, Indianapolis, IN, May 16-17, 1991.

93. B.W. Cheung, L.E. Riad and R.J. Sawchuk. "Comparative uptake of selected anticonvulsant drugs into rabbit brain." 1991 Symposium on Microdialysis and Allied Analytical Techniques, Indianapolis, IN May 16-17, 1991.

94. L.E. Riad, K.K. Chan, J.A. Maloney and R.J. Sawchuk. "Reversibility of carbamazepine autoinduction upon dose termination in normal volunteers." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

95. S.L. Wong, M.A. Hedaya and R.J. Sawchuk. "Modeling the competitive inhibition of renal and nonrenal clearance of zidovudine by probenecid." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

96. K. Van Belle, S.L. Wong, Y.-F. Wang and R.J. Sawchuk. "Comparison of pharmacokinetics and CNS distribution of coadministered AZT and AZddU by microdialysis." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

97. Y.-F. Wang, S.L. Wong and R.J. Sawchuk. "*In vitro* and *in vivo* calibration of microdialysis probes using retrodialysis: application to the study of brain/plasma distribution of zidovudine." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

98. W.F. Elmquist, L.E. Riad, I.E. Leppik and R.J. Sawchuk. "The relationship between urine and plasma concentrations of carbamazepine and phenytoin in epileptic patients on chronic therapy." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

99. S.L. Wong, Y.-F. Wang, and R.J. Sawchuk. "Effect of dose on distribution of zidovudine (AZT) into rabbit brain using microdialysis with *in vivo* calibration." AAPS Sixth Annual Meeting, Washington, DC, November 17-21, 1991.

100. W.F. Elmquist, I.E. Leppik and R.J. Sawchuk. "Physiological modeling of the dependence of renal clearance on urine flow II: phenytoin and HPPH in humans." American Association of Pharmaceutical Scientists Annual Meeting, Washington, DC, November 17-21, 1991.

101. R.J. Sawchuk. "Study of zidovudine distribution into the CNS utilizing microdialysis." 25th Annual Higuchi Research Seminar, Lake of the Ozarks, MO, March 8-11, 1992.

102. Y.F. Wang and R.J. Sawchuk. "Microdialysis studies of brain/plasma distribution of AZT during intraventricular and intravenous infusion." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

103. S.L. Wong, K. Van Belle, and R.J. Sawchuk. "A microdialysis study of probenecid's effect on the transport kinetics of zidovudine in rabbit brain." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

104. S.L. Wong, and R.J. Sawchuk. "Pharmacokinetic interaction of zidovudine and salicylic acid during continuous infusion." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

105. S.L. Wong, and R.J. Sawchuk. "Effect of salicylic acid on the distribution of zidovudine between plasma and cerebrospinal fluid." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

106. R.C. Brundage, K.K.H. Chan, and R.J. Sawchuk. "Population pharmacokinetic modeling of nicotine following transdermal drug administration." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

107. R.C. Brundage, K.K.H. Chan, and R.J. Sawchuk. "Population pharmacokinetics of diclofenac potassium using routinely collected experimental data." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

108. W.F. Elmquist and R.J. Sawchuk. "Simulation of the effect that the time delay in sampling from the bladder has on urine concentrations: implications for therapeutic drug monitoring using urine specimens." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

109. J.P. Zhong, Y.F. Wang and R.J. Sawchuk. "Absorption of three antiviral nucleosides from different anatomic regions of rabbit intestine." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

110. Y.F. Wang, S.L. Wong, and R.J. Sawchuk. "On-line microdialysis calibration using retrodialysis and the zero-net flux method: application to a study of the distribution of AZT to rabbit CSF and thalamus." AAPS Seventh Annual Meeting, San Antonio, TX, November 15-19, 1992.

111. R.J. Sawchuk. "Comparative distribution of AZT into brain tissue extracellular fluid during intravenous and intraventricular infusion using microdialysis." 26th Annual Higuchi Research Seminar, Lake of the Ozarks, MO, March 14-17, 1993.

112. Y. Wang and R.J. Sawchuk, "Comparison of renal clearance of AZdU following IV bolus and constant-rate Infusion." 8th Annual Meeting, American Association of Pharmaceutical Scientists, Orlando, FL, November 14-18, 1993.

113. Y. Wang and R.J. Sawchuk. "Assessment of oral absorption of AZT and AZdU in the rabbit using deconvolution." 8th Annual Meeting, American Association of Pharmaceutical Scientists, Orlando, FL, November 14-18, 1993.

114. Y. Wang, Y. Wei and R.J. Sawchuk. "Microdialysis studies of carrier-mediated transport of AZT from brain to plasma during intracerebroventricular infusion." 8th Annual Meeting, American Association of Pharmaceutical Scientists, Orlando, FL, November 14-18, 1993.

115. B.K. Malhotra, M. Lemaire, and R.J. Sawchuk. "Investigation of the CNS distribution of EAB 515 in freely moving rats by microdialysis." 8th Annual Meeting, American Association of Pharmaceutical Scientists, Orlando, FL, November 14-18, 1993.

116. A.K. Shah, R.C. Brundage, K.D. Lake and R.J. Sawchuk. "Estimation of plasma free fraction (fu) of cyclosporine (CYA) in the rabbit and heart transplant (HT) patients by NONMEM using a physiological model of renal clearance (CLr)." 8th Annual Meeting, American Association of Pharmaceutical Scientists, Orlando, FL, November 14-18, 1993.

117. B.K. Malhotra, R.C. Brundage, M. Lemaire, and R.J. Sawchuk. "Modeling of the CNS distribution of EAB 515 following IV and ICV administration." 5th Symposium: Frontiers of Pharmacokinetics and Pharmacodynamics, Baltimore, MD, April 18-20, 1994.

118. R.C. Brundage, B.K. Malhotra, J.A. Maloney and R.J. Sawchuk. "Brain distribution of tacrine and the 1-hydroxy and 2-hydroxy tacrine metabolites determined by microdialysis in freely-moving rats." 5th Symposium: Frontiers of Pharmacokinetics and Pharmacodynamics, Baltimore, MD, April 18-20, 1994.

119. Y. Wang and R.J. Sawchuk. "CNS Distribution of inulin-[^{14}C]-carboxylic acid in rabbits." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

120. B.K. Malhotra, R.C. Brundage and R.J. Sawchuk. "Simultaneous microdialysis of portal and jugular blood following IV bolus and oral lavage in freely-moving rats." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

121. R.C. Brundage, B.K. Malhotra, J.A. Maloney and R.J. Sawchuk. "Brain distribution of tacrine and its 1- and 2-hydroxylated metabolites determined by microdialysis in freely-moving rats." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

122. B.K. Malhotra, R.C. Brundage, Y. Wang and R.J. Sawchuk. "Dialysis membrane-limited and aqueous boundary layer-limited *in vitro* microdialysis recovery." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

123. B.W.Y. Cheung, Y. Wang and R.J. Sawchuk. "Preliminary studies of effects of hydroxy-propyl-beta-cyclodextrin on carbamazepine distribution into rabbit brain." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

124. R.J. Sawchuk, J.A. Maloney, L.L. Cartier, R.J. Rackley, K.K.H. Chan and H.S.H. Lau. "Analysis of diclofenac and four of its metabolites in human urine by HPLC." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

125. R.C. Brundage, M. Lemaire and R.J. Sawchuk. "Modeling of the CNS distribution of EAB 515 following IV and ICV administration." 9th Annual Meeting, American Association of Pharmaceutical Scientists, San Diego, CA, November 6-10, 1994.

126. B.K. Malhotra, M. Lemaire, J.F. Brouillard and R.J. Sawchuk. "High-performance liquid chromatographic (HPLC) analysis of EAB 515 in brain and blood microdialysate (on-line) and in plasma ultrafiltrate of freely-moving rats." 10th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, November 5-9, 1995.

127. R.J. Sawchuk, R.C. Brundage, E.D. Kharasch and M.D. Karol. "Physiological-based pharmacokinetic (PBPK) modeling of sevoflurane, a volatile anesthetic." 10th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, November 5-9, 1995.

128. R.C. Brundage, S. Thomas Forgue and R.J. Sawchuk. "Comparative distribution of a series of aminoacridines of varying polarities into rat cortex using microdialysis." 10th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, November 5-9, 1995.

129. Z. Yang, R.C. Brundage, L.L. Cartier, J.A. Maloney and R.J. Sawchuk. "Development of a microdialysis method to study brain distribution of stavudine (d4t) in freely-moving rats." 10th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, November 5-9, 1995.

130. B.K. Malhotra, R.C. Brundage and R.J. Sawchuk. "Estimation of presystemic disposition of drugs based upon combination of area ratios and deconvolution." 10th Annual Meeting, American Association of Pharmaceutical Scientists, Miami Beach, FL, November 5-9, 1995.

131. M.A. Osman, R. J. Sawchuk, and M.K. Youssef. "In Situ Absorption of the Antiviral drug, stavudine, from the rabbit intestine." European Symposium on Formulation of Poorly Available Drugs for Oral Administration, Paris, February 5- 6, 1996.

132. M.A. Osman, R.J. Sawchuk, and M.K. Youssef. "Ganciclovir (DHPG), an antiviral nucleoside that exhibits high absorptive clearance in the rabbit colon *in situ*." European Symposium on Formulation of Poorly-available Drugs for Oral Administration, Paris, February 5- 6, 1996.

133. B. K. Malhotra, M. Lemaire, J.F. Brouillard, and R.J. Sawchuk. "High-performance liquid chromatographic (HPLC) analysis of EAB 515 in brain and blood microdialysate (on-line) and in plasma ultrafiltrate of freely-moving rats." 11th Annual Meeting, American Association of Pharmaceutical Scientists, Seattle, WA, October 29-31, 1996.

134. R.J. Sawchuk, R.C. Brundage, E.D. Kharasch, and M.D. Karol. "Physiologically-based pharmacokinetic (PBPK) modeling of sevoflurane, a volatile anesthetic." 11th Annual Meeting, American Association of Pharmaceutical Scientists, Seattle, WA, October 29-31, 1996.

135. R.C. Brundage, S.T. Forgue, and R.J. Sawchuk. "Comparative distribution of a series of aminoacridines of varying polarities into rat cortex using microdialysis." 11th Annual Meeting, American Association of Pharmaceutical Scientists, Seattle, WA, October 29-31, 1996.

136. Z. Yang, R.C. Brundage, L.L. Cartier, J.A. Maloney, and R.J. Sawchuk. "Development of a microdialysis method to study brain distribution of stavudine (d4T) in freely-moving rats." 11th Annual Meeting, American Association of Pharmaceutical Scientists, Seattle, WA, October 29-31, 1996.

137. B.K. Malhotra, R. C. Brundage, and R. J. Sawchuk. "Estimation of presystemic disposition of drugs based upon combination of area ratios and deconvolution." 11th Annual Meeting, American Association of Pharmaceutical Scientists, Seattle, WA, October 29-31, 1996.

138. Z. Yang and R.J. Sawchuk. "A modified solvent drag model and its application in studying intestinal absorption of polar drugs." 12th Annual Meeting, American Association of Pharmaceutical Scientists, Boston, MA, November 2-6, 1997.

139. Z. Yang and R.J. Sawchuk. "Estimating the intestinal absorptive clearance of drugs: consideration of water absorption during in situ single-pass perfusion studies." 12th Annual Meeting, American Association of Pharmaceutical Scientists, Boston, MA, November 2-6, 1997.

140. Z. Yang, P. Manitpisitkul, F.P. LaCreta, C.K. Knupp, R.H. Barbhaiya, and R.J. Sawchuk. "*In situ* studies of the regional absorption of lobucavir and ganciclovir from rabbit intestine." American Association of Pharmaceutical Scientists Annual Meeting, San Francisco, CA, November 15-19, 1998.

141. Z. Yang, Y. Huang, G. Gan, and R.J. Sawchuk. "Microdialysis evaluation of the brain distribution of stavudine following intranasal administration." American Association of Pharmaceutical Scientists Annual Meeting, San Francisco, CA, November 15-19, 1998.

142. Z Yuan, P. Ji, S. Giebink, and R.J. Sawchuk. "Antibiotic Middle Ear Pharmacokinetics by Microdialysis." American Association of Pharmaceutical Scientists Annual Meeting, San Francisco, CA, November 15-19, 1998.

143. R.J. Sawchuk, P. Ji, Y. Huang. "Distribution of Amoxicillin to Middle Ear Fluid Using Microdialysis Sampling." Higuchi Research Seminar, Lake of the Ozarks, MO, March 14-17, 1999.

144. Y. Huang, and R.J. Sawchuk. "Antibiotic Pharmacokinetics in Chinchilla Middle Ear using Microdialysis." Association of Pharmaceutical Scientists Midwest Regional Meeting, Chicago, IL, May 17, 1999

145. R.J. Sawchuk, P. Ji, Y. Huang, and S. Giebink. "Kinetics of Transport of Antibiotics to Middle Ear Fluid Using Microdialysis Sampling." Seventh International Symposium on Recent Advances in Otitis Media, Fort Lauderdale, FL, June 1-5, 1999.

146. G. Gan, and R.J. Sawchuk. "Intestinal Absorption and Pre-Systemic First Pass Elimination of Minocycline and Propranolol in Rabbits" *American Association of Pharmaceutical Scientists Annual Meeting*, New Orleans, LA, November 14-18, 1999.

147. B.W.Y. Cheung, L.L. Cartier, H. Q. Russlie, and R.J. Sawchuk. "Using Sample Pooling Methods in the Determination of AUC and AUMC in Pharmacokinetic Studies" *American Association of Pharmaceutical Scientists Annual Meeting*, New Orleans, LA, November 14-18, 1999.

148. Y. Huang, L.L. Cartier, and R.J. Sawchuk. "Analysis of Clarithromycin by Chemiluminescence: In Vitro/InVivo Microdialysis Studies" *American Association of Pharmaceutical Scientists Annual Meeting*, New Orleans, LA, November 14-18, 1999.

149. P. Guo, P. Ji, B.W.Y. Cheung, J.B. McCarthy, and R.J. Sawchuk. "Fibronectin Peptide (FN C/H V-Y) Assay and Stability in Human and Rat Plasma" *American Association of Pharmaceutical Scientists Annual Meeting*, New Orleans, LA, November 14-18, 1999.

150. R. J. Sawchuk, B. W. Y. Cheung, L. L. Cartier, H. Q. Russlie, T. Zhu, Y. Huang, G. S. Giebink, D. Mulford and M. Mayer. "Kinetics of Cefditoren Distribution to Middle Ear Fluid in The Unanesthetized Chinchilla" *40th Interscience Conference on Antimicrobial Agents and Chemotherapy.* Toronto, ON, September 17-20, 2000

151. G.S. Giebink, T.M. Sheehy, M. Quartey, R.J. Sawchuk, M. Mayer "Cefditoren Pharmacodynamics for Streptococcus Pneumoniae (Pnc) Acute Otitis Media (AOM) in the Chinchilla Model" *40th Interscience Conference on Antimicrobial Agents and Chemotherapy.* Toronto, ON, September 17-20, 2000.

152. Y. Huang, R. J. Sawchuk. "Studies of the Middle Ear Distribution Kinetics of Amoxicillin in the Awake Chinchilla Using Microdialysis". *American Association of Pharmaceutical Scientists Annual Meeting*, Indianapolis, IN, October 29- November 2, 2000.

153. J.Z. Peng, R.C. Brundage, and R.J. Sawchuk. "Study of Presystemic Elimination of 4-mono-methylamino-antipyrine (MAAP) after Consecutive Doses in Freely Moving Rats Using On-line Microdialysis". *American Association of Pharmaceutical Scientists Annual Meeting*, Indianapolis, IN, October 29- November 2, 2000.

154. T. Zhu, Y. Huang, L.L. Cartier, R. J. Sawchuk "In Vitro Microdialysis and Protein Binding Studies of Cefditoren" *American Association of Pharmaceutical Scientists Annual Meeting*, Indianapolis, IN, October 29- November 2, 2000.

155. G. Gan, L. L. Cartier, Y. Huang, Z. Yang, R. J. Sawchuk "Intestinal Absorption and Presystemic Elimination of the Prokinetic Agent, EM574, in Rabbits" *American Association of Pharmaceutical Scientists Annual Meeting*, Indianapolis, IN, October 29- November 2, 2000.

156. L. C. Musib, J. C. Cloyd, A.K. Birnbaum, T. J. Hietpas, R. J. Sawchuk, I. E. Leppik, T. R. Browne, S. F. Holloway, G. S. Holden, J. O. Rarig. "Preliminary Report on Phenytoin Bioavailability in the Elderly Using an Intravenous Stable-Labeled Isotope". *American Association of Pharmaceutical Scientists Annual Meeting*, Indianapolis, IN, October 29- November 2, 2000.

157. Z. Yang, L. M. Zadjura, C. J. D'Arienzo, D. B. Wang-Iverson, R. J. Sawchuk "Use of Sample Pooling in Drug Discovery to Screen for Pharmacokinetic Properties of Compounds in Rats" *American Association of Pharmaceutical Scientists Annual Meeting*, Indianapolis, IN, October 29- November 2, 2000.

158. R.J. Sawchuk, Y. Huang, P. Ji, M. Quartey, G.S. Giebink. "Influx/Eflux Penetration Clearance of Amoxicillin between Plasma and Middle Ear Fluid in Freely Moving Chinchillas using Microdialysis" *4th Extraordinary International Symposium on Recent Advances in Otitis Media,* Sendai, Japan, April 16-20, 2001.

159. T. Zhu, B. W. Cheung, L.L. Cartier, G. S. Giebink, D.J. Mulford, M.D. Mayer, R.J. Sawchuk. "Study of Cefditoren Distribution Kinetics to Middle Ear Fluid in Freely-moving Chinchillas Using Microdialysis." *American Association of Pharmaceutical Scientists Annual Meeting*, Denver, CO, October 21-25, 2001.

160. W. Liu, B.W. Cheung, L.L. Cartier, T. Zhu, M.M. Paris, R.J. Sawchuk. "In vitro/In vivo Microdialysis and Protein Binding Studies of the ketolide antibiotic, ABT-773." *American Association of Pharmaceutical Scientists Annual Meeting*, Denver, CO, October 21-25, 2001.

161. Y. Huang, R.J. Sawchuk. "Estimation of Amoxicillin Influx and Efflux Clearance between Plasma and Middle Ear Fluid Following Simultaneous Systemic and Local Ear Doses in Awake Chinchilla Using Microdialysis." *American Association of Pharmaceutical Scientists Annual Meeting*, Denver, CO, October 21-25, 2001.

162. J.Z. Peng, R.C. Brundage, R.J. Sawchuk. "The Influence of Drug Pre-exposure on First-pass Metabolism of Tacrine in Rats." *American Association of Pharmaceutical Scientists Annual Meeting*, Denver, CO, October 21-25, 2001.

163. J.Peng, R.J.Sawchuk, and R.P.Remmel "Mechanism-based inactivation of CYP1A2 by tacrine" *11th North American Meeting of the International Society for the Study of Xenobiotics*, Orlando, FL. October 27-31, 2002.

164. Y. Song, L.L.Cartier, B.W Cheung, R J Sawchuk. "An Animal Model for Multi-site CSF Disposition Studies of Intrathecally Administered Agents". *American Association of Pharmaceutical Scientists Annual Meeting*, Toronto, Ontario, Canada. November 10-14, 2002.

165. J.Z. Peng, R.Remmel, R.J.Sawchuk. "Modeling And Simulation Of In Vivo PK Profiles Based On Mechanism-based Inhibition From In Vitro Studies: Inactivation Of CYP1A2 by Tacrine" *American Association of Pharmaceutical Scientists Annual Meeting*, Toronto, Ontario, Canada. November 10-14, 2002.

166. Y. Song, L.L.Cartier, B. Cheung, R.J. Sawchuk. "Multi-site CSF Disposition Studies of Intrathecally Administered Antiviral Nucleosides in a Novel Animal Model". *8th International Meeting of the International Society for the Study of Xenobiotics*, Dijon France. April 27-31, 2003

167. W. Liu, B. W. Y. Cheung, R. J. Sawchuk. "Distribution Kinetics of Cethromycin in the Chinchilla Middle Ear". *8th International Symposium on Recent Advances in Otitis Media.* Fort Lauderdale, FL. June 3 - 7, 2003

168. P. Ji, L. Cartier, B. W. Y. Cheung, R. J. Sawchuk. "Distribution Kinetics of Cefdinir Between Plasma And Middle Ear Fluid In The Freely Moving Chinchillas". *American Association of Pharmaceutical Scientists Annual Meeting*, Salt Lake City, UT. October 26-30, 2003.

169. W. Liu, B. W. Y. Cheung, R J Sawchuk. "Efflux Transport Of Cethromycin Following Direct Intra-bulla Dosing In The Chinchilla Middle Ear". *American Association of Pharmaceutical Scientists Annual Meeting*, Salt Lake City, UT. October 26-30, 2003.

170. Y. Song and R. J. Sawchuk. "Pharmacokinetics of Zidovudine and Stavudine in the Cerebrospinal Fluid after Intrathecal Administration in a Novel Rabbit Model". *American Association of Pharmaceutical Scientists Annual Meeting*, Baltimore, MD. November 8, 2004.

171. N. Mostafa and R. J. Sawchuk. "Determination of Ofloxacin Clearance from the Middle Ear Fluid using Microdialysis". *American Association of Pharmaceutical Scientists Annual Meeting*, Nashville, TN. November 7, 2005.

172. Z. Li, B. W. Y. Cheung, L. Cartier, and R. J. Sawchuk. "The Possible Role of P-glycoprotein in the Distribution of Clarithromycin to the Middle Ear". *American Association of Pharmaceutical Scientists Annual Meeting*, Nashville, TN. November 7, 2005.

173. R. J. Sawchuk, L. M. Page, and R. L. Rauck. "Pharmacokinetics of Gabapentin Injection in Cerebrospinal Fluid and Plasma with Intrathecal Administration". FDA Science Forum, Washington, DC. April 18, 2006.

174. R. J. Sawchuk. "Bugs and Drugs: Does the Anti-infective Agent get to the Target Site?" *American Pharmacists Association Annual Meeting*, Atlanta, GA. March 18, 2007.

175. R. J. Sawchuk. "Future Perspectives on the Contributions of Microdialysis in Drug Research and Development" Fifth International Symposium on Microdialysis in Drug Research and Development. Leiden, NE. April 25, 2007.

176. R.J. Sawchuk. "Drug Delivery to the Middle Ear across the Tympanic Membrane for Therapy of Acute Otitis Media". Global Gators 6th Symposium on Clinical Pharmacy and Clinical Pharmacology. Munich, Germany. June 9, 2007.

177. T. Wang, R. J. Sawchuk and W. F. Elmquist. "Modeling Distributional Kinetics: Comparison of Two Methods Based on a Partial-Areas Analysis". *American Association of Pharmaceutical Scientists Annual Meeting*, San Diego, CA, November 13, 2007.

178. L. Laksiri, C. Dahyot-Fizelier, S. Lefeuvre, S. Marchand, O. Mimoz, R. J. Sawchuk, and W. Couet. "Microdialysis Study of Imipenem Distribution in the Peritoneal Fluid of Patients with Peritonitis". *Interscience Conference on Antimicrobial Agents and Chemotherapy*, Washington, DC. October 26, 2008.

179. R. J. Sawchuk, G. M. Wall, B. W. Y. Cheung, L. L. Cartier, and D. B. Madhura. "Trans-tympanic Membrane Delivery of an Antibiotic into Chinchilla Middle Ear: a Model for the Treatment of Otitis Media". *European Society for Pediatric Infectious Diseases Meeting 2010*, Nice, FR, May 4-8, 2010.

180. R. J. Sawchuk, B. W. Y. Cheung, L. L. Cartier, D. B. Madhura, and L. Maertens. "An Acute Otitis Middle Ear Model in the Chinchilla with Implanted Tympanostomy Tubes". *European Society for Pediatric Infectious Diseases Meeting 2012*, Thessaloniki, GR, May 8-11, 2012.

EXHIBIT B

MATERIALS CONSIDERED LIST

Exhibit	Description
1001	U.S. Patent No. 8,329,680 ("the '680 patent")
1007	Howell et al., *Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer*, 74 Brit. J. Cancer 300–08 (1996) ("Howell")
1008	McLeskey et al., *Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant in vivo to the antiestrogen ICI 182,780 and two aromatase inhibitors*, 4 Clin. Cancer Research 697–711 (1998) ("McLeskey")
1009	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")
1011	Institution Decision in *Mylan Pharms. Inc. v. AstraZeneca AB*, Paper No. 11, IPR2016-01325 (P.T.A.B. Dec. 14, 2016)
1012	Declaration of Diane Burgess, Ph.D. (portions)
1013	Declaration of Richard Bergstrom, Ph.D. and Accompanying Exhibits
1015	Declaration of Adrian Harris, M.B., Ph.D. (portions)
1019	Declaration Under 37 C.F.R. § 1.132 of Ronald J. Sawchuk in Application No. 12/285,887
1020	Declaration Under 37 C.F.R. § 1.132 of Paul Richard Gellert in Application No. 10/872,784
1032	Nicholson, R.I. et al., *Responses To Pure Antiestrogens (ICI 164384, ICI 82780) In Estrogen-Sensitive And –Resistant Experimental And Clinical Breast Cancer*, 61 Annals Of The New York Academy Of Sciences, 148-163 (1995) ("Nicholson")
1036	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")
1037	WO 03/006064
1038	DeFriend et al., *Investigation of a New Pure Antiestrogen (ICI 182780) in Women with Primary Breast Cancer*, 54 Cancer Research 408–414 (1994) ("DeFriend")
1042, at 549-556	Copy of Prosecution History for U.S. Patent No. 8,329,680 (downloaded from PAIR)

Exhibit	Description
1053	Nicholson, *Pure Antioestrogens in Breast Cancer: Experimental and Clinical Observations, in Sex Hormones and Antihormones in Endocrine Dependent Pathology: Basic and Clinical Aspects*, Proceedings of an International Symposium, Milano 347-60 (1994) ("Nicholson")
1055	EP 0 346 014
1057	Dukes, *Antiuterotrophic Effects of the Pure Antioestrogen ICI 182,780 in Adult Female Monkeys (*Macaca nemestrina*): Quantitative Magnetic Resonance Imaging*, 138 J. Endocrinology 203-09 (1993)
1058	Wakeling, *The Future of New Pure Antioestrogens in Clinical Breast Cancer*, 25 Breast Cancer Research & Treatment 1-9 (1993) ("Wakeling")
1062	Freireich, *Quantitative Comparison of Toxicity of Anticancer Agents in Mouse, Rat, Hamster, Dog, Monkey, and Man*, 50 Cancer Chemotherapy Reports 219-44 (1966)
1075	Robertson, J.F.R. et al., *A Partially-Blind, Randomised, Multicentre Study Comparing the Anti-Tumor Effects of Single Doses (50, 125 and 250 mg) Of Long-Acting (LA) 'Faslodex' (ICI 182,780) With Tamoxifen In Postmenopausal Women With Primary Breast Cancer Prior To Surgery*, in 22nd Annual San Antonio Breast Cancer Symposium, Abstract No. 28 (Dec. 8-11, 1999) ("Robertson 1999")
1082	Adam, *Pharmacokinetics of Agents in Relation to Response, in Endocrine Management of Cancer: Biological Bases* 112-24 (1988)
1083	Baselga, *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14 J. Clinical Oncology 737-44
1085	Goldenberg, *Trastuzumab, a Recombinant DNA-Derived Humanized Monoclonal Antibody, a Novel Agent for the Treatment of Metastatic Breast Cancer*, 21 Clinical Therapeutics 309-18 (1999)
1086	Wilkinson, *Tamoxifen (Nolvadex*) Therapy – Rationale for Loading Dose Followed by Maintenance Dose for Patients with Metastatic Breast Cancer*, 10 Cancer Chemotherapy Pharmacology 33-35 (1982)

Exhibit	Description
1090	Robertson, *Fulvestrant (Faslodex)—How to Make a Good Drug Better*, 12 Oncologist 774-84 (2007)
2043	Declaration of Sandra McLeskey, Ph.D. (Oct. 1, 2014) ("McLeskey Declaration")
2048	E. J. Thomas et al., *The effects of ICI 182780, a pure antioestrogen on reproductive endocrinology in normal pre-menopausal women*, 137S J. Endocrinol. 183 (1993) ("Thomas 1993")
2080	Mark A. Longer et al., *Sustained-Release Drug Delivery Systems, in Remington's Pharmaceutical Sciences*, Ch. 91 (Alphonso R. Gennaro ed., 18th ed. 1990) ("Remington's Ch. 91")
2134	Nicholas G. Lordi, *Sustained Release Dosage Forms, in The Theory & Practice of Industrial Pharmacy*, Ch. 14 (Leon Lachman et al. eds., 1986) ("Lachman's")
2168	Ralph B. D'Agostino et al., *A Suggestion for Using Powerful and Informative Tests of Normality*, 44 American Statistician 316 (1990) ("D'Agostino")
2169	Physician's Desk Reference, 53d ed., 3309-11 (1999) ("PDR 1999 Inderal® LA")
2170	*Variability, in Clinical Pharmacokinetics Concepts and Applications*, Ch. 13 (Malcolm Rowland et al. eds., 3d ed. 1995) ("Rowland Ch. 13")
2171	S. S. Shapiro et al., *An analysis of variance test for normality (complete samples)*, 52 Biometrika 591 (1965) ("Shapiro")