UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INNOPHARMA LICENSING, LLC.

Petitioner

v.

ASTRAZENECA AB

Patent Owner

Case IPR2017-00904

U.S. Patent 6,774,122

DECLARATION OF LISBETH ILLUM, Ph.D. IN SUPPORT OF PATENT OWNER'S PRELIMINARY RESPONSE

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I, Lisbeth Illum, 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 £500 per hour for my consultation in connection with this proceeding. My compensation is in no way dependent on the outcome of my analysis or opinions rendered in this proceeding. A copy of my curriculum vitae, which includes my educational background, work / research history, and lists of selected publications and presentations, is attached to this declaration as Exhibit A.

II) QUALIFICATIONS AND EXPERIENCE

3. My name is Lisbeth Illum, Ph.D. I am a Danish citizen, born in Aalborg, Denmark in 1947. Currently, I am a resident of the United Kingdom, and have been since 1987. I gained my Danish A levels at Horsens Statsskole in 1966, my MPharm First Class Honours Degree from the Royal Danish School of Pharmacy in 1972, and my Ph.D. and D.Sc. in Pharmaceutical Sciences in 1978 and 1987, respectively, both from the Royal Danish School of Pharmacy.

4. I worked as a lecturer / senior lecturer in the Royal Danish School of Pharmacy between 1972 and 1990. I upheld a Postgraduate Scholarship between 1975 and 1978 and a Senior Research Fellowship between 1982 and 1985. I was a

Visiting Research Fellow in the Pharmacy Department at University of Nottingham during several periods between 1981 and 1990.

5. I was made a Docent (Full Professor equivalent) in the Department of Pharmaceutical Sciences, Royal Danish School of Pharmacy, in 1989. I was made a Special Professor at the University of Nottingham, UK, in the Department of Pharmaceutical Sciences in 1990, and in the Department of Chemistry in 2007.

6. I was the founder, and for twelve years the Managing Director, of DanBioSyst UK Ltd. (later West Pharmaceutical Services, now Archimedes Ltd) (1989-1998), a company that specializes in development of drug delivery systems for pharmaceutical drugs, and when sold to West Pharmaceutical Services employed 45 scientists. In addition, I was the founder and Managing Director of Phaeton Research Ltd. (2003-2005) until it was sold and the CEO of Critical Pharmaceuticals Ltd, a drug delivery company based in BioCity in Nottingham from 2007-2011. I am presently the Founder and Director of Eurocage Ltd., a drug delivery consultancy company, the directors of which also act as pharmaceutical experts in litigation cases.

7. My research expertise covers the area of novel drug delivery systems for difficult to formulate drugs such as peptides, proteins, polar and lipophilic small molecular weight compounds. I have extensive experience in novel

approaches to the delivery of such drugs including the use of various routes of delivery such as oral, nasal, buccal, pulmonary, vaginal and parenteral.

8. I have published more than 350 scientific papers (about 90 in the last ten years) and I am among the top 100 most cited scientists on pharmacology, with an h index of more than 60. I have co-edited four books related to drug delivery, drug therapy, and drug transport. I am the inventor or co-inventor on nearly fifty patent family applications on novel drug delivery systems. A large number of patents has been granted worldwide from this patent portfolio.

9. I have been the recipient of several scientific awards and have been elected a Fellow of the American Association of Pharmaceutical Scientists and of the Controlled Release Society as one of the first recipients. I have lectured widely throughout the world at conferences and workshops on drug delivery systems. I am or have been on the Editorial Boards of eleven pharmaceutical scientific journals, and a reviewer for many more journals. I was in 2008/2009 the President of the U.S.-based Controlled Release Society, with over 2000 members dedicated to the science of delivery of bioactive agents.

10. A list of U.S. cases in which I have testified at trial or by deposition within the preceding four years is attached at Exhibit B.

III) MY UNDERSTANDING OF THE PROCEEDING

11. I have been informed that this proceeding is a petition for Inter Partes Review before the Patent Trial and Appeal Board of the United States Patent and Trademark Office ("the Board"). I have been informed that an Inter Partes Review 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.

12. I have been informed that InnoPharma Licensing, LLC ("InnoPharma") filed a Petition requesting Inter Partes Review ("Petition") of U.S. Patent No. 6,774,122 ("the '122 Patent"), which issued to John R Evans and Rosalind U Grundy on August 10, 2004 and is assigned to AstraZeneca AB. I have reviewed the Petition, and understand that it alleges that claims 1, 2, 5, and 9 of the '122 Patent are unpatentable over Howell 1996 (Ex. 1007) and, alternatively, over the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008), and the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008) and O'Regan (Ex. 1009).

IV) MY OPINIONS AND THEIR BASES

13. I have been asked to give my opinion on whether InnoPharma has shown with reasonable likelihood that a person of ordinary skill in the art ("POSA") would understand claims 1, 2, 5, and 9 of the '122 Patent to be rendered

obvious by: (1) Howell 1996 (Ex. 1007); (2) the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008); or (3) the combination of Howell 1996 (Ex. 1007) with McLeskey (Ex. 1008) and O'Regan (Ex. 1009). Most of my opinions herein are a direct repeat of the opinions in my declaration submitted in support of AstraZeneca's Preliminary Patent Owner Response in *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, Case IPR2016-01325 (*see* AstraZeneca Ex. 2001) attached hereto for the Board's convenience as Ex. 2135 (Illum Decl.).

14. 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 '122 Patent claims priority.

15. For the reasons explained below, in my opinion, InnoPharma has not shown that there is a reasonable likelihood that it would prevail in an *inter partes* review of claims 1, 2, 5, and 9 of the '122 Patent.

V) DOCUMENTS CONSIDERED

16. The materials that I have considered, in addition to the exhibits to the Petition, are listed in Exhibit C. My opinions as stated in this Declaration are based on the understanding of a POSA in the art as defined above and in ¶ 25, below.

VI) THE '122 PATENT SPECIFICATION AND CLAIMS

17. I have been informed that the priority date of the '122 Patent is January 10, 2000. The invention relates to "a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound [fulvestrant], more particularly to a formulation adapted for administration by injection containing the compound [fulvestrant] in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle." Ex. 1001 at Abstract.

18. The specification of the '122 Patent explains that "[f]ulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult." Ex. 1001 at 2:46-48. Specifically, "[f]ulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$." Ex. 1001 at 2:48-51.

19. The inventors of the '122 Patent "surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 $mgml^{-1}$." Ex. 1001 at 5:48-51. This was surprising because "[t]he solubility of fulvestrant in non-aqueous ester solvents . . . is significantly lower

than the solubility of fulvestrant in an alcohol" and "in castor oil." Ex. 1001 at 5:52-57. In addition, the inventors noted that "[s]imply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site." Ex. 1001 at 9:20-22.

20. Therefore, the inventors further found that the claimed inventions "provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time." Ex. 1001 at 8:30-32. The specification of the '122 Patent states that "[b]y use of the term 'therapeutically significant levels' we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient." Ex. 1001 at 9:1-6. Further, the specification describes "extended release" as "at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved." Ex. 1001 at 9:7-9. In addition, the inventors found that "the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site." Ex. 1001 at 10:52-55.

21. Independent claim 1 of the '122 Patent is provided below.

> 1. A method of treating a hormonal dependent benign or malignant disease of the breast or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation

comprising fulvestrant, a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle, whereby a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ is attained for at least 2 weeks after injection.

22. Claim 2 limits claim 1 to a method wherein the benign or malignant disease is breast cancer.

23. Independent claim 5 of the '122 Patent is provided below.

> 5. A method of treating a hormonal dependent benign or malignant disease of the br[east] or reproductive tract by administration to a human in need of such treatment an intra-muscular injection of a pharmaceutical formulation comprising fulvestrant, a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and a sufficient amount of a castor oil vehicle whereby the formulation comprises at least 45 mgml of fulvestrant.

24. Claim 9 limits claim 5 to a method wherein the benign or malignant disease is breast cancer.

VII) PERSON OF ORDINARY SKILL IN THE ART

25. I have been asked to provide my opinion on the novelty and obviousness of the asserted claims from the perspective of a person of ordinary skill in the relevant art. The skilled person with respect to the '122 Patent is 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, preclinical models, or the clinical treatment of hormone dependent diseases of the breast and reproductive tract. Because the drug discovery and development process is complicated and multidisciplinary, it would require a team of individuals including, at least, medical doctors, pharmacokineticists, and formulators.

26. As considered from the perspective of the formulator member of that team, the invention of the '122 Patent is novel, and not obvious, for the following reasons.

VIII) LEGAL PRINCIPLES

27. I am not a lawyer. I have relied on the explanations of counsel for an understanding of certain principles of U.S. patent law that govern the determination of patentability. The discussion set forth below regarding the law of

obviousness is intended to be illustrative of the legal principles I considered while preparing my declaration, and not an exhaustive list.

28. I understand that to institute an *inter partes* review, InnoPharma must show that there is a reasonable likelihood that it would prevail in an *inter partes* review. I am informed by counsel that there is no presumption of validity. If an *inter partes* review is instituted, InnoPharma must show unpatentability by a preponderance of the evidence, and preponderance of the evidence means "more probable than not."

29. I am informed by counsel that for a patent claim to be invalid as anticipated by a prior art reference, that reference must disclose every limitation of the claim. Thus, if the limitations of a patent claim were already disclosed, in their entirety, by a single prior art reference, that claim is anticipated and not novel.

30. I am informed by counsel that for an invention to be obvious, the patent statute requires that the differences between the invention and the prior art be such that the "subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art to which such subject matter pertains."

31. I understand that the obviousness evaluation must be from the perspective of the time the invention was made. In the current proceeding, I understand that the relevant date is considered to be the earliest priority date of the

applications, which is January 10, 2000. The obviousness inquiry must guard against slipping into use of hindsight.

32. I understand that even in circumstances where each component of an invention can be found in the prior art, there must have been an apparent reason to combine the known elements in the fashion claimed by the patent at issue. For an invention to be found obvious, to protect against the distortion caused by hindsight bias, there must be a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

33. To be obvious, the claimed method of treatment must have been among a finite number of identified, predictable solutions to the problems at hand.

IX) CLAIM CONSTRUCTION

34. In independent claim 1, the term "whereby a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ is attained for at least 2 weeks after injection" is a claim limitation entitled to patentable weight. Independent claim 1 does not specify the total amount of fulvestrant to administer to the patient. Instead, the desired blood plasma level of fulvestrant, for example, limits the method of claim 1 to an amount of fulvestrant that achieves and maintains 2.5 $ngml^{-1}$ for at least two weeks after injection. The claimed methods cannot be practiced without knowing the target blood plasma levels, which then

allows administration of an appropriate amount of fulvestrant to reach those levels. Hence, the blood plasma levels absolutely inform how the method of administering the fulvestrant formulation to a human patient is carried out.

35. The formulator would understand "whereby a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ is attained for at least 2 weeks after injection" to mean that the blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ is achieved and maintained for at least two weeks. The plain meaning of the words "attained" and "at least" indicate to the formulator that the patient's blood plasma level must remain at or above 2.5 for the entire specified time period. This is consistent with the Board's finding in *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, Case IPR2016-01325, Paper No. 11 (Dec. 14, 2016) (Ex. 1011) ("PTAB Decision") which InnoPharma does not dispute. 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."); Petition at 18. Further, these limitations give meaning to and provide defining characteristics of the method of treatment.

36. 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 (citing Ex. 2136 (Robertson Decl.) at ¶¶ 37-39, Ex. 2135 (Illum Decl.) at ¶¶ 33-37. And, "[t]hat these parameters are further limited in claim 2, [] further indicates that the wherein clauses provide defining characteristics." *Id.* (citing Ex. 2133 (Sawchuk Decl.) at ¶ 60). InnoPharma does not dispute this finding. Petition at 18. This understanding is also supported by authoritative treatises in the art. Ex. 2080 (Remington's Ch. 91) at 6 ("The objective in designing a sustained-release system is to deliver drug at a rate necessary to ***achieve and maintain*** a constant drug level.") (emphasis added); *see also* Ex. 1010 (Order by Judge Bumb of the District of New Jersey).

37. The specification indicates that a goal of the invention is sustained release. The specification describes the problem of formulating fulvestrant: "when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate." Ex. 1001 at 5:25-30. The inventors noted that "[s]imply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site." Ex. 1001 at 9:20-22. Thus, the inventors faced the problem not

only of dissolving a sufficient amount of fulvestrant in a formulation but also engineering a therapeutically significant release rate and duration and furthermore developing a formulation that could provide such a pharmacokinetic profile without causing precipitation at the injection site.

38. The inventors "surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and [in] an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 $mgml^{-1}$." Ex. 1001 at 5:48-51. The inventors further found that the claimed formulations "provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time." Ex. 1001 at 8:30-32. In addition, Table 4 of the patent showed that the claimed methods avoid precipitation that occurred in other fulvestrant formulations. Ex. 1001, Table 4. The inventors concluded that "the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site." Ex. 1001 at 10:52-55.

X) STATE OF THE RELEVANT ART

A) Formulation Background

39. "The development of an optimum formulation is not an easy task, and many factors readily influence formulation properties." Ex. 2081 (Remington's

Ch. 75) at 5. Such factors include biopharmaceutical considerations, drug factors, and therapeutic considerations. Ex. 2082 (Aulton Ch. 1) at 5.

40. A successful formulation of an active pharmaceutical ingredient must deliver the active ingredient in such a way that it is biologically effective. This often requires meeting certain parameters, such as blood plasma concentrations and/or duration. Ex. 1091 (Ansel Ch. 4) at 5 ("The magnitude of the response is related to the concentration of the drug achieved at the site of its action."). In such cases, the delivery method and formulation must ensure that a sufficient amount of the active ingredient enters the circulation when introduced into the body to deliver the active ingredient to the site of action (normally via the bloodstream).

B) The Claimed Blood Plasma Levels Are Critical To The Inventions

41. The skilled formulator would know that the release profile of a drug from the formulation, its absorption into the blood stream and hence its pharmacokinetic profile are critical factors influencing the action of the drug on the patient. Ex. 1091 (Ansel Ch. 4) at 43 ("[T]he objective of pharmacokinetic dosing is to design a dosage regimen that will continually maintain a drug's therapeutic serum or plasma concentration within the drug's therapeutic index, i.e., above the minimum effective concentration but below the minimum toxic level."); Ex. 2080 (Remington's Ch. 91) at 5 ("The goal of any drug delivery system is to provide a

therapeutic amount of drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration.").

42. Depot formulations are particularly challenging. For instance, if too much drug is released immediately from the formulation, the blood plasma concentration may reach the minimum toxic level and cause side effects. Ex. 2080 (Remington's Ch. 91) at 5. Additionally, if too much of a drug reaches the blood stream immediately after the injection and is eliminated, insufficient drug will be left at the depot to sustain the therapeutic levels over the long term. On the other hand, if too little drug reaches the blood stream immediately after injection, the therapeutic effect of the treatment could be delayed or be limited. Ex. 2080 (Remington's Ch. 91) at 5. If the release rate is inconsistent and plasma levels spike and plummet, the biological threshold necessary to trigger a therapeutic response may not be reached at all.

43. The inventors surprisingly discovered a treatment method that combined a specific pharmacokinetic profile (fulvestrant blood plasma levels maintained over a particular time) with a specific administration method for therapeutic action. From my perspective as a formulator, the fulvestrant blood plasma levels in the claims are a clear limitation on the frequency of administration (every two weeks) and of the amount of fulvestrant to be dosed. That the claims differ make that clear. The entire combination of the invention ensures that the

level of fulvestrant in the patient's blood plasma is consistent, steady, and maintained over a relatively long period of time at therapeutically effective levels. The successful use of the benzyl benzoate ingredient was particularly surprising in that the addition of benzyl benzoate to the formulation would have been predicted to be associated with a lower fulvestrant solubility in the formulation, leading to a greater chance of precipitation. In sum, the claimed inventions (and, with that, the use of benzyl benzoate) surprisingly achieved and maintained therapeutically significant fulvestrant plasma levels, as compared to other fulvestrant formulations.

C) Formulation Options

44. A person wishing to formulate a highly lipophilic molecule, such as fulvestrant, for administration to humans on a commercial basis, had many choices for each step of the process. The field of drug formulation was wide open, replete with multi-variable and interconnected possibilities, and lacking clear guideposts to suggest a particular direction. Most importantly, there was (and currently is) no "one size fits all," or single best approach to formulation. Thus, a formulator would be aware of the many options available for formulating an active pharmaceutical ingredient.

45. Each active pharmaceutical ingredient has unique characteristics. For each active ingredient, there will be many potential choices for administration route, dosage form, and formulation. Physical and chemical properties of drug

substances important in dosage form design, include organoleptic properties, particle size, surface area, solubility, dissolution, partition coefficient, ionization constant, crystal properties, polymorphism, and stability. Ex. 2082 (Aulton Ch. 1) at 10.

46. "Drugs may be administered by a variety of dosage forms and routes of administration." Ex. 1091 (Ansel Ch. 4) at 24. Examples of routes of administration are oral, buccal, sublingual, nasal, pulmonary, transdermal, vaginal, rectal, and parenteral. Ex. 2082 (Aulton Ch. 1) at 5-9; Ex. 1091 (Ansel Ch. 4 1999) at 24-32. Parenteral administration further included many options: intravenous, subcutaneous, intradermal, intramuscular, intraarticular and intrathecal. Ex. 2084 (Remington's Ch. 84) at 5. "The nature of the product will determine the particular route of administration that may be employed. Conversely, the desired route of administration will place requirements on the formulation." Ex. 2084 (Remington's Ch. 84) at 5.

47. Each of the routes of administration listed above are fundamentally different, and would result in different absorption profiles of the drug after administration, because the drug is delivered to fundamentally different biological environments. Each biological environment is different anatomically and physiologically and has different barriers to drug absorption. Ex. 2082 (Aulton Ch. 1) at 7 ("The absorption pattern of drugs varies considerably between one

another as well as between each potential administration route."); Ex. 1091 (Ansel Ch. 4) at 24 ("The difference in drug absorption between dosage forms is a function of the formulation and the route of administration."); Ex. 1099 (Aulton Ch. 21) at 7 ("[F]ormulation, coupled with variation in the site of administration may affect markedly the biopharmacy of drugs."); Ex. 2086 (Groves Ch. 2) at 16 ("The effect (i.e., rate and intensity of action) produced by a drug may vary according to the route of administration.").

48. The formulator must also decide on a dosage form from the many available options for each administration route. Examples of oral dosage forms are tablets, capsules, solutions, syrups, elixirs, suspensions, magmas, gels, and powders. *See* Ex. 1091 (Ansel Ch. 4) at 25. For injectable drugs, dosage forms include aqueous and oil-based solutions and dispersed systems, such as suspensions, emulsions, liposomes, and other microparticulate systems. Ex. 2087 (Gupta Ch. 1) at 20. Additionally, parenteral products may be lyophilized (freeze-dried) and then reconstituted before use. Ex. 2086 (Groves Ch. 2) at 11.

49. An excipient is a natural or synthetic substance included in a formulation alongside the active ingredient for the purpose of producing the dosage form. Excipients can also have specific functions in, for example, a parenteral formulation, such as stabilizing the drug or formulation, facilitating drug absorption, adjusting pH, reducing viscosity, enhancing solubility, acting as a

solvent, and providing a modified release profile. Many excipients can serve more than one function.

50. The selection of appropriate excipients also depends upon the route of administration and the dosage form, as well as the active ingredient and other factors. For parenteral administration, many excipients had previously been used in approved commercial products. *See* Ex. 1102 (Nema) at 1 (listing categories of excipients, including solvents and co-solvents; solubilizing, wetting, suspending, emulsifying or thickening agents; chelating agents; antioxidants and reducing agents; antimicrobial preservatives; buffers and pH adjusting agents; bulking agents, protectants, and tonicity adjustors; and special additives); Ex. 1105 (Powell) (listing over 140 excipients used in marketed parenteral formulations).

XI) REFERENCES CITED IN THE PETITION AND BURGESS DECLARATION

51. Dr. Burgess's discussion of the "scope and content of the prior art" is limited to three references selected by hindsight: Howell 1996 (Ex. 1007); McLeskey (Ex. 1008); and O'Regan (Ex. 1009). Ex. 1012 (Burgess Decl.) at ¶¶ 76-96; Petition at 19-26. This limited selection looks backwards from the present day, ignoring the perspective that a skilled formulator would have had at the time of the invention. As I discuss above, the universe of options for formulations of a drug such as fulvestrant available to a skilled formulator was broad, with many options available at every step of the process to the finished dosage form. In my

view, the references in the Petition and Burgess 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.

52. This selection of prior art is itself driven by hindsight. As discussed above, there were numerous formulation handbooks and treatises available to a formulator, as well as many examples of successful formulations of lipophilic or poorly-soluble molecules in the art, including many marketed formulations using different routes of administration such as oral, nasal, pulmonary, transdermal and parenteral. In addition, as discussed in more detail below (*infra* ¶¶ 144-146, 208-212), there were many experimental formulations of fulvestrant known in the art, other than those discussed by Dr. Burgess. Dr. Burgess ignores the broad range of disclosures in the art and uses knowledge of the invention formulation to select, without providing any reason or motivation, the three references deemed closest to the claimed invention. For instance, Dr. Burgess apparently selects Howell 1996 based on Dr. Harris' argument that it "provides the most robust clinical data on fulvestrant at the time of the invention." Ex. 1012 (Burgess Decl.) at ¶ 83. But, Dr. Burgess ignores other clinical studies (Thomas and DeFriend), and tries to combine Howell 1996 with experiments in an in vitro cell model and an engineered mouse model that have nothing to do with clinical treatment (McLeskey).

A) McLeskey (Ex. 1008)

53. The study in McLeskey is related to a model of a hormone-*in*dependent pathway for cancer cell growth. In particular, the model described in McLeskey comprises a MCF-7 (breast carcinoma) cell line engineered to express a fibroblast growth factor (FGF). Ex. 1008 at 1. The authors injected the cells into mice and used this model to evaluate whether tamoxifen resistance is related to FGF signaling pathways. Ex. 1008 at 1. To validate this model, McLeskey described the experimental use of multiple antiestrogen drugs, including two different fulvestrant formulations, tamoxifen and two aromatase inhibitors, letrozole and 4-OHA. Ex. 1008 at 1-2.

54. McLeskey administered fulvestrant "s.c. at a dose of 5 mg in 0.1 ml of vehicle every week" in either a peanut oil or a castor oil based formulation. Ex. 1008 at 2. The title of McLeskey declares that the tumors studied were "Cross-Resistant *in Vivo* to the Antiestrogen ICI 182,780." Ex. 1008 at 1. The abstract explains that the fulvestrant formulations "did not slow estrogen-independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice." Ex. 1008 at 1. And, in the discussion section McLeskey concluded that ICI 182,780 was a "treatment failure." Ex. 1008 at 10.

55. McLeskey tested two formulations of fulvestrant: for one, "powdered [fulvestrant] was first dissolved in 100% ethanol and spiked in warmed peanut oil"

to a final concentration of 50 mg/ml; the other was 50 mg/ml fulvestrant "in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil." Ex. 1008 at 2. As noted above, McLeskey did not state whether the fulvestrant formulations described in that reference were solutions or suspensions, nor did McLeskey contain any solubility data for fulvestrant.

1) McLeskey Describes A "Treatment Failure"

56. Dr. Burgess ignores the clear statement in McLeskey that the fulvestrant formulations were "treatment failure[s]." Ex. 1008 at 10. The issue is whether the skilled artisan would understand from McLeskey that the specific castor oil-based formulation in McLeskey successfully delivered fulvestrant. The skilled formulator would not select a self-described "treatment failure" as a reference for formulation design. There is nothing in McLeskey that would suggest the castor oil-based formulation successfully delivered the fulvestrant—no efficacy results and no pharmacokinetics data.

2) McLeskey Did Not Test Formulations For Human Use

57. A skilled formulator would recognize that the drug formulations in McLeskey were not suitable for human use. For example, McLeskey used subcutaneous "tamoxifen pellets" from Innovative Research of America, which are a research formulation only. Ex. 2044 (Innovative Research) at 13 ("All products in this catalog are sold for investigational use in laboratory animals only and are

not intended for diagnostic or drug use."); In contrast, for humans, tamoxifen was marketed in oral tablet form. Ex. 2045 (PDR 1999 Nolvadex®) at 4. Likewise, the authors of McLeskey administered letrozole in a liquid vehicle of 0.3% hydroxypropyl cellulose via gavage—for humans, letrozole was approved and sold as oral tablets, with excipients including ferric oxide, microcrystalline cellulose, and magnesium stearate. Ex. 2046 (PDR 1999 Femara®) at 12. The McLeskey authors administered 4-OHA, also known as formestane, in an aqueous vehicle of 0.3% hydroxypropyl cellulose by subcutaneous injection once daily, six days a week—for humans, it was approved in Europe for intramuscular injection every two weeks. Ex. 1054 (Santen) at 8.

58. In fact, InnoPharma and Dr. Burgess agree. InnoPharma acknowledges that the tamoxifen and letrozole formulations were special mouse formulations and similarly argue that the peanut oil formulation of fulvestrant would also not be acceptable for humans. Innopharma describes the tamoxifen pellet and letrozole gavage formulations in McLeskey as "formulations of drugs that are typically administered orally in the clinical setting and necessarily need to be ***specially formulated*** for administration to mice." Petition at 24 (emphasis added). Moreover, Dr. Burgess argues that "[o]ne skilled in the art would recognize that this [peanut oil] formulation would not be preferred for use in humans due to potential allergy concerns." Ex. 1012 (Burgess Decl.) at ¶ 87.

59. And, the use by McLeskey of formulations designed for animal administration is consistent with the fact that the work being done in McLeskey was basic biological research, not work aimed directly at human treatment, which Dr. Burgess also acknowledges. Ex. 1012 (Burgess Decl.) at ¶¶ 84-87, 209-210, 252.

3) McLeskey Provides No Pharmacokinetic Data

60. McLeskey does not provide any pharmacokinetic data for any formulation. An ordinary researcher would not find the lack of pharmacokinetic data surprising, given that the study was designed to look at issues relating to basic science and not drug formulation. McLeskey does not teach treatment of hormonal dependent disease, treatment of humans, intramuscular injection of fulvestrant with the claimed combination of formulation excipients in their respective amounts, dosing frequency or minimum plasma levels.

4) McLeskey Does Not Disclose The Units For The Excipient Percentages

61. InnoPharma claims that McLeskey discloses "the exact same formulation recited in the challenged claims." Petition at 2. However, McLeskey does not disclose the units of the percentages of excipients: McLeskey only states that "50 mg/ml preformulated drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil, was supplied by B.M. Vose (Zeneca Pharmaceuticals)." Ex. 1008 at 2. McLeskey says nothing

about whether the percentages are in weight per volume (% v/v) or volume per volume (% w/v). In fact, Dr. McLeskey confirmed that she assumed that the castor oil-based formulation that she used in McLeskey was in % v/v and not % w/v. Ex. 2043 (McLeskey Declaration) at ¶ 8.

62. The difference between % v/v and % w/v results in different amounts of each component in the formulation, as the below table summarizes. A skilled formulator would not know if the differences in percentages of each component would affect the activity of fulvestrant in humans; the results would be unpredictable.

Table XVI: Percent Difference of Ethanol, Benzyl Alcohol, and Benzyl Benzoate When Calculated in % w/v and % v/v

Component	% v/v	Volume (ml)	Density (mg/ml)	Weight (g)	% w/v	% Difference
Ethanol	10	10	0.808	8.08	8.1	-19%
Benzyl alcohol	10	10	1.04156	10.42	10.4	+4%
Benzyl benzoate	15	15	1.118	16.77	16.8	+12%

63. The reference cited by Dr. Burgess, the United States Pharmacopeia, teaches:

Percentage concentrations are expressed as follows:

Percent Weight in Weight — (w/w) expresses the number of g of a constituent in 100 g of solution.

Percent Weight in Volume — (w/v) expresses the number of g of a constituent in 100 mL of solution, and is used regardless of whether water or another liquid is the solvent.

Percent Volume in Volume — (v/v) expresses the number of mL of a constituent in 100 mL of solution.

The term percent used without qualification means, for mixtures of solids, percent weight in weight; for solutions or suspensions of solids in liquids, percent weight in volume; ***for solutions of liquids in liquids, percent volume in volume;*** and for solutions of gasses in liquids, percent weight in volume.

Ex. 2132 (Remington's Ch. 9) at 32 (emphasis added); *see* Ex. 1012 (Burgess Decl.) at ¶ 222. All of the excipients in the castor oil-based formulation of McLeskey (benzyl alcohol, ethanol, benzyl benzoate, and castor oil) are liquids. According to the USP's statement that "for solutions of liquids in liquids, percent volume in volume" is used, the skilled artisan would expect these excipients to be measured in % v/v.

64. Dr. Burgess argues that "formulators generally prefer to use w/v measurements rather than v/v measurements because measuring by weight is more accurate and more consistent than measuring by volume," but provides no support for this statement. Ex. 1012 (Burgess Decl.) at ¶ 221. In fact, the skilled

formulator would understand that making a research formulation in small quantities would be easier in the lab using % v/v than % w/v.

65. Dr. Burgess argues that "one skilled in the art would be familiar with the numerous injectable formulations that are described with weight per volume units." Ex. 1012 (Burgess Decl.) at ¶ 223. But, Dr. Burgess ignores the many examples of liquid excipients in liquid formulations disclosed in % v/v. *See, e.g.*, Ex. 1102 (Nema) at 2 (tabulating various excipients included in approved injectable formulations in the United States, and listing liquids and reporting commercial descriptions of liquids in terms of % v/v, including benzyl benzoate (20% v/v) and ethanol (80% v/v)); Ex. 1033 (Riffkin) at Tables IV, V, and VI (describing components in percentages that add up to 100%, and therefore must be % v/v and not % w/v). As the above examples demonstrate, there was clearly no requirement that formulations be described in % w/v, as many liquid components were described in % v/v.

66. Although McLeskey provides the units of % w/v for fulvestrant concentration, the excipients in the description of the formulation in McLeskey are all liquids. It was (and is) common to describe liquid excipients in % v/v, notwithstanding solid active ingredients being described in % w/v. *See, e.g.*, Ex. 2089 (Vidal 1999) at 3 (Tocogestan); Ex. 2090 (Vidal 1997) at 2-3 (Trophobolene); Ex. 2091 (ABPI 1999-2000) at 3-4 (Sustanon 100).

67. Dr. Burgess states that without knowing the units of the castor oil-based formulation in McLeskey, "the formulator would simply make the formulation according to both weight by volume and volume by volume units to determine which one, or whether both, gave the desired fulvestrant concentration." Ex. 1012 (Burgess Decl.) at ¶ 224. But, Dr. Burgess previously asserted that the skilled formulator would know that the castor oil-based formulation in McLeskey was a solution just by looking at the excipients, ***without knowing the units***. *See* Ex. 1012 (Burgess Dec.) at ¶¶ 89, 199-201. Here, Dr. Burgess says that the formulator would need to determine "***which one, or whether both***, gave the desired fulvestrant concentration." Ex. 1012 (Burgess Decl.) at ¶ 224. Dr. Burgess clearly does not know "which one or whether both are solutions," which, to me, shows that her claims about the skilled artisan choosing McLeskey for solubility are based on hindsight. In any case, Dr. Burgess does not address the patent's teaching that solubility information is not sufficient to determine the intramuscular release profile and tolerability. Only in vivo studies can provide this information. And, indeed that was well-known for intramuscular administration. For example, as described in the literature cited above, the skilled artisan would understand that even small differences in formulation compositions can influence release profile and tolerability. Moreover, as explained below, McLeskey does not describe how to make the castor oil-based formulation in that reference. *See* ¶ 221.

5) McLeskey Does Not Disclose Any Solubility Information

68. McLeskey tested two formulations of fulvestrant: for one, "powdered [fulvestrant] was first dissolved in 100% ethanol and spiked in warmed peanut oil" to a final concentration of 50 mg/ml; the other was 50 mg/ml fulvestrant "in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil." Ex. 1008 at 2. McLeskey nowhere discloses whether either formulation is a solution or a suspension and includes no fulvestrant solubility data. Moreover, no formulation of fulvestrant described in the art as a solution contained the excipients used in the castor oil-based formulation of McLeskey. Furthermore, no solubility data for fulvestrant in castor oil or any other solvent had been published in the prior art.

69. Without any literature support or explanation, Dr. Burgess claims that "[o]ne skilled in the art would immediately recognize that [McLeskey used] a solution based on the high concentrations of solvents included." Ex. 1012 (Burgess Decl.) at ¶ 89. In my opinion, the skilled formulator would not jump to this conclusion. McLeskey never describes ethanol, benzyl alcohol, or benzyl benzoate as cosolvents, and the skilled formulator would not assume that each of these excipients functioned as a cosolvent. Indeed, Dr. Burgess explains other functions for each, citing "anesthetic effects" and "more favorable viscosity." Ex. 1012 (Burgess Decl.) at ¶¶ 123, 114. The skilled formulator would not have

assumed that all of the ingredients were "co-solvents" or that the castor oil-based formulation in McLeskey had a "high" level of cosolvents.

70. Moreover, Dr. Burgess does not explain what makes the level of cosolvents "high" or compare the level of cosolvents in marketed oily suspensions to oily solutions. For example, "[a] review of currently marketed parenteral products shows that [solvent] percentages range from 10 to 100%." Ex. 2052 (Sweetana) at 7.

71. "Solubility in the USP and NF is expressed as the number of milliliters of a solvent that will dissolve 1 g of a solid." Ex. 2132 (Remington's Ch. 9) at 39. Based on this definition, the skilled formulator would know that the amount of solvent necessary to solubilize an active ingredient depends on the amount of the active ingredient and the active ingredient's solubility in the particular solvent. But, in concluding that McLeskey uses a "high" amount of solvents, Dr. Burgess never mentions or considers these factors. In my view, this lack of explanation or support in the literature suggests an argument based on hindsight.

72. Dr. Burgess further states that "[o]ne skilled in the art would also know this formulation was a solution based on the selection of castor oil as the vehicle." Ex. 1012 (Burgess Decl.) at ¶ 89. There is no basis in the prior art to conclude this—the solubility of fulvestrant in castor oil or other oils was not

published. The '122 Patent further contradicts this, stating that "even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate." Ex. 1001 at 5:25-30.

73. Dr. Burgess furthermore asserts that the skilled artisan "would assume the formulations were solutions given that solutions are the preferred vehicle for depot injections." Ex. 1012 (Burgess Decl.) at ¶ 201. McLeskey nowhere characterizes the formulation as a depot. And, Dr. Burgess cites nothing for this "preference." In contrast, as formulation texts describe, there were good reasons to start with a suspension for a depot preparation: "by using suspended drugs in oily vehicles a preparation exhibiting slower absorption characteristics can be formulated to provide a depot preparation." Ex. 2082 (Aulton Ch. 1) at 8-9. Indeed, there are many such examples. Depo Provera® is "a long acting aqueous suspension of medroxyprogesterone acetate administered once every three months" by intramuscular injection. Ex. 2157 (Wright Ch. 4) at 11. As another example, a microsphere formulation for Lupron Depot is reconstituted as a suspension for intramuscular administration. Ex. 2158 (Strickley II) at 26. As the names of Depo Provera and Lupron Depot suggest, depots are not necessarily solutions and have been marketed as suspensions. Other marketed aqueous suspensions include a

variety of penicillin G products, Depo-Medrol, Percoten Pivalate, Aristospan, and Celeston Soluspan. Ex. 2080 (Remington's Ch. 91) at 16.

74. Regardless, McLeskey provides no indication whether fulvestrant in either formulation, peanut oil-based or castor oil-based, is in solution. Dr. Burgess' argument is a misplaced attempt to add a disclosure to McLeskey that is not there.

B) Howell 1996 (Ex. 1007)

75. Howell 1996 is a non-randomized, non-placebo controlled early stage clinical study, seeking to investigate fulvestrant's biological activity in 19 tamoxifen-resistant patients with advanced breast cancer. Howell 1996 discloses the preliminary results from the study.

76. Of the 19 patients treated, 7 had partial responses, 6 showed no change and 6 showed progression of the tumor. Ex. 1007 at 5. Howell 1996 concludes: "[s]ince [fulvestrant] appears devoid of agonist activity, treatment failure via a similar mechanism should not occur, and it is possible, therefore, that this new agent may improve the rate and duration of response in patients with advanced breast cancer. However, further studies are required to confirm the response rate and also to determine the long-term effects of this agent on bone, plasma lipids and the endometrium." Ex. 1007 at 7. This is clearly an early stage

clinical trial as described above, given its limited number of patients with advanced disease and the lack of treatment controls.

77. A person of ordinary skill would interpret the results of Howell 1996 with caution because of the limited patient population. In fact, Howell 1996 suggests that tamoxifen withdrawal could account for some of the 13 (partial and no-change) responders in the study. Ex. 1007 at 7.

78. Regarding the formulation, the authors of Howell 1996 state that "ICI 182780 was administered as a long-acting formulation contained in a castor oil-based vehicle by monthly i.m. injection (5 ml) into the buttock." Ex. 1007 at 2. Howell nowhere states that the formulation administered was a solution. Furthermore, the dose given was disclosed as 250 mg.

79. The Petition never explains why Innopharma considers the Howell 1996 formulation a solution, but Dr. Burgess relies on a separate reference published in the same year for this conclusion, referred to as Howell Breast, that is not a part of any ground and is not mentioned in the Petition. Ex. 1012 at ¶ 78 ("Howell Breast confirms that this formulation was a solution.").

80. Because Howell 1996 does not disclose the specific formulation used, nor whether the formulation is an oil-based solution or suspension formulation, it teaches the ordinary researcher nothing regarding what results would be obtained using any given fulvestrant formulation; those results would have been understood

to differ based on the formulation used and cannot be predicted without conducting a clinical trial. Howell is not a formulation paper investigating one or more formulations of fulvestrant but rather a paper reporting on the therapeutic effect of fulvestrant in tamoxifen resistant breast cancer patients. The authors do not suggest that the formulation used in the study is the final (marketable) version of the formulation for treatment of humans. Hence, nothing in Howell 1996 would have taught the skilled formulator that "the primary goal . . . would have been to develop a formulation that successfully solubilized fulvestrant in castor oil at 50 mg/ml," as suggested by Dr. Burgess. *See* Ex. 1012 (Burgess Decl.) at ¶ 174.

81. Although a dose of 250 mg fulvestrant was used in the Howell study, the "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. Additionally, "[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." Ex. 1007 at 7. Based on these statements, a person of ordinary skill in the art would be motivated to use doses of fulvestrant below 250 mg and to target lower blood fulvestrant levels.

82. Howell 1996 notes that larger trials are necessary to confirm the potential advantages of fulvestrant: "[t]he lack of apparent adverse effects of [fulvestrant] seen in the present study would, if confirmed in future larger trials,

give the specific anti-oestrogen potential advantages over currently available second-line endocrine agents." Ex. 1007 at 6; *see also* Ex. 1038 (DeFriend) at 5 ("[T]he pure antagonist profile of activity of [fulvestrant] in human subjects will need to be confirmed in future clinical studies."). In their "Discussion" section, the authors of Howell further state: "it is possible, therefore, that this new agent may improve the rate and duration of response in patients with advanced breast cancer. However, further studies are required to confirm the response rate and also to determine the long-term effects of this agent on bone, plasma lipids and the endometrium." Ex. 1007 at 7. The skilled artisan would recognize that Howell 1996 is a report of an early-stage clinical trial, given the limited number of patients, advanced disease, and lack of controls. Moreover, the authors refer to the patients as "highly selected." Ex. 1007 at 7.

C) DeFriend (Ex. 1038)[1]

83. DeFriend is a first-in-humans randomized and placebo controlled study in 56 women with primary breast cancer to evaluate the biological activity of fulvestrant as an estrogen antagonist in primary breast tumors *in vivo*. DeFriend

[1] Although not included in any ground that challenges the claims of the '122 patent, InnoPharma and Dr. Burgess cite DeFriend in ground 4 related to the '680 Patent.

provides only "preliminary evidence to suggest" biological activity in primary tumors, i.e., inhibition of tumor cell proliferation. Ex. 1038 at 6. DeFriend suggests that fulvestrant should be further evaluated to determine "whether a pure estrogen antagonist offers any additional benefit in the treatment of human breast cancer" over traditional treatments, such as tamoxifen. Ex. 1038 at 1. In particular, the authors caution that "the pure [estrogen] antagonist profile of activity of [fulvestrant] in human subjects will need to be confirmed in future clinical studies." Ex. 1038 at 5. In other words, additional early stage work would need to be done to test biological activity in humans.

84. In terms of the fulvestrant formulation, DeFriend administered for seven consecutive days, an intramuscular injection of a short-acting formulation containing 20 mg/ml fulvestrant in a propylene glycol-based vehicle at two dose levels, 6 mg and 18 mg. Ex. 1038 at 2. DeFriend stated that the formulation was "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.

85. DeFriend reports that "[a]nimal studies have demonstrated considerable interspecies variability in the elimination half-life of [fulvestrant], with a half-life of about 4 h in rats and 2 days in dogs after [intramuscular] administration." Ex. 1038 at 5. DeFriend provides fulvestrant serum

concentrations for the seven-day treatment period in Figure 1, but the data do not establish specific therapeutically significant fulvestrant blood plasma concentrations over 2 weeks from one dose. Additionally, Figure 1 shows accumulation of fulvestrant in the blood stream after repeated injections. Furthermore, the paper provides no basis for predicting the blood plasma levels of any different fulvestrant formulation. DeFriend would have encouraged the investigation of a short-acting formulation such as the propylene glycol fulvestrant formulation or a once-daily tablet.

86. DeFriend only mentions a future study planned for a long-acting castor oil-based fulvestrant formulation, and says that "[i]t is possible, therefore, that these adverse events were related either to the drug itself, or to the propylene glycol-based vehicle used in the short-acting formulation. This question will be addressed in future studies which are planned with a different, long-acting formulation of ICI 182780 contained in a castor-oil based vehicle." Ex. 1038 at 5. No further information regarding the components of this long-acting castor oil based fulvestrant formulation is provided. It is clear from DeFriend that this next planned study is another early stage research study on basic safety and biological action.

D) Riffkin (Ex. 1033)

87. Riffkin considers the suitability of castor oil as a vehicle for parenteral administration of two specific typical steroids, estradiol valerate and hydroxyprogesterone caproate. Riffkin shows that differences in concentrations or substitutions of ingredients resulted in marked differences in lesions in animal experiments. Riffkin demonstrates that there would be no reasonable expectation of success with the formulations of the inventions.

88. Sesame oil was "chosen as the 'standard' vegetable oil to be compared to castor oil," because it was "universally accepted as a parenteral oil vehicle." Ex. 1033 at 3. The lesions and irritation caused by the castor oil formulations in rabbits disclosed in Table IV teach the continued use of the sesame oil vehicle. Ex. 1033 at 3. Riffkin provides examples of changing the type of excipient and excipient amounts to arrive at many different formulation combinations, each with different properties.

89. Fulvestrant is an atypical steroid, with different lipophilicity and solubility characteristics than most other steroids. Hence, the skilled formulator would not have been able to predict the result of substituting fulvestrant for estradiol valerate or hydroxyprogesterone caproate in Riffkin. Many formulations disclosed in Riffkin were not tested clinically because of the undesirable characteristics or adverse effects caused by a change in percent composition of the

excipients. Ex. 1033 at Table V. Thus, the importance of the physicochemical characteristics of the active ingredient become apparent.

90. Table IV of Riffkin teaches away from the claimed inventions. To begin, a formulator would learn from Table IV that the combination of castor oil, benzyl benzoate, and benzyl alcohol caused large lesions in rabbits. Ex. 1033 at 3 (Vehicle Identification No. SHY-47-7). The lesions caused by a formulation with all three of these components were larger (worse) than the lesions caused by vehicles containing just castor oil and benzyl benzoate, or just castor oil and benzyl alcohol. Ex. 1033 at 3 (*Compare* SHY-47-7 with 14-5 or 47-5). Thus, a formulator would be taught away from using the combination of castor oil, benzyl benzoate, and benzyl alcohol—the excipients found in the formulation of the patented inventions. Vehicles containing castor oil or sesame oil, with 2% benzyl alcohol, produced smaller lesions than vehicles containing benzyl benzoate and/or higher concentrations of benzyl alcohol. Ex. 1033 at 3 (Compare Vehicle Identification No. SHY-47-2 and 47-4 to the remaining formulations in Table IV). For example, an increase of benzyl alcohol from 2% to 5% causes a significant increase in local irritation. Ex. 1033 at 3 (*Compare* 47-2 and 47-4 with 47-3 and 47-5).

91. Dr. Burgess notes that "Riffkin tested its formulations in rabbits, which it is careful to concede are not predictive of muscle damage *in humans*."

Ex. 1012 (Burgess Decl.) at ¶ 146. Thus, Dr. Burgess agrees that results in animal models are not always predictive of results in humans. But, the McLeskey formulation was tested in mice, and furthermore, no data on pharmacokinetics, effect or tolerability is available from the McLeskey animal model for the castor oil formulation). In any case, Table V of Riffkin actually provides "remarks on clinical testing" in humans, confirming that small formulation changes can have significant effects in human patients. Ex. 1033 (Riffkin) at Table V. For 17-hydroxyprogesterone caproate, three of the five formulations were rejected in humans for showing 20.6%, 23.2% and 10.7% reactions, respectively. Ex. 1033 (Riffkin) at Table V.

92. Riffkin demonstrates that changes in the combination of excipients lead to different results in terms of size of lesions in the rabbit muscle. The size of the lesions would most likely impact on the resultant pharmacokinetics.

93. The physical, physicochemical and biological interactions after injection affect the release, absorption and elimination of a drug. Changes in the shape of the depot may influence absorption. Ex. 2115 (Ballard 1968) at 2. Composition changes in the formulation over time may affect physicochemical properties, such as fulvestrant solubility, possibly leading to precipitation. Ex. 2082 (Aulton Ch. 1) at 11. The drug may bind to tissue proteins, preventing absorption. Ex. 1094 (Tse I) at 4. And, biological factors may affect absorption.

Ex. 2114 (Zuidema 1994) at 13-14. Absorption and metabolism of the vehicle must also be considered. Ex. 2116 (Hirano 1981) at 4. These factors all depend, to some extent, on the species tested, as Dr. Burgess implies. Ex. 1012 (Burgess Decl.) at ¶ 146. However, it should be possible to get a good indication of the difference in severity of lesions seen for the different formulations and the impact of changing excipients or their concentrations.

94. Dr. Burgess asserts that Riffkin "specifically advocates" the use of benzyl benzoate and "points out two examples of commercially sold castor oil-based steroid injection products, both of which contain significantly more benzyl benzoate than the formulation recited in the claims." Ex. 1012 (Burgess Decl.) at ¶ 146. But no formulation in Riffkin uses the claimed combination of excipients. And, Riffkin shows that small changes in excipients and excipient amounts can lead to meaningful differences upon injection.

95. Dr. Burgess notes that "Riffkin tested its formulations in rabbits, which it is careful to concede are not predictive of muscle damage *in humans*." Ex. 1012 (Burgess Decl.) at ¶ 146 (emphasis in original); Petition at 35-36. This further confirms the unpredictability of the *in* vivo pharmacokinetics of these types of formulations especially when transferred from animal models to man.

E) O'Regan (Exhibit 1009)

96. O'Regan describes a study in ovariectomized mice with implanted endometrial tumors evaluating the risks of promoting endometrial cancer after treatment with toremifene or fulvestrant. Ex. 1009 at 1. There is no connection in O'Regan of the authors or the study to AstraZeneca.

97. In terms of formulation, the only fulvestrant formulation used in the study was fulvestrant 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. O'Regan does not address formulations generally or discuss them in detail; despite this, Dr. Burgess points to O'Regan for a disclosure that "[c]linically, [fulvestrant] must be given by depot intramuscular injection because of low oral potency." Ex. 1012 (Burgess Decl.) at ¶ 96. The article does not cite any specific support for that conclusion, nor is any reference paper quoted, but the next few sentences discuss the results of Howell 1996. At most, O'Regan is reiterating that in the small early stage clinical trial of Howell intramuscular injection was used. As such, it says nothing about any relationship between subcutaneous and intramuscular administration for the castor oil formulation as suggested by Dr. Burgess.

98. I note that although Dr. Burgess characterizes O'Regan as a "follow up study to Howell," O'Regan did not use the castor oil-based formulation that is

partially described in Howell. *See* Ex. 1012 (Burgess Decl.) at ¶ 249. And, in my view, given the absence of any connection between the authors and the studies' objectives, the skilled formulator would not view O'Regan as a "follow up study" to Howell. I note that the authors of O'Regan appear primarily concerned about toremifene, placing less emphasis on fulvestrant: "Our aim was to replicate the situation seen . . . 1) where toremifene will be used as first-line adjuvant therapy and 2) where toremifene will be used after adjuvant tamoxifen therapy. In addition we have compared and contrasted the effects of tamoxifen with those of [fulvestrant]." Ex. 1009 (O'Regan) at 2.

99. In terms of formulation, the work in O'Regan uses formulations of fulvestrant in arachis oil for weekly subcutaneous administration to mice. Moreover, "[t]amoxifen and toremifene were each suspended in a solution of 90% CMC (1% carboxymethylcellulose in double-distilled water) and 10% PEG 400/Tween 80 (99.5% polyethylenegly[c]ol 400 and 0.5% Tween 80)," and both compounds were administered "orally." Ex. 1009 (O'Regan) at 2. O'Regan does not teach treatment of humans, intramuscular injection of fulvestrant with the claimed combination of formulation excipients in their respective amounts, dosing frequency, or minimum plasma levels.

F) Dukes 1989 (Ex. 1047)

100. Dukes 1989 relates to therapeutic products comprising an estrogen and a pure antiestrogen for use in treating perimenopausal and postmenopausal conditions, particularly perimenopausal or postmenopausal osteoporosis. Ex. 1047 at 1:8-126.

101. From the perspective of a formulator, Dukes 1989 teaches many options. For example, compositions of the invention "may be in a form suitable for oral use (for example as tablets, capsules, aqueous or oily suspensions, emulsions or dispersible powders or granules), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions; for example for use within a transdermal patch), for parenteral administration (for example as a sterile aqueous or oily solution or suspension for intravenous, subcutaneous, intramuscular or intravascular dosing), or as a suppository for rectal dosing or as a pessary for vaginal dosing." Ex. 1047 at 4:55-65. Dukes 1989 also teaches various excipients for each of the methods of administration. Ex. 1047 at 5:1-6:39. In this way, Dukes 1989 teaches the breadth of options available to a formulator.

102. Examples 1-3 of Dukes 1989 describe experimental formulations of fulvestrant given to rats. Example 1 provides an oily solution of fulvestrant in arachis oil, administered subcutaneously. Ex. 1047 at 9:52-63. Example 2 provides a daily intramuscular injection of an aqueous solution, comprising 25 mg

fulvestrant, 100 mg ethanol (96%), 100 mg water, 20 mg poloxamer 407 and sufficient propylene glycol to bring the solution to a volume of 1 ml. Ex. 1047 at 10:29-41. Example 3 provides a solution formulation of "50 mg of [fulvestrant], 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml." Ex. 1047 at 11:2-16. A person of ordinary skill in the art would understand this latter formulation to have 50 mg/ml of fulvestrant, 40% w/v of benzyl alcohol and sufficient castor oil to bring to volume. This formulation was administered by intramuscular injection to rats biweekly. Ex. 1047 at 11:11-13. Dukes 1989 does not indicate any preference among the example formulations.

103. Citing Dr. Gellert's declaration, Dr. Burgess argues that "one skilled in the art would have rejected the Dukes '814 patent formulation because of the high amount of benzyl alcohol used," leaving only the McLeskey formulation. Ex. 1012 at ¶ 181, 38; *see also* Petition at 46. Dr. Gellert's declaration does not compare the Dukes formulation to the McLeskey formulation and does not address which formulation would have been preferred. However, if a skilled artisan were to compare the Dukes formulation to the McLeskey formulation in an attempt to match Howell (the question that Dr. Burgess poses), the Dukes formulation would have been preferred, notwithstanding the higher benzyl alcohol concentration. The Dukes formulation was administered intramuscularly, like Howell, and was shown to inhibit antiestrogen activity. Ex. 1047 (Dukes 1989) at 9 ("[A]t all doses tested

the compound selectively inhibits the action of the animals' endogenous oestrogen.").

G) Gellert Declaration (Ex. 1020)

104. The Gellert Declaration dated August 8, 2008 was submitted in response to the March 17, 2008 rejection, during the prosecution of the application that issued as U.S. Patent No. 7,456,160. Thus, I understand that the Gellert Declaration is not prior art at the time of the inventions and the skilled artisan could not have relied on the Gellert Declaration as a reference.

1) Background Of The Gellert Declaration

105. The Gellert Declaration responded to the Office Action dated March 17, 2008 rejecting the claims for obviousness over Dukes (EP 0346 014) in view of Lehmann et al. (US Patent Re. 28,690), GB 1 569 286 . . . Osborne et al., Journal of National Cancer Institute 1995;87(10):746-750, and Remington." Ex. 1046 (March 17, 2008 Office Action) at 134. In that Office Action, the examiner stated that "[c]astor oil and benzyl alcohol are known to be effective as vehicle for fulvestrant. Ethanol is a commonly used pharmaceutical solvent. Benzyl benzoate is known to be effective as [a] solvent for steroidal compounds. Since fulvestrant is a[n] estrogen derivative, benzyl benzoate would be reasonably expected to be useful as a solvent for fulvestrant." Ex. 1046 (March 17, 2008 Office Action) at 136. The Gellert Declaration thus addressed only the examiner's statement that

"benzyl benzoate would be reasonably expected to be useful as a solvent for fulvestrant." To do so, Dr. Gellert explained that a skilled formulator using the inventors' inventive non-published work that showed that fulvestrant was poorly soluble in benzyl benzoate, "would have expected that benzyl benzoate would not act as a co-solvent for fulvestrant in castor oil because the solubility of fulvestrant in benzyl benzoate was significantly lower than its solubility in castor oil." Ex. 1020 (Gellert Declaration) at ¶ 20.

2) The Gellert Declaration Describes Extensive Experimentation Based On Information Not Known In The Art

106. Dr. Gellert begins by assuming that the skilled artisan, given the task of formulating a sustained release depot formulation of fulvestrant, would have adopted the narrower objective posed that "a reasonable starting point would have been to investigate intramuscular injection of an aqueous or oil suspension of fulvestrant." Ex. 1020 (Gellert Decl.) at ¶ 13 (emphasis added). After significant, unpublished experimentation the inventors discovered 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 (Gellert Decl.) at ¶ 13. 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 (Gellert Decl.) at ¶ 16. The skilled formulator could have conducted experiments on a variety of oils or combination of oils, as the

inventors did. Ex. 1001 at Table 4. Again, these results were unpublished. Then, 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 (Gellert Decl.) at ¶¶ 22-24. The possibilities were infinite. Dr. Gellert explained that a high concentration of alcohol was disfavored, yet the inventors used 20% w/v alcohols in total. 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 (Gellert Decl.) ¶ 24. None of this information was taught in the prior art. The skilled artisan could not have relied on the Gellert Declaration to teach these steps. Below I describe this more specifically.

107. Because the examiner of the '160 patent provided his Office Action with the claimed invention in mind, Dr. Gellert noted the claimed invention's objectives: "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 . . . and would have a target fulvestrant content of at least 45 mg/mL." Ex. 1020 (Gellert Decl.) at ¶ 11. He took this approach to demonstrate that, even using the invention work as a guide, this would not have led to the use of benzyl

benzoate in the formulation. Dr. Gellert's declaration does not describe all of the different formulation approaches taken by the inventors and does not mean, that the skilled artisan would necessarily have followed, or have been able to follow, the exact approach that he described. Indeed, many other options existed at every step of the way and much of the information on which Dr. Gellert relied was not in the prior art.

108. Even if one selected to look only to intramuscular administration for fulvestrant, Dr. Gellert noted that the "traditional administration options to explore were intramuscular (IM) injection of a sustained release aqueous or oil suspension or an oil-based solution (depot)." Ex. 1020 (Gellert Decl.) at ¶ 12. Of course, without the claim limitation to intramuscular injection in mind, the skilled formulator would have considered many other administration options (which looked equally if not more promising, as described further below).

109. Dr. Gellert then explained that "[b]ecause of the extremely low solubility of fulvestrant in water, a reasonable starting point would have been to investigate intramuscular injection of an aqueous or oil suspension of fulvestrant." Ex. 1020 (Gellert Decl.) at ¶ 13.[2] And, this was indeed where the inventors started.

[2] However, no solubility data for fulvestrant in water existed in the art at the time of the invention—that information resulted from the work on the invention.

110. Dr. Gellert next cites to the inventors' work as reported in the patent ("paragraph [0042] of the Evans Application") to state that "the formulator would have found 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 (Gellert Decl.) at ¶ 13. This information was not available in the prior art. Indeed, the poor performance of aqueous suspensions as a possibility for fulvestrant was part of the inventive work disclosed for the first time in the patent: "[p]reviously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the injection site as well as a poor release profile." Ex. 1001 8:38-40.

111. Relying on the inventors' confidential conclusions on their experiments (not available in the art) to exclude suspensions, Dr. Gellert turns to oily solutions. After consulting the literature to identify "potential oil vehicles, co-solvents and other excipients that already had been found to be tolerated" and to seek "guidance with respect to concentration levels," the skilled formulator would "conduct[] a preformulation solubility screen, ***separately*** measuring the solubility of fulvestrant in a range of pure solvents, including the potential oil and co-solvent candidates that had been identified in the above literature." Ex. 1020 (Gellert Decl.) at ¶¶ 14-16 (emphasis added). No solubility data on fulvestrant was

available in the prior art. Conducting the literature review, determining potential solvents, and testing fulvestrant solubility would have required significant work. Only after conducting this work, reported in the patent for the first time (Table 2), would the skilled formulator have known that fulvestrant solubility is highest in ethanol, benzyl alcohol and castor oil. As Dr. Gellert notes, if the skilled artisan had considered benzyl benzoate as a solvent based on previous steroid products, this solubility screen would have necessarily informed the skilled artisan that fulvestrant had "low solubility in benzyl benzoate." Ex. 1020 (Gellert Decl.) at ¶ 16.

112. Dr. Gellert then describes the results of the inventors' solubility screen. Those results, which were not in the prior art, revealed the "higher solubility of fulvestrant in castor oil relative to the other oils tested." Ex. 1020 (Gellert Decl.) at ¶ 17. Of course, the skilled artisan could have tried any number of other oils or combinations of oils, as the inventors did. Ex. 1001 at Table 4. Dr. Gellert's declaration picks castor oil to show that even using the presence of castor oil in the claims as a guide would not make the invention obvious.

113. Dr. Gellert's declaration explains that far from suggesting that the prior art taught the invention or that it would have been a matter of routine experimentation to come up with the invention, only after the research finding that the preferred aqueous fulvestrant suspension was not a viable option (not in the

prior art) and after a pre-formulation solubility screen had been carried out (again, not in the prior art), did the inventors choose to use castor oil for the fulvestrant formulation since this was the oil in which fulvestrant was most soluble. However, the solubility of fulvestrant in castor oil was still not sufficient to produce the required concentration of the drug (again, not in the art). Ex. 1020 (Gellert Decl.) at ¶ 16. Indeed, "routine" experimentation would have concluded that this formulation approach was unlikely to succeed given the poor solubility of fulvestrant. Ex. 1020 (Gellert Decl.) at ¶ 17.

114. For the other excipients, Dr. Gellert relies on the specification's description of the inventors' work: "even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration." Ex. 1001 at 5:25-30. Dr. Gellert's declaration shows that even following the inventors' steps as described in the patent would still not have led to the invention. In his declaration, Dr. Gellert relies on the inventor's confidential work, a preformulation screen, as the basis for including ***either*** ethanol and/or benzyl alcohol as co-solvent candidates—work that was not published. Ex. 1020 (Gellert Decl.) at ¶ 21. And, Dr. Gellert acknowledges that even the concentrations of benzyl alcohol and ethanol in the invention are outside the norm—he describes how benzyl alcohol and ethanol had been used separately at lower concentrations. Ex. 1020 (Gellert

Decl.) at ¶ 23. Dr. Gellert noted that the 40% w/v benzyl alcohol used in Dukes patent is higher than the usual amount of "about 2% or less, occasionally at a concentration up to 5%, but only rarely at higher concentrations." Ex. 1020 (Gellert Decl.) at ¶ 23. Dr. Gellert also noted that "with few exceptions, ethanol was not included in [marketed] formulations in excess of about 10%." Ex. 1020 (Gellert Decl.) at ¶ 23. The formulation in the invention has higher concentrations of benzyl alcohol and the combination of ***both*** alcohols is also higher than alcohol levels typically used. At the time, no marketed intramuscular formulation used a combination of alcohols at that high level.

115. Next, even if these alcohols were chosen as excipients in the formulation, Dr. Gellert then explains that the results from the inventors' solubility screen would necessarily lead a skilled person to eliminate benzyl benzoate as a possible excipient and thereby teach away from the invention. He noted that the skilled artisan "would have expected that benzyl benzoate would *not* act as a co-solvent for fulvestrant in castor oil because the solubility of fulvestrant in benzyl benzoate was significantly lower than its solubility in castor oil." Ex. 1020 (Gellert Decl.) at ¶ 20.

116. Dr. Gellert acknowledges that a literature review would have identified commercial formulations of steroids formulated with benzyl benzoate, but Dr. Gellert explains that "the skilled formulator would have appreciated from

the fulvestrant solubility data generated in the preformulation screen that fulvestrant had very different solubility characteristics relative to the steroids of previous commercial formulations." Ex. 1020 (Gellert Decl.) at ¶¶ 18-19. In Fact, Dr. Gellert cites examples of steroids with solubility in benzyl benzoate ranging from ***200 to 400 mg/ml***, in contrast to 3.8 mg/ml for fulvestrant, less than the solubility of fulvestrant in castor oil (20 mg/ml). Ex. 1020 (Gellert Decl.) at ¶ 19. Thus, "[t]he addition of benzyl benzoate to castor oil, ***for whatever reason***, would have been expected to *decrease, rather than increase*, the solubility of fulvestrant in the resulting castor oil/benzyl benzoate mixture." Ex. 1020 (Gellert Decl.) at ¶ 20. If the skilled formulator wanted to check this, Dr. Gellert cites to the inventors own work in Table 4 of the patent to show that fulvestrant's solubility is lower in castor oil and benzyl benzoate (12.6 mg/ml) than in castor oil alone (20 mg/ml). Ex. 1020 (Gellert Decl.) at ¶ 20. The use of benzyl benzoate in the invention formulation was counterintuitive.

117. Dr. Gellert's declaration also explains that even if the examiner suggested the problem as being to reduce the benzyl alcohol concentration in Dukes, "[b]enzyl benzoate clearly would not be considered to solve this dilemma, but rather would be expected to have a negative effect on fulvestrant solubility since fulvestrant was even less soluble in benzyl benzoate than in castor oil, that is, one would have expected that adding benzyl benzoate [to the Dukes for

formulation] would require still ***more*** alcohol to maintain the target fulvestrant concentration." Ex. 1020 (Gellert Decl.) at ¶ 24.

118. Dr. Gellert explains that "the skilled formulator would have appreciated from the fulvestrant solubility data generated in the preformulation screen that fulvestrant had very different solubility characteristics relative to the steroids of previous commercial formulations." Ex. 1020 (Gellert. Decl.) at ¶ 19. For instance, "the solubility of fulvestrant in castor oil and in sesame oil (20 mg/mL and 0.58 mg/mL, respectively, from Table 2 of the Evans Application) is appreciably lower than the solubility of the other steroids [in Riffkin] in these oils." Ex. 1020 (Gellert Decl.) at ¶ 19. Similarly, the Huber Patent provides "concentration in benzyl benzoate of five named steroids . . . ranging from 200 to 400 mg/ml," but "the solubility of fulvestrant in benzyl benzoate is reported in Table 2 of the Evans Application as being only 6.15 mg/mL, and only 3.8 mg/mL as determined in the recently conducted tests reported in Attachment C." Ex. 1020 (Gellert Decl.) at ¶ 19; Ex. 2124 (Huber). As a result, the skilled artisan could not have and would not have looked to other commercially marketed steroids formulated in castor oil to predict the results of castor oil-based formulations of fulvestrant.

119. In sum, Dr. Gellert starts with the inventors' goals and shows even with the inventors' work in the specification, the use of the formulation

components was counterintuitive. However, the inventors' work was not in the prior art and, in my opinion, would have required many separate and lengthy experiments to obtain. Moreover, at each decision point, the skilled artisan could have chosen a different path. The point of the Gellert Declaration was to show that, even with the inventors' own knowledge, the skilled artisan would not have obtained the claimed invention. This is because the increase in fulvestrant solubility in the presence of benzyl benzoate was truly surprising even to the inventors: "[w]e have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and alcohol surprisingly eases the solubilisation of fulvestrant." Ex. 1001 at 5:48-51.

120. I note that the Gellert Declaration does not support Dr. Burgess' implication that the only "improvement over this established prior art was the 'surprising' discovery that benzyl benzoate—a non-aqueous ester solvent—increased the solubility of fulvestrant." Ex. 1012 (Burgess Decl.) at ¶ 24. Rather, the Gellert Declaration only addresses the argument by the examiner that "benzyl benzoate would be reasonably expected to be useful as a solvent for fulvestrant." Ex. 1046 (March 17, 2008 Office Action) at 136. The Gellert Declaration does not attempt to address other inventive aspects of the invention. Even if the skilled artisan had all of the invention knowledge described in the Gellert Declaration and then counterintuitively added benzyl benzoate as a solvent, the skilled artisan

would still need to conduct significant experimentation to discover the exact combination of excipients and excipient amounts, and determine the therapeutic release profile with acceptable tolerability. Nothing in the Gellert Declaration suggests one skilled in the art could reasonably expect the release profile and tolerability of the invention.

121. In my opinion, even if the information in the Gellert Declaration was in the prior art, which it was not, the skilled formulator would not reach the claimed invention. The invention work described in the specification reiterates the common knowledge that simply solubilizing an active ingredient in a solvent cannot assure a preferred amount of the active released and certainly not a particular release rate. Ex. 1001 at 9:20-22. The patent states that "[s]imply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site." Ex. 1001 at 9:20-22. Indeed, Table 3 of the patent shows that many other combinations of excipients could solubilize the fulvestrant to a greater degree. yet, the release rates, release profiles and precipitation in the muscle were not satisfactory. This is echoed in the remarks accompanying the Gellert Declaration in the Prosecution History, which noted that the formulation "provides for the satisfactory sustained release of fulvestrant over an extended period of time as

specified in the present claims." Ex. 1096 (Aug. 21, 2008 Amendment and Response) at 14.

XII) THE SKILLED FORMULATOR'S APPROACH TO FORMULATING FULVESTRANT

122. Without access to the claimed inventions in 2000, the formulator would have had to approach the task of formulating fulvestrant by looking at the entirety of the art. The fulvestrant art taught both daily, weekly, biweekly and monthly administration of fulvestrant. Additionally, the art of endocrine therapy explicitly preferred oral formulations and taught that fulvestrant (based on the potency of oral versus subcutaneous administration) had a relative oral bioavailability of 10 percent. Ex. 1031 (Wakeling 1991) at 2. As described below, the art was replete with examples of oral formulations for active ingredients with low solubility and low oral bioavailability. *See infra* ¶¶ 132-136.

A) The Fulvestrant Art Taught Once-A-Day Administration And Once-A-Month Administration

123. Two randomized and placebo controlled clinical studies of fulvestrant, DeFriend in 56 women with primary breast cancer (Ex. 1038) and Thomas in 30 women scheduled for hysterectomy (Ex. 1061) described the administration of a daily formulation of fulvestrant by intramuscular injection. Ex. 1038 (DeFriend) at 1; Ex. 1061 (Thomas) at 1. DeFriend described the formulation used therein as "a 20 mg/ml drug in a propylene glycol-based vehicle".

Ex. 1038 at 2. Thomas did not describe the formulation at all. Ex. 1061 at 1-2. On the other hand, Howell 1996, a non-randomized and non-placebo controlled study in 19 women with tamoxifen resistant advanced breast cancer administered fulvestrant intramuscularly monthly in a long-acting castor oil based formulation. Ex. 1007 at 2. Neither DeFriend, Thomas, nor Howell provided any other information about the excipients used in the respective formulations. Thus, DeFriend, Thomas and Howell do not primarily study the effect of a particular fulvestrant formulation, but, rather, use the individual formulations of fulvestrant to determine the preliminary effects of the fulvestrant molecule in patients.

124. DeFriend uses language referring to the fulvestrant molecule, not the formulation: "treatment with ICI 182,780" (Ex. 1038 at 1, 3-6); "patients randomized to receive ICI 182780" (Ex. 1038 at 2); "ICI 182,780 caused no serious drug-related adverse events" (Ex. 1038 at 3); "ICI 182,780 was well tolerated after short term administration" (Ex. 1038 at 1). And, it states that the use of ICI 182,780 is preliminary: "first investigation of short term administration of ICI 182780 to women" (Ex. 1038 at 5); "provide preliminary evidence" (Ex. 1038 at 5); "produced preliminary evidence" (Ex. 1038 at 6).

125. Howell uses similar language to DeFriend and is similarly focused on the molecule, not the formulation: "the aims of the study reported here were to assess the long-term efficacy and toxicity of the specific anti-oestrogen ICI

182780" (Ex. 1007 at 1); "we have assessed the pharmacokinetics, pharmacological and anti-tumour effects of the specific steroidal anti-oestrogen ICI 182780" (Ex. 1007 at 1); "administration of ICI 182780 was associated with a lower than expected incidence of side effects" (Ex. 1007 at 1).

126. DeFriend found that daily administration of fulvestrant "produced demonstrable antiestrogenic effects in human breast tumors." Ex. 1038 at 1. Thomas found "a potent anti-oestrogenic activity *in vivo*." Ex. 1061 at 5. Similarly, Howell concluded that fulvestrant given monthly was "active as an anti-tumor agent in patients with advanced breast cancer who have previously relapsed on tamoxifen." Ex. 1007 at 7. The Dukes 1993 studies in monkeys had previously shown that "no significant differences emerged between the effects of the different formulations [daily versus monthly] and doses of [fulvestrant]." Ex. 1057 at 5. Thus, the formulator would understand that once daily administration was an option for fulvestrant.

127. After reading Howell 1996, the formulator would be further encouraged to try daily administration. In particular, Howell 1996 taught that "lower doses of the drug may be effective in maintaining therapeutic serum drug levels." Ex. 1007 at 6; 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."). Howell's teaching to use lower doses of fulvestrant would have

encouraged the formulator to look at other formulation options. For example, lower doses mean that the oral bioavailability issue asserted by Dr. Burgess would be less of a concern, since less fulvestrant would need to be administered to reach and maintain therapeutic plasma levels. Ex. 1012 (Burgess Decl.) at ¶ 97.

B) The Formulator Would Prefer Oral Fulvestrant Formulations

128. The formulation art, viewed as a whole, teaches that oral administration would have been the preferred option for fulvestrant in 2000. In fact, Dr. Burgess acknowledges that oral administration would be the first option considered: "[p]arenteral dosage forms are appealing in circumstances where the oral route is not feasible or desirable." Ex. 1012 (Burgess Decl.) at ¶ 63.

129. The FDA-approved gold standard of endocrine therapy, tamoxifen, and the aromatase inhibitor, anastrozole, were both administered orally. *See* Ex. 2045 (PDR 1999 Nolvadex®) at 4; Ex. 2126 (PDR 1999 Arimidex®) at 4. As a result, the skilled formulator would have strongly preferred an oral formulation of any new endocrine therapy to compete with the oral treatment options then available. Ex. 2020 (Jordan Supp. 1992) at 4 ("An orally active agent should be an essential component of any strategy to introduce a new antiestrogen. Oral tamoxifen is so well tolerated that patients would be reluctant to consider injections or sustained-release implants as an alternative."). Dr. Burgess fails to address this clear incentive toward oral formulations of fulvestrant.

130. Oral delivery is by far the most common route of administration and widely viewed as the most preferred route. *See, e.g.*, Ex. 2093 (Remington's Ch. 89) at 5 ("Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules"); Ex. 2094 (Aulton Ch. 13) at 5 ("Almost all new drugs which are active orally are marketed as tablets, capsules, or both," citing Table 13.1 showing that 74.8% of dosage form types manufactured in the UK are for oral administration as tablets, capsules or liquid oral forms).

131. Dr. Burgess argues that "the sources Dr. Illum cites in support state only that oral routes are safe and convenient." Ex. 1012 (Burgess Decl.) at ¶ 135. However, the sources actually state that the oral route is ***the most*** "natural, uncomplicated, convenient, and safe" route, all factors which influence patient compliance. Thus, a skilled formulator would have known that oral formulations resulted in the best patient compliance. *See* Ex. 1091 (Ansel Ch. 4) at 26 ("Compared with alternate routes, the oral route is considered the most natural, uncomplicated, convenient, and safe means of administering drugs"); Ex. 2082 (Aulton Ch. 1) at 7 ("The oral route is the most frequently used route for drug administration. . . . Compared with other routes, the oral route is the simplest, most convenient and safest means of drug administration."). A skilled formulator would view the broad acceptance of oral formulations, and likely patient compliance with dosing regimens, as a strong reason to choose an oral formulation.

132. Dr. Burgess claims that "patient compliance is a major issue with medications taken at home." Ex. 1012 (Burgess Decl.) at ¶ 135. However, Dr. Burgess admits that 5 ml is a "relatively large injection volume" and "near the maximum volume of fluid that can be injected into that muscle." Ex. 1012 (Burgess Decl.) at ¶¶ 255, 173. And, Dr. Burgess admits that an intramuscular injection would need to be "administered in a clinical setting by a nurse or doctor." Ex. 1012 (Burgess Decl.) at ¶ 135. Moreover, the endocrine therapies tamoxifen and anastrozole were both administered orally, like the majority of medications. As far as I am aware patients with breast cancer are highly motivated to comply with the medication regimen for oral drugs, due to the seriousness of their condition especially if untreated. The skilled formulator would have been concerned about the acceptability of an intramuscular fulvestrant injection to patients.

C) The Formulator Would Not Have Excluded Oral Formulations

133. Dosage forms for oral administration were well-known in the art. References available to a skilled formulator taught a wide variety of solid oral dosage forms, such as tablets and capsules, and liquid oral dosage forms, such as elixirs, apart from dosage forms for oral mucosal administration, such as buccal or sublingual administration—including formulations appropriate for steroids or other lipophilic molecules. Ex. 2095 (Ansel Ch. 7) at 5-54; Ex. 2096 (Ansel Ch. 12) at

14-32; Ex. 2097 (Ansel Ch. 13) at 17-20; Ex. 2098 (Aulton Ch. 18) at 4-21; Ex. 2099 (Aulton Ch. 19) at 4-22. A skilled formulator would hence have had a variety of options of dosage forms for oral administration.

134. Dr. Burgess states that "fulvestrant, like most steroid hormones, is insoluble in water, resulting in a low oral bioavailability." Ex. 1012 (Burgess Decl.) at ¶ 129. But, many drugs with low solubility, similar to that of fulvestrant or lower (*e.g.*, itraconazole 0.009 mg/ml, diclofenac 0.004 mg/ml; tamoxifen 0.04 µg/ml), including many steroids, are formulated for oral administration. For instance, tamoxifen is a highly lipophilic drug that is marketed in an oral dosage form, despite a reported solubility in water of 0.04 $\mu g ml^{-1}$. Ex. 2100 (Gao 1998) at 3. Haloperidol, with a solubility in water of 0.014 $mg ml^{-1}$, is marketed in an oral dosage form. Ex. 2101 (Merck Index) at 26. Hydrocortisone, with a solubility in water of 0.28 $mg ml^{-1}$, is marketed in an oral dosage form. Ex. 2101 (Merck Index) at 27. Despite being "practically insol[uble] in water," ethinyl estradiol, indomethacin, griseofulvine, itraconazole, and carbamazepine are marketed in oral dosage forms. Ex. 2101 (Merck Index) at 22 (ethinyl estradiol); 29 (indomethacin); 25 (griseofulvine); 30 (itraconazole); 17 (carbamazepine). Despite being "almost insol[uble] in water," digoxin, and diethylstilbestrol are marketed in oral dosage forms. Ex. 2101 (Merck Index) at 20 (digoxin); 19 (diethylstilbestrol). Despite being "insol[uble] in water," norethandrolone and progesterone are

marketed in oral dosage forms. Ex. 2101 (Merck Index) at entry 32 (norethandrolone); 33 (progesterone). Similarly, other highly lipophilic drugs were developed for oral administration, for example, diclofenac (partition coefficient (n-octanol / aq. buffer): 13.4) and itraconazole (partition coefficient (n-octanol / aq. buffer of pH 8.1): 5.66. Ex. 2101 (Merck Index) at 18 (diclofenac); Ex. 2101 (Merck Index) at 30 (itraconazole). Estrogen (as estradiol) is formulated for both transdermal and oral (tablet) administration. Ex. 2102 (Ansel Ch. 10) at 9, 17-18; Ex. 2127 (PDR 1999 Estrace®) at 4.

135. Dr. Burgess argues that fulvestrant was particularly insoluble compared to other steroids, but only cites one of the many examples above, hydrocortisone, as "not analogous." Ex. 1012 (Burgess Decl) at ¶¶ 136, 142. In any case, Dr. Burgess' asserted solubility for fulvestrant (unknown at the time) of 0.007 mg/ml is orders of magnitude higher than tamoxifen's 0.04 $\mu g ml^{-1}$ [0.00004 mg/ml] solubility. Ex. 2100 (Gao 1998) at 3; *see* Ex. 1012 (Burgess Decl.) at ¶ 142.

136. Wakeling 1991 contained the only publicly known information about fulvestrant's oral bioavailability. In Wakeling 1991, fulvestrant was added to ethanol and diluted into arachis oil with gentle warming. With this formulation, "[c]omplete antagonism of estrogen action was achieved with a dose of 0.5 mg [fulvestrant] kg/day s.c.," and "[t]he effects of [fulvestrant] administered p.o.

[perorally] were qualitatively similar but potency was reduced by an order of magnitude," suggesting an oral bioavailability in this formulation of 10%. And, no efforts were specifically made with this formulation to improve oral bioavailability.

137. A skilled formulator would be aware of many excipient-based methods for improving drug solubility and oral bioavailability. Possibilities included: co-solvents; surfactants and other solubilizing excipients; solid dispersions; solid solutions; micro- and nanoparticles; osmotic delivery systems; complexation of drug; liposomes; micelles; cyclodextrin conjugation; pH adjusting excipients. *See*, *e.g.*, Ex. 2103 (Avis Ch. 4) at 23-31 (use of salts, cosolvents, complexation, prodrugs, and the alteration of pKa in order to improve solubility); Ex. 2104 (Aulton Ch. 6) at 22-25, 27-29 (use of surface active agents); Ex. 2082 (Aulton Ch. 1) at 11 (use of salts, esters, micronization, or solid dispersion techniques).

138. Dr. Burgess cites the unsupported statement preceding a discussion of Howell 1996 in O'Regan that "clinically, [fulvestrant] must be given by depot intramuscular injection because of low potency." Ex. 1012 (Burgess Decl.) at ¶¶ 74, 96, 97, 132, 144, 211, 255, 265. In other words, Dr. Burgess infers that because it was suggested that oral bioavailability was an issue for fulvestrant, intramuscular injection was the only option for administration. The totality of

formulation art suggests otherwise. Regardless, O'Regan teaches administration of fulvestrant "dissolved in ethanol and administered in peanut oil (following the evaporation of ethanol under N_2)" which teaches toward the peanut oil formulation used in McLeskey, and not the castor oil formulation. Ex. 1009 (O'Regan) at 2.

139. Dr. Burgess also argues that "Wakeling 1993 reported that the 'relatively low oral bioavailability of ICI 182,780 necessitated development of alternative dosing regimens.'" Ex. 1012 (Burgess Decl.) at ¶ 97. But, Wakeling 1991 (Ex. 1031) states that results from oral administration of fulvestrant to immature female rats "were qualitatively similar" to that achieved by subcutaneous administration, resulting in "[c]omplete antagonism of estrogen action." Ex. 1031 (Wakeling 1991) at 2-3. Wakeling 1991 also found "p.o. [peroral] antiuterotropic activity of [fulvestrant] in intact rats," although with less potency than parenteral administration. Ex. 1031 at 3. Wakeling 1991 characterizes the difference in potency between fulvestrant administered subcutaneously and orally as an "order of magnitude." Ex. 1031 at 2-3. Thus, Wakeling 1991 teaches that the oral bioavailability of fulvestrant (based on the oral versus the subcutaneous potency) was 10% relative to subcutaneous administration. The skilled formulator would not have been discouraged from attempting oral administration by the 10% relative bioavailability of fulvestrant reported in Wakeling 1991. For example, the members of the bisphosphonates class of FDA-approved drugs are known to have

oral bioavailability around 1% but are administered orally. Ex. 2105 (Porras) at 1-2.

140. Dr. Burgess relies on the fact that intramuscular administration had been used in earlier clinical trials as somehow dispositive. Ex. 1012 (Burgess Decl.) at ¶ 132. And, tellingly, the only citation in O'Regan for "clinical use" is the early stage Howell study. Ex. 1009 (O'Regan) at 2. But, the skilled formulator would know that formulations used in the early phases of clinical discovery/development are geared toward target validation and/or proof of concept of the molecule, most often using experimental formulations. Ex. 2051 (Cohen) at 14 ("The early Phase I and even Phase II trials are frequently conducted with experimental formulations which will not be marketed. Furthermore, the trial formulation may differ from that used in the toxicology studies and have a different bioavailability."). In particular, first-in-man studies similarly often use parenteral routes of delivery to evaluate drug activity while guaranteeing "precise drug and dose deposition." Ex. 2094 (Aulton Ch. 13) at 5.

141. Quoting AstraZeneca's remarks submitted with the Gellert Declaration, Dr. Burgess argues that "AstraZeneca conceded" that the "traditional administration options to explore were intramuscular injection of a sustained release aqueous or oil suspension or an oil-based solution (depot)." Ex. 1012 (Burgess Decl.) at ¶ 136. This is not true. The "traditional administration options"

refer to "aqueous or oil suspension or an oil-based solution" and were explicitly based on the invention limitations of a sustained release intramuscular injection. Ex. 1096 (Aug. 21, 2008 Amendment and Response) at 15. Dr. Burgess admits that "Dr. Gellert's declaration related to "a formulator tasked with developing a 'sustained release injectable formulation.'" Ex. 1012 (Burgess Decl.) at ¶ 173. There was no concession of a preference for intramuscular injection over oral formulation and that would be contrary to the art.

D) The Formulator Would Be Concerned About Intramuscular Administration Of Fulvestrant

142. The formulator would have appreciated many disadvantages to intramuscular administration, particularly when viewed in light of the oral products then-available for endocrine therapy. Ex. 2020 (Jordan Supp. 1992) at 4 ("An orally active agent should be an essential component of any strategy to introduce a new antiestrogen. Oral tamoxifen is so well tolerated that patients would be reluctant to consider injections or sustained-release implants as an alternative."). In particular, possible injuries from intramuscular injection include "paralysis resulting from neural damage, abscesses, cysts, embolism, hematoma, sloughing of the skin, and scar formation." Ex. 2106 (Ansel Ch. 14) at 9. For this reason, intramuscular injections must be administered by a healthcare professional thus requiring patient visits, an example of patient inconvenience.

143. Riffkin, cited by Dr. Burgess, noted the possibility of "necrosis, which is the most damaging situation, [and] means that the cellular structure was destroyed and repair must take place." Ex. 1033 (Riffkin) at 4. Other references taught similar concerns. *See, e.g.* Ex. 2107 (Avis Ch. 2) at 13 ("Occasionally, when a large bolus of drug is injected into the muscle, local damage or muscle infarction may result, leading to a sterile abscess or to elevation of serum levels of muscle enzymes.").

144. The formulator would have appreciated that intramuscular injections may also have issues with drug release. Ex. 1094 (Tse I) at 8 ("[D]rugs are not always completely available following intramuscular injection. Slow or incomplete absorption from intramuscular sites has been reported for chlordiazepoxide, diazepam, digoxin, phenytoin, and phenobarbital, and the extent of absorption may also be influenced by the patient's age.").

E) The Prior Art Disclosed Numerous Fulvestrant Formulations

145. Dr. Burgess cites publications that contain a variety of fulvestrant formulations: Ex. 1008 (McLeskey), Ex. 1007 (Howell 1996), Ex. 1047 (Dukes 1989), Ex. 1031 (Wakeling 1991), Ex. 1040 (Wakeling 1992), Ex. 1009 (O'Regan 1998), Ex. 1036 (Dukes 1992), Ex. 1038 (DeFriend 1994), Ex. 1058 (Wakeling 1993), Ex. 1089 (Chwalisz); Ex. 1088 (Wunsche); Ex. 1012 (Burgess Decl.) at ¶ 179. Other publications also use formulations of fulvestrant for basic biological

research, Ex. 2159 (Martel 1998) (in polyethylene glycol and ethanol in a gelatin-NaCl solution), Ex. 2160 (Huynh 1993) (in peanut oil), Ex. 2109 (Wade 1993) (in sesame oil vehicle, ethanol, and estradiol benzoate), Ex. 2161 (Chatterjee) (in sesame oil and benzyl benzoate), Ex. 1048 (Parczyk) (in castor oil and benzyl benzoate), Ex. 2163 (Dipippo) (in sesame oil, benzyl alcohol, and ethanol), Ex. 2110 (Lundeen 1997) (in ethanol and corn oil), Ex. 1039 (Osborne 1995) (in castor oil), Ex. 2164 (Sibonga 1998) (in ethanol stock solution and resuspended in sesame oil), Ex. 2165 (Al-Matubsi) (in ethanol and peanut oil). In addition, a PubMed search for publications that mention fulvestrant prior to 2000 reveals over 250 hits. Dr. Burgess specifically, on the non-substantiated basis of having selected a castor oil-based formulation as the only option for a fulvestrant depot formulation, lists six publications all disclosing castor oil based formulations. She then goes on to pick out the McLeskey formulation as the only possible option. Ex. 1012 (Burgess Decl.) at ¶ 182. However, Dr. Burgess provides no basis in the art for preferring the combination of excipients in the McLeskey castor oil-based formulation over other fulvestrant formulations in the prior art.

146. When describing the scope of the art, Dr. Burgess lists several "[c]ommon excipients for depot injections. Ex. 1012 (Burgess Decl.) at ¶ 71. However, when it comes to solubility and safety, Dr. Burgess only analyzes the combination of the four excipients used in the claimed inventions. Ex. 1012

(Burgess Decl.) at ¶¶ 119, 124. Dr. Burgess ignores all the other excipient combinations in which fulvestrant, and other marketed steroid products, had been formulated. This is a hindsight justification of the excipients that the inventors actually used, rather than an explanation of why the skilled artisan would have selected those excipients over the other available options.

147. Aside from castor oil, fulvestrant had been formulated in arachis (peanut) oil (Ex. 1031 (Wakeling 1991) at 2), in sesame oil (Ex. 2109 (Wade 1993) at 2), in propylene glycol (Ex. 1038 (DeFriend) at 2), and in corn oil (Ex. 2110 (Lundeen 1997) at 2. A reference cited by Dr. Burgess, Powell, ***does not even list castor oil*** as used in a single marketed parenteral product. *See* Ex. 1105 at 11 (listing consecutive alphabetical entries of "carboxymethylcullose" to "chloride").

148. Further, the formulator would have known of many other excipients used in previously marketed formulations of lipophilic and poorly water-soluble molecules, including surfactants, such as lecithin, polyoxyethylene-polyoxypropylene ethers, polyoxyethylene sorbitan monolaurate, polysorbate 80, silicone antifoam, and sorbitan trioleate; solubilizing agents, such as polyethylene glycol 300 and propylene glycol; and citric acid and sodium citrate for pH adjustment. Ex. 1018 (Avis Ch. 5) at 49. Additional co-solvent options include cremophor EL, glycerin N-methyl-2-pyrrolidone (Pharmasolve), monothioglycerol, sorbitol. Ex. 2112 (Strickley I) at 7-8.

149. Dr. Burgess characterizes each individual excipient in the castor oil-based formulation of McLeskey as "common." Ex. 1012 (Burgess Decl.) at ¶ 71. However, Dr. Burgess has cited no previously-marketed formulation that contains all the excipients of the claimed formulations, and I am not aware of any. Indeed, I am aware of no marketed oil-based formulation that contains a co-solvent system of benzyl alcohol and ethanol, and Dr. Burgess has cited none. Other references cited by Dr. Burgess formulated fulvestrant in castor oil and benzyl alcohol but did not include ethanol or benzyl benzoate. Ex. 1047 (Dukes 1989) at 11:6-8. Consistent with this, the specification of the '122 Patent disclosed commercial products that used some but not all of the claimed excipients. Ex. 1001 at Table 1.

150. As I explain below, the skilled artisan would not adopt Dr. Burgess' proposed motivation for preferring the castor oil-based formulation in McLeskey over these other options.

XIII) NON-OBVIOUSNESS OVER HOWELL (GROUND ONE)

151. InnoPharma (and with that Dr. Burgess) relies on a purportedly new obviousness ground based on Howell 1996 alone. InnoPharma claims that "Howell would have been the logical starting point for any POSA interested in developing a method for treating hormone-dependent breast cancer with fulvestrant," based on the "positive results reported in Howell." Petition at 36. InnoPharma then argues that "[t]he way to develop that formulation was readily

available to a POSA, as reflected in Dr. Gellert's Declaration." Petition at 37. In particular, InnoPharma alleges that a solubility screen would have identified castor oil as the oil vehicle and ethanol and/or benzyl alcohol as the best co-solvent candidates. Petition at 38. InnoPharma then asserts that "[b]enzyl benzoate would have been the logical choice," because of a number of commercialized formulations have a substantial benzyl benzoate component. Petition at 38.

152. I disagree that, with only Howell and common sense as guides, a formulator of ordinary skill would have been motivated to choose the excipients and excipient amounts of the invention and reasonably expected the pharmacokinetic and physiological results of the invention.

A) The Board Already Rejected The Same Argument Based On Routine Experimentation

153. The previous Petitioner, Mylan, already cited Howell 1996 in an obviousness ground and made the same arguments based on known excipients and "routine experimentation." InnoPharma repackages the previous Petitioner's argument by using out of context statements from the Gellert Declaration, which I understand is not prior art.

154. In the PTAB Decision, the Board considered the argument that "the ordinarily skilled artisan would have known that that steroidal compounds such as fulvestrant would be formulated in oily vehicles for long-acting intramuscular injections . . . and that the art taught castor oil as particularly desirable." Ex. 1011

(PTAB Decision) at 25. The Board considered the assertion that "one of ordinary skill in the art would have applied basic principles of pharmaceutical formulation to determine the solubility parameters of a drug solute and a solvent mixture, and 'determined which solvents should be included in a solvent mixture to optimize the solubility of a drug solute." Ex. 1011 (PTAB Decision) at 25. The Board further considered the argument that "one of ordinary skill in the art, beginning with a castor-oil base, would have been able to reasonably predict that fulvestrant would have been more soluble in a mixture containing benzyl alcohol, benzyl benzoate, ethanol, than in castor oil alone." Ex. 1011 (PTAB Decision) at 25. The Board noted the assertion that "1) benzyl alcohol and benzyl benzoate lower the viscosity of castor oil-based compositions, making them easier to inject; 2) benzyl alcohol may provide preservative and local anesthetic properties; and 3) ethanol is widely used in pharmaceutical formulations as a solubility aid." Ex. 1011 (PTAB Decision) at 26. The Board further noted that Petitioner "contends that the benzyl alcohol, benzyl benzoate, and ethanol in McLeskey's castor oil-based formulation were conventional excipients that '*could* be used for their ordinary purposes to create a fulvestrant formulation to treat breast cancer.'" Ex. 1011 (PTAB Decision) at 25 (emphasis in original). The Board stated that Petitioner's Declarant "indicates that castor oil, ethanol, and benzyl alcohol have been used in other castor oil-based fulvestrant formulations, whereas '[b]enzyl benzoate is a

conventional synthetic solvent often used for steroid hormones.'" Ex. 1011 (PTAB Decision) at 26. InnoPharma adds nothing new to these previously-rejected assertions. I understand that with regard to the previous Mylan IPR, the Board noted that even assuming that "one of ordinary skill in the art *could* have combined fulvestrant with benzyl alcohol, benzyl benzoate, ethanol, and castor oil," there was "insufficient evidence that one of ordinary skill in the art would have reasonably expected the physiologic effects of the claimed combination upon intramuscular injection to human patients." Ex. 1011 (PTAB Decision at 28 (emphasis in original). I agree with that conclusion. Dr. Burgess fails to address this defect, as explained below.

B) The Skilled Formulator Would Not Have Been Motivated To Combine The Howell Reference With The Specific Amounts Of Specific Excipients

1) The Choices Of Potential Excipients Would Be Infinite

155. Howell does not disclose any other excipient than castor oil, and the possibilities are infinite. Dr. Burgess noted that "[c]ommon excipients for depot injections at the time included sesame oil, cottonseed oil, castor oil, benzyl benzoate, benzyl alcohol, methanol, ethanol, and propanol, among others." Ex. 1012 (Burgess Decl.) at ¶ 71; *see* Ex. 1102 (Nema) at 1 (listing categories of excipients, including solvents and co-solvents; solubilizing, wetting, suspending, emulsifying or thickening agents; chelating agents; antioxidants and reducing

agents; antimicrobial preservatives; buffers and pH adjusting agents; bulking agents, protectants, and tonicity adjustors; and special additives); Ex. 1105 (Powell) at 3-74 (listing over 140 excipients used in marketed parenteral formulations). Even with a small number of excipients, unlimited combinations of excipient amounts are possible. Each seemingly small change requires research because as was well known, small changes in the amounts of excipients can have significant effects. *See* Ex. 1033 (Riffkin) at 4; *infra* ¶¶ 176-185.

156. To try to narrow down the choice of other excipients for a castor oil-based formulation, Dr. Burgess relies on the inventors' own unpublished work described in the Gellert Declaration. Based solely on the invention work, Dr. Burgess argues "ethanol and/or benzyl alcohol . . . as the best co-solvent candidates for raising the fulvestrant solubility to the 45 mg/mL target. Ex. 1012 (Burgess Decl.) at ¶ 106; *see also* Petition at 38.

157. The Gellert Declaration responded to rejections in the examiner's Office Action dated March 17, 2008, citing Dukes, not Howell. To rebut the examiner's statement that "[b]enzyl benzoate would be reasonably expected to be useful as a solvent for fulvestrant," the Gellert Declaration explained that even with the extra, confidential internal research by the AstraZeneca inventors, benzyl benzoate would ***not*** be reasonably expected to act as a solvent for fulvestrant. Ex. 1020 (Gellert Decl.) at ¶ 20 ("The experienced formulator thus would have

expected that benzyl benzoate would *not* act as a co-solvent for fulvestrant in castor oil because the solubility of fulvestrant in benzyl benzoate was significantly lower than its solubility in castor oil.").

158. The Gellert Declaration refers to the inventors' own goals and experiments, to explain that even following the inventor's path, with all of the insights gained through confidential unpublished research would not lead to selection of the particular excipient ingredients in the specific combinations used by the invention. See Ex. 1020 (Gellert Declaration) at ¶ 13 ("[T]he formulator would have found 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, such as reported in paragraph [0042] of the Evans Application."); ¶ 14 ("[T]he experienced formulator would have conducted a literature review or otherwise would have become familiar with commercially marketed injectable formulations, particularly injectable sustained release formulations of steroids or other relatively insoluble compounds such as those listed in Table 1 of the Evans Application"); ¶ 16 ("When carrying out such a preformulation solubility screen with fulvestrant, the formulator would have found that fulvestrant had extremely low solubility in water, low solubility in most oils (but highest in castor oil), low solubility in benzyl benzoate, and the highest solubility in ethanol and benzyl alcohol, such as reported in Table 2 of the Evans Application."); ¶ 20 ("This is confirmed in Table

4 of the Evans Application, which reports a fulvestrant solubility of only 12.6 mg/mL in the castor oil vehicle containing only 15% benzyl benzoate, compared to the 20 mg/mL solubility of fulvestrant in castor oil alone as reported in Table 2."); ¶ 21 ("[b]ased on the solubility data determined in the preformulation screen (such as reported in Table 2 of the Evans Application . . ."). None of this is in the prior art.

159. Even with information from the claims to set the approach, the experiments in the Gellert Declaration would require extensive and complicated work. The experiments to eliminate suspensions could have taken years and involved making and testing tens or hundreds of formulations. *See* Ex. 1020 (Gellert Decl.) at ¶ 13. The solubility screen could have included and tested different solvents or conditions. *See* Ex. 1020 (Gellert Decl.) at ¶ 16. Even if castor oil were selected, the skilled artisan could have tested combinations of oils, as the inventors did. Ex. 1001 at Table 4. The tests to increase solubility with other excipients could have gone in many different directions. *See* Ex. 1020 (Gellert Decl.) at ¶¶ 16-17. The skilled artisan could have experimented with only ethanol or only benzyl alcohol, or a combination of only one of those excipients with another solvent or solvents. Even if the skilled artisan selected ethanol and benzyl alcohol, Table 3 of the patent shows that this combination could lead to a

variety of fulvestrant solubilities higher than the claimed invention. Ex. 1001 at Table 3.

160. Dr. Gellert suggests "minimiz[ing] the amount of co-solvents and excipients in any injectable formulation." Ex. 1020 (Gellert Decl.) at ¶ 22. Yet, Dr. Burgess asserts that "a person of skill in the art would look to the higher end of the approved ranges." Ex. 1012 (Burgess Decl.) at ¶ 125. But, Dr. Burgess admits that the highest approved level of benzyl alcohol was 46% w/v and the highest range of benzyl alcohol is 15% w/v. Ex. 1012 (Burgess Decl.) at ¶ 124. In my opinion, the experiments necessary to determine the optimum excipient amounts by balancing solubility, release profile, and tolerance would be lengthy and uncertain, especially starting at the levels suggested by Dr. Burgess of 46% benzyl benzoate and 15% benzyl alcohol.

161. Innopharma argues that "a routine solubility screen would confirm that castor oil, benzyl alcohol, and ethanol could not solubilize fulvestrant at the target 50 mg/ml concentration." Petition at 38. This is plainly incorrect. Table 3 of the '122 Patent shows that 15% w/v ethanol and 15% w/v benzyl alcohol solubilized fulvestrant in castor oil to 76 $mgml^{-1}$.[3]

[3] The Gellert Declaration corrected this from 76 mg to 77 mg. Ex. 1020 (Gellert Decl.) at 16.

162. Dr. Burgess further argues that a skilled formulator would recognize that "a formulation comprising fulvestrant, ethanol, benzyl alcohol, and castor oil would not be able to adequately solubilize fulvestrant at the target concentration of at least 50 mg/ml, without exceeding 20% total alcohol." Ex. 1012 (Burgess Decl.) at ¶ 109. To begin, the "20% total alcohol" limitation appeared nowhere in the prior art. And, the Gellert Declaration upon which Dr. Burgess relies for support, never said that alcohols should not exceed 20%. At most, the Gellert Declaration only said that the skilled artisan would want to "substantially reduce the benzyl alcohol content" in the Dukes reference from 40%. Ex. 1020 (Gellert Decl.) at ¶ 24. Further refuting Dr. Burgess' argument, the Gellert Declaration shows that at 25°C, 10% w/v ethanol and 5% w/v benzyl alcohol solubilized fulvestrant to 64.6 $mgml^{-1}$—a total of 15% w/v alcohols. Ex. 1020 (Gellert Decl.) at 19 (Attachment C). Thus, even under Dr. Burgess' argument, and even with the non-prior art invention work as a guide from the Gellert Declaration, there was no reason for adding an additional solvent such as benzyl benzoate.

163. Even if "a POSA would have been motivated to add another co-solvent to the formulation" after this series of experiments, Dr. Gellert explained that the skilled artisan would not have considered benzyl benzoate based on the previously-conducted solubility screen of pure solvents, which would have showed that benzyl benzoate was not a good solvent for fulvestrant: "[t]he addition of

benzyl benzoate to castor oil, for whatever reason, would have been expected to *decrease, rather than increase*, the solubility of fulvestrant in the resulting castor oil/benzyl benzoate mixture." Ex. 1020 (Gellert Decl.) at ¶ 20. Dr. Burgess repeatedly states that a skilled formulator would conduct a solubility screen, but then later ignores what the skilled artisan would learn from such a screen regarding the poor fulvestrant solubility in benzyl benzoate. Ex. 1012 (Burgess Decl.) at ¶¶ 36, 71.

164. To argue that the skilled formulator would discount this information, Dr. Burgess claims that "every castor oil-based formulation Dr. Gellert identifies contains benzyl benzoate." Ex. 1012 (Burgess Decl.) at ¶ 111. But, Dr. Gellert's purpose was expressly stated in one of the paragraphs cited by Dr. Burgess as disclosing to the examiner that benzyl benzoate had, in fact, occasionally been used with castor oil: "[a] number of the commercialized formulations that would have been identified in the literature review (including castor oil-based formulations) have a substantial benzyl benzoate component." Ex. 1020 (Gellert Decl.) at ¶ 18.

165. And, Dr. Burgess cites Riffkin as teaching that ""despite better solubility of steroids in castor oil, other cosolvents were necessary to dissolve"", specifically mentioning benzyl benzoate. Ex. 1012 (Burgess Decl.) at ¶ 110. However, AstraZeneca disclosed to the examiner in remarks submitted with the

Gellert Declaration that "[m]any commercialized steroids were *more* soluble in benzyl benzoate than in the oil base of the vehicle as disclosed in Riffkin (1965)." Ex. 1046 (March 17, 2008 Office Action) at 156 (emphasis in added).

166. In contrast, Dr. Burgess cites no marketed oil-based formulation that included all of the excipients. In fact, Dr. Burgess cites no marketed oil-based formulation that included ***both*** ethanol and benzyl alcohol as cosolvents, and provides no explanation why the skilled artisan would try combinations of alcohols in equal parts as cosolvents. There was no precedent for such a combination.

2) Routine Experimentation Would Not Lead To The Claimed Excipient Amounts

167. Innopharma does not provide citation support for its statement that "Dr. Gellert[] opined that it would have been routine experimentation for a POSA to adjust prior art formulations to achieve the claimed percentages." Petition at 42. That is because Dr. Gellert nowhere says anything like this. *See* Section XI(G), above.

168. Dr. Burgess argues that the IIG indicates that ethanol had been used in amounts up to 11%, benzyl alcohol had been used up to 15%, and benzyl benzoate had been used up to 46% for IM injections. Ex. 1012 (Burgess Decl.) at ¶ 124. What this shows is that there were infinite possibilities even if one were limited to using a combination of these three excipients which is not mentioned in the Howell reference. "Acceptable levels of cosolvent in parenteral formulations are not easily

defined." Ex. 2052 (Sweetana) at 7. For example, "[a]ppropriate product amounts are often a matter of considering a diverse set of factors such as; 1) administration conditions, 2) total dose, 3) target population and 4) duration of therapy." Ex. 2052 (Sweetana) at 7.

169. Dr. Burgess tries to narrow the choices by saying "[b]ecause of the poor solubility of fulvestrant, a person of skill in the art would look to the higher end of the approved ranges." Ex. 1012 (Burgess Decl.) at ¶¶ 124-125. This is contradicted by Dr. Burgess' statement that she "agree[s] with Dr. Gellert that one skilled in the art will typically use as little cosolvent as possible." Ex. 1012 (Burgess Decl.) at ¶ 121. And, of course, the benzyl benzoate amount in the invention (15%) is not at that "higher end" (46%). There would be an infinite number of possible formulations falling within the wide range of excipient amounts suggested by Dr. Burgess.

170. Dr. Burgess claims, without any experimentation and based solely on chemical structure, that "a person of skill in the art would understand that ethanol and benzyl alcohol would work in tandem with benzyl benzoate to solubilize fulvestrant in castor oil." Ex. 1012 (Burgess Decl.) at ¶ 117. She says that "[i]t is well known that combining multiple co-solvents can have a ***synergistic*** effect, *i.e.*, a mixture of solvents can have a greater solubilizing power than the sum of its parts." Ex. 1012 (Burgess Decl.) at ¶ 116 (emphasis in original). The critical word

is "can"—synergistic solubility effects cannot be predicted: "[n]o single theory can adequately explain solubility behavior of uncharged molecules in a variety of solvent systems." Ex. 2052 (Sweetana) at 2. This is because "[s]olubilzation processes are amazingly complex," and "[t]heories of solubilization are not easy to understand". Ex. 2052 (Sweetana) at 2. In fact, scientists at the time "***still need[ed] to rely on the empirical experimentation*** to screen for systems which offer the most promise in solubilizing water-insoluble drugs." Ex. 2052 (Sweetana) at 3.

171. The Chien publication quoted by Dr. Burgess does not support any expectation of synergistic solubility behavior in castor oil based formulations. And, Chien does not discuss fulvestrant, castor oil, benzyl alcohol, or benzyl benzoate. Chien discusses ***formulating steroids in aqueous formulations***, not in oils: "[t]o solve such problems, scientists often incorporate one or more co-solvents with distilled water to overcome the poor aqueous solubility." Ex. 1098 (Chien) at 1. Chien recommends combinations of ethanol, dimethylacetamide, propylene glycol, and solketal. Ex. 1098 (Chien) at 5. Thus, Chien actually teaches that steroids should be formulated in aqueous formulations using different excipients than the claimed invention. Notably, Chien does not speculate about solubility based on the molecular structure of the solvents but, instead, performs actual experiments. *See* Ex. 1012 (Burgess Decl.) at ¶¶ 117-119. Moreover, Chien

cautions that the "use of high co-solvent concentrations may unfavorably affect the desired viscosity, and the esthetic acceptability of the resultant formulations." Ex. 1098 (Chien) at 5.

172. Just by looking at the molecular structure of the claimed excipients, Dr. Burgess argues that "ethanol and benzyl alcohol have hydroxyl groups that would hydrogen bond with the double-bonded oxygen on the sulphoxide group in fulvestrant" and that "benzyl benzoate has a double-bonded oxygen that would hydrogen bond with either of the hydroxyl groups on the fulvestrant steroidal ring structure." Ex. 1012 (Burgess Decl.) at ¶ 119. Similarly, Dr. Burgess argues that "[b]enzyl benzoate contains two benzene rings, which would interact favorably with the benzene rings on benzyl alcohol and on fulvestrant." Ex. 1012 (Burgess Decl.) at ¶ 120. Dr. Burgess cites to no reference to support a hydrogen bonding theory; provides no example of synergy from benzyl benzoate and alcohols in the art; and offers no evidence that hydrogen bonding actually caused the solubility increase from benzyl benzoate in the case of fulvestrant. Ex. 1012 (Burgess Decl.) at ¶¶ 119-120. To the contrary, the effect of hydrogen bonding, in particular, was impossible to predict at the time. "The majority of parenterally acceptable cosolvents—such as propylene glycol, polyethylene glycol, ethanol and water—are capable of self association through hydrogen bond formation. Such interactions

may alter solvent structure and, as a result, ***influence solubility in an unpredictable manner***." Ex. 2052 (Sweetana) at 2 (emphasis added).

173. Similar hypotheses could be made for thousands of solvent systems with no way to predict which, if any would work to solubilize fulvestrant. Many solvents could have provided "additional hydrogen bonding and polarity" to the system. For instance, water is a very polar molecule with potential hydrogen bonding. Yet, Dr. Burgess does not explain why a skilled artisan would have selected benzyl benzoate over any other solvent. And, even using these hypotheses, Dr. Burgess does not explain how the synergistic solubility would come about or why. Ex. 2052 (Sweetana) at 2-3 ("[n]o single theory can adequately explain solubility behavior of uncharged molecules in a variety of solvent systems," because "[s]olubilzation processes are amazingly complex," and "[t]heories of solubilization are not easy to understand," so scientists at the time "still need[ed] to rely on the empirical experimentation to screen for systems which offer the most promise in solubilizing water-insoluble drugs."). Dr. Burgess works backwards from the invention and suggests why it might have worked.

C) Dr. Burgess Fails To Address a Reasonable Expectation Of Success Regarding The Physiological Effects Of The Formulation

174. Dr. Burgess admits that "[t]he goal of a depot formulation is to ensure that the serum concentration of the d[r]ug stays within the desired pharmacokinetic parameters once the patient reaches steady state." Ex. 1012 (Burgess Decl.) at ¶

66. Dr. Burgess further states that "[t]he goal of [a] depot formulation is to sustain the levels of drug concentration for extended periods of time." Ex. 1012 (Burgess Decl.) at ¶ 67. Moreover, Dr. Burgess claims that "it is of prime importance to ensure the drug is maximally inhibiting tumor growth." Ex. 1012 (Burgess Decl.) at ¶ 100. Yet, Dr. Burgess does not even attempt to explain how the skilled artisan could have reasonably expected the invention's physiologic effects upon intramuscular injection of the McLeskey formulation to human patients. Ex. 1011 (PTAB Decision) at 28.

175. Instead, Dr. Burgess states that "castor oil, ethanol, benzyl alcohol, and benzyl benzoate had been previously approved by FDA as safe for intramuscular use in humans at or above the concentrations claimed." Ex. 1012 (Burgess Decl.) at ¶ 147; *see also* Petition at 39. However, Dr. Burgess does not cite to any approved formulation with the claimed ***combination*** of excipients. Moreover, Dr. Burgess' argument completely ignores the duration of action, blood plasma fulvestrant concentration or lack of side effects (including lack of precipitation and local irritation) of the claimed inventions.

176. Dr. Burgess relies only on arguing that solubility predicts physiological effects and pharmacokinetic profile. Stated differently, Dr. Burgess' argument is that as long as castor oil is present and the concentration of fulvestrant of 50 mg/ml can be achieved, the physiological effects and pharmacokinetic profile

of the drug will be achieved whatever the amount and type of other excipients: "Thus, the person skilled in the art would appreciate that because both the Howell 1996 formulation and the McLeskey 1998 formulation comprise a solution of fulvestrant at the same concentration (50 mg/ml), both using castor oil as the base of the vehicle, the McLeskey 1998 castor oil-based formulation would be expected to achieve the same day-28 results as reported in Howell 1996." Ex. 1012 (Burgess Decl.) at ¶ 187. Dr. Burgess argues that the release of the fulvestrant from the formulation in situ is controlled by the castor oil alone. Ex. 1012 (Burgess Decl.) at ¶¶ 187-194. But, the specification states that "[s]imply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site." Ex. 1001 at 9:20-22. And, it was and remains well known that "[i]n the absence of *in vivo* data, it is generally i*mpossible* to make valid conclusions about bioavailability from the dissolution data alone." Ex. 2162 (Applied Biopharmaceutics) at 28. Here, there was neither *in vivo* nor dissolution data.

177. A skilled artisan would know that excipients of a formulation can have significant effects on formulation characteristics. In particular, for injections, a change in excipient may alter drug solubility and formulation viscosity, which, in turn, can influence the shape of the formulation depot upon administration or cause precipitation of the drug at the site of injection. Ex. 1099 (Aulton Ch. 21) at 11

(viscosity affects release rate); Ex. 2113 (Avis Ch. 3) at 10 (change in solubility can cause precipitation). The shape and the area of deposition and the distribution of the injection in the area of deposition influence the release and absorption of the drug. Ex. 2115 (Ballard 1968) at 2.

178. In fact, "[m]any factors may affect the release from an intramuscular or subcutaneous injection site." Ex. 2114 (Zuidema 1994) at 14. These factors include, "molecular size, pK_a, drug solubility, initial drug concentration, injection depth, body movement, blood supply at the injection site, injection technique and **properties of the vehicle in which the drug is formulated**." Ex. 2114 (Zuidema 1994) at 1-2 (emphasis added). Moreover, "[t]he composition of the mobile phase (the injection vehicle) and possible alterations of the stationary phase (the cell material) by injection components such as surfactants determine the initial absorption rate." Ex. 2114 (Zuidema 1994) at 14. As an example, "cosolvents such as propylene glycol, glycerol and polyetheylene glycol 400 have been reported contradictorily to diminish and to enhance absorption rate of model compounds." Ex. 2114 (Zuidema 1994) at 7; *see also* Ex. 1099 (Aulton Ch. 21) at 7 ("However, formulation, coupled with variation in the site of administration may affect markedly the biopharmacy of drugs."); Ex. 2107 (Avis Ch. 2) at 12 ("Many factors affect the rate of drug absorption from an intramuscular injection."); Ex. 2107 (Avis Ch. 2) at 31-32 (listing factors that affect absorption, including

solubility of the drug, partition coefficient of the drug, rate of blood flow at the injection site, degradation of the drug at the injection site, particle size of the drug, and formulation ingredients); Ex. 2107 (Avis Ch. 2) at 32 ("Such effects may be manifested in diverse ways, such as complexation, which reduces the rate of drug dissolution, and as increased viscosity, which retards the transport of the drug from injection site to the systemic circulation.").

179. In addition to affecting release profile, excipients may also affect the irritation and inflammation from an injection. For example, Table IV of Riffkin, cited by Dr. Burgess, shows differences in "local irritation produced in rabbit muscle by injection of various oil vehicles." Ex. 1033 (Riffkin) at 3. Table IV reports a lesion size of "too small to measure" for 98% castor oil and 2% benzyl alcohol, but a lesion size of 262 mm^2 for 63% castor oil, 35% benzyl benzoate and 2% benzyl alcohol. Ex. 1033 (Riffkin) at 3. Thus, based on Table IV, benzyl benzoate appeared responsible for an increase in lesion size. Moreover, other combinations of solvents and oils produced lesions with a range of 61 mm^2 to 506 mm^2. Riffkin concludes that "[t]he nature of the irritative response depended on the particular hormone, its concentration in the formulations, and/or the composition of the vehicle." Ex. 1033 (Riffkin) at 4. Based on Riffkin, the skilled formulator would have understood that co-solvents could contribute significantly to the formulation characteristics, such as injection site irritation.

180. In Riffkin, Table V and Table VI provide data on injection site reactions in humans for various formulations of 17-hydroxyprogesterone caproate and estradiol valerate, respectively. Ex. 1033 (Riffkin) at 4. The 17-hydroxyprogesterone caproate formulation of 58% castor oil, 40% benzyl benzoate, and 2% benzyl alcohol was "rejected," but the same formulation with estradiol valerate substituted for 17-hydroxyprogesterone was "accepted." Ex. 1033 (Riffkin) at 4. Even for the same active ingredient, Table V shows that some formulations of 17-hydroxyprogesterone caproate with castor oil were "rejected," while other formulations of hydroxyprogesterone caproate containing castor oil were "accepted." The same is true for estradiol valerate and castor oil, as shown in Table VI. Thus, the skilled formulator would know from Riffkin that co-solvents and the active ingredient both contribute to injection site reactions, and, accordingly, the skilled formulator would separately develop the formulation for each compound based on experience with that specific compound.

181. Without support from Dr. Burgess, Innopharma argues that Riffkin cannot be used to "create unpredictability," because "the challenged claims are silent on a side effect profile, and so cannot avoid obviousness on that basis." Petition at 34-35. This argument entirely misses the point. The skilled formulator would know that differences in degree and type of irritation and inflammation could affect the release profile. "Absorption via the mechanisms of lymphatic

transport and inflammation-mediated appearance of phagocytosing macrophages (24-48 h after injection) have been demonstrated for iron complexes." Ex. 2114 (Zuidema 1994) at 8. Indeed, in the specification, the inventors attributed poor release profiles of aqueous suspensions to "the extent of inflammation/irritation present at the injection site and this was variable and difficult to control." Ex. 1001 at 8:42-45.

D) There Is No Way To Predict How A Formulation Will Behave Upon Injection

182. Many factors affect how a formulation and the active ingredient will behave once it enters the body:

> The design of sustained-release delivery systems is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy, and the properties of the drug. Each of these variables are interrelated and this imposes certain constraints upon choices for the route of delivery, the design of the delivery system and the length of therapy.

Ex. 2080 (Remington's Ch. 91) at 8; *see also supra* ¶¶ 43-48, 176-185. A skilled formulator could not have predicted the effect of changing any one parameter on blood plasma levels.

183. Additionally, differences in the injection site environment and the biological reaction to the injection would have prevented extrapolating blood plasma levels from one species to a different species. After injection into the muscle, the release, absorption and elimination of a drug is determined by physical, physicochemical, and biological interactions. For instance, small changes in the physical shape of the formulation as it spreads within the muscle may influence absorption. Ex. 2115 (Ballard 1968) at 2. Changes in composition of the formulation in the muscle over time may change physicochemical properties, such as the solubility of fulvestrant in the formulation, possibly leading to precipitation of solid fulvestrant particles in the muscle. Ex. 2082 (Aulton Ch. 1) at 11. As the drug leaves the formulation, it may bind to tissue proteins, preventing absorption. Ex. 1094 (Tse I) at 4. Biological factors, such as lymphatic transport and inflammation caused by the formulation may affect absorption after subcutaneous injection. Ex. 2114 (Zuidema 1994) at 13-14. Absorption and metabolism of the vehicle itself and changes at the injection must also be considered. Ex. 2116 (Hirano 1981) at 4. These factors all depend, to some extent, on the species tested.

184. To take one example, precipitation of the active ingredient in the tissue could cause pain and tissue damage and also lead to the accumulation of active ingredient at the injection site, and a poor release profile:

> Following i.m. injection, [] a biphasic rate of absorption was evident in the majority of subjects. This would be consistent with rapid drug precipitation at the injection site followed by slow drug redissolution, and has been previously suggested as a possibility with chlordiazepoxide, as well as with phenytoin and quinidine . . . . Thus intramuscular injection of chlordiazepoxide, like that of many other drugs, may not be an optimal mode of administration. . . . . When intravenous administration is not feasible, oral administration may be preferable to intramuscular injection.

Ex. 2117 (Greenblatt 1978) at 6-7.

185. There was no suitable *in vitro* test that could predict the *in vivo* pharmacokinetics and hence *in vivo* release profiles (let alone pharmacodynamics) for an intramuscular injection. The inventors found that the determination of the fulvestrant solubility in a formulation in a test tube cannot predict whether the drug stays in solution in the muscle after injection, or what its release profile or plasma levels would be: "[s]imply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site." Ex. 1001 at 9:20-22; *see also* Ex. 1001 at Table 4.

186. InnoPharma states that "the challenged claims are silent on any requirement concerning a particular side effect profile, and so cannot avoid an obviousness finding on that basis." Petition at 35. However, the '122 patent notes that suspensions were rejected for precisely this reason: "Previously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the injection site as well as a poor release profile." Ex. 1001 at 8:36-40. Additionally, Table 4 of the '122 patent provides data on other fulvestrant formulations that resulted in precipitation. Ex. 1001 at Table 4.

XIV) NON-OBVIOUSNESS OVER HOWELL COMBINED WITH MCLESKEY (GROUND TWO)

187. I understand that the Board previously denied institution on the combination of Howell and McLeskey, finding no "motivation to combine the references or a reasonable expectation of success from that combination." Petition at 9-10. I submitted an expert declaration expressing that opinion, I agree with the Board's conclusion, and the materials submitted by InnoPharma do not change my opinion.

A) The Board Already Considered Howell As The Starting Point And Correctly Denied Institution

188. As I understood the declarations in the previous IPR, the arguments were to start with Howell. Dr. Forrest argued that the invention "was obvious over

Howell 1996 in view of McLeskey." IPR2016-01325, Ex. 2092 (Forrest Mylan Decl.) at ¶ 129 (emphasis added). Dr. Forrest asserted that "***[a]fter reading*** Howell 1996," the formulator would have "had to find a castor oil-based formulation that would solubilize fulvestrant," and "would have quickly found this formulation in McLeskey." IPR2016-01325, Ex. 2092 (Forrest Mylan Decl.) at ¶ 131 (emphasis added). Thus, Dr. Forrest started with Howell and proceeded to McLeskey. I noted this argument in my previous declaration, saying that "Dr. Forrest appears to argue that Howell 1996 points to McLeskey." IPR2016-01325, Ex. 2135 (Illum Mylan Decl.) at ¶ 172.

B) No Reason To Combine Howell And McLeskey

189. Dr. Burgess argues that a skilled formulator "would have been motivated to develop a formulation that would solubilize fulvestrant at the same concentration as Howell, *i.e.*, 50 mg/ml." Ex. 1012 (Burgess Decl.) at ¶¶ 173-174; *see also* Petition at 45. Dr. Burgess argues that a literature review of "the published literature would have revealed articles disclosing the [] 6 castor oil-based formulations of fulvestrant," and that "only the formulations used in the Dukes '814 patent and in McLeskey 1998 are taught to solubilize fulvestrant at that concentration." Ex. 1012 (Burgess Decl.) at ¶¶ 179-184; *see also* Petition at 45-47. But, there is no evidence in McLeskey that the 50 mg/ml fulvestrant is solubilized in the formulation, there are no solubility data and no mention that the castor oil

formulation is a solution formulation. Dr. Burgess then argues that "one skilled in the art would have rejected the Dukes '814 patent formulation because of the high amount of benzyl alcohol used." Ex. 1012 (Burgess Decl.) at ¶ 181; *see also* Petition at 46.

190. For the reasons below and explained in my previous declaration, the skilled artisan would not have followed this approach. But, even if the skilled artisan had adopted this approach, it would not have led to the choice of the McLeskey formulation.

1) There Would Have Been No Reason To Assume That The Howell Formulation Was Disclosed In The Prior Art

191. InnoPharma states that "Howell—and not McLeskey—is the appropriate starting point," because "Howell closely mirrors the challenged claims and called for a castor oil-based vehicle that a POSA would necessarily have looked to McLeskey to find." Petition at 10; *see also* Petition at 19 ("Howell tracks the challenged claims."). InnoPharma's reason for selecting Howell as "mirror[ing] the challenged claims" suggests to me an express reliance on hindsight. Further, InnoPharma's statement that Howell "called for a castor oil-based vehicle that POSA would necessarily have looked to McLeskey to find" assumes without any support that the Howell formulation was published in the prior art. In my opinion, this unsupported assumption about the Howell

formulation is a critical unaddressed flaw in the reasoning of both InnoPharma and Dr. Burgess and confirms the use of hindsight.

192. The skilled artisan would not have approached the problem this way. Howell states only that "ICI 182780 was administered as a long-acting formulation contained in a castor oil-based vehicle by monthly i.m. injection (5 ml) into the buttock." Ex. 1007 (Howell 1996) at 2. In Dr. Burgess' words, Howell does not "actually disclose the composition of the castor-oil based formulation." Ex. 1012 (Burgess Decl.) at 79, n. 11 (noting that Howell was excluded from the list of "6 castor oil-based formulations" for this reason). Nothing in Howell teaches the formulator to focus on concentration or on castor oil as the defining characteristics of the formulation. In my view, Dr. Burgess' reliance on concentration to narrow down prior art formulations reveals a hindsight bias.[4]

[4] Dr. Burgess uses inconsistent criteria. For example, Dr. Burgess says she excluded formulations from her consideration that provided incomplete formulation details. Ex. 1012 (Burgess Decl.) at 79 n. 11 ("I do not include articles such as Howell 1996 or Dukes 1992 that reveal that a castor oil-based formulation were used but do not fully disclose the composition of the formulation."). She notes Ogasawara as one such example that met her 50 mg/ml concentration

193. The skilled formulator would conclude from the limited formulation information in Howell that the authors of Howell either did not know the makeup of the formulation or it was confidential. There would be no reason to assume it could be found in the prior art. Indeed, InnoPharma confirms this—it cites a 2003 publication (after the patent application) to argue that Howell "utilized the ***same long-acting castor oil-based formulation that AstraZeneca has claimed***." Petition at 19 (emphasis in original).

2) The Skilled Artisan Would Not Choose A Formulation Based Solely On Fulvestrant Concentration

194. Ignoring the differences between Howell and McLeskey, Dr. Burgess bases the entire argument for combining Howell with McLeskey on solubility: "the primary goal of the formulator would have been to develop a formulation that successfully solubilized fulvestrant in castor oil at 50 mg/ml." Ex. 1012 (Burgess Decl.) at ¶ 174. Dr. Burgess also cites the Gellert Declaration (not in the prior art)

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criteria, but she excludes it because it "does not list the cosolvents used to obtain that concentration." Ex. 1012 (Burgess Decl.) at 79 n. 11. Yet, included in the 6 formulations on which she relies is Osborne, which similarly does not identify the excipients and in fact does not even identify the concentration of fulvestrant. Ex. 1012 (Burgess Decl.) at ¶ 179.

which indicated the invention's "target fulvestrant content of at least 45 mg/mL." Ex. 1012 (Burgess Decl.) at ¶ 174.

195. Dealing with the Gellert Declaration first, it used the invention and patent specification to identify the "goal." Turning to Howell, it never indicates the formulation is a solution, or gives any solubility parameters, much less says solubility is linked in any way to formulation performance. McLeskely similarly does not state that the castor oil is a solution. *See supra* ¶¶ 66-72. The skilled formulator would not find motivation to combine Howell with McLeskey based on a purportedly shared characteristic that neither reference discloses.

196. Dr. Burgess incorrectly states that "[t]he solubility of fulvestrant in the McLeskey 1998 formulation is the same as that of the formulation used in Howell 1996 (50 mg/ml)." Ex. 1012 (Burgess Decl.) ¶ 214. Neither publication discloses solubility—rather the ***concentrations*** of the formulations are 50 mg/ml, ***not the solubility***. Table 3 of the '122 Patent shows that 10% w/v ethanol, 10% w/v benzyl alcohol, and 15% w/v benzyl benzoate ***does not*** have a fulvestrant solubility of 50 mg/ml, but, rather, 64 mg/ml.[5] In fact, this exposes the flaws in Dr. Burgess' reasoning—different castor oil-based formulations could be made to the

[5] The Gellert Declaration corrects the solubility at 4° C to 64 mg from 65 mg. Ex. 1020 (Gellert Decl.) at 16.

same concentration even if the fulvestrant had different solubility in the formulations. And, conversely, different castor oil formulations in which fulvestrant had the same solubility could be made to different concentrations. None of the references identified by Dr. Burgess indicate the solubility of fulvestrant in the formulation.

3) McLeskey Disparaged The Results Of Howell 1996

197. There was no reason to combine McLeskey and Howell 1996. In fact, McLeskey disparages the results in Howell 196. "[E]arly results for small numbers of tamoxifen resistant patients have shown that only about 30-40% of such patients have a positive response to subsequent [fulvestrant]." Ex. 1008 at 2. McLeskey is investigating, and, indeed, suggests an alternative approach to endocrine treatments instead of using a drug such as fulvestrant: "Therapy of such tumors with agents directed against the autocrine or paracrine effects of FGFs might result in beneficial effects in such cases." Ex. 1008 at 12-13. Hence, the skilled formulator would not combine McLeskey with Howell 1996.

198. Additionally, before the inventions of the '122 patent, 4 ml was considered a high volume to administer for intramuscular injections. Ex. 2054 (Beyea) at 1 ("For a large muscle such as the gluteus medius, use no more than 4 mL for adults and 1 to 2 mL for children and persons with less developed muscles."). The skilled artisan would have been concerned about a formulation

that required the high volume injection (5 ml) used in Howell 1996. In fact, such a large injection was unprecedented for intramuscular administration on a chronic basis. The large volume injection displaces the surrounding tissue and causes damage. Ex. 2079 (Gupta Ch. 2) at 20 ("The volume of the injection relates to pain intensity."); *see also* Ex. 2107 (Avis Ch. 2) at 13 ("Occasionally, when a large bolus of drug is injected into the muscle, local damage or muscle infarction may result, leading to a sterile abscess or to elevation of serum levels of muscle enzymes."). In fact, "damage to muscle cells seems to occur with each intramuscular injection," and "duration of contact of the concentrated injection to the tissue is long, when compared to IV injections." Ex. 2079 (Gupta Ch. 2) at 20. It can take "several weeks" for the muscle to regain normal function and histological appearance. Ex. 2079 (Gupta Ch. 2) at 21. Thus, repeated intramuscular injections over a short interval could prevent the muscle from recovering.

4) The Formulator Would Not Have Found McLeskey

199. From a practical standpoint, a skilled formulator would not come across McLeskey during routine literature searches for formulation strategies, even if such a formulator had been searching for formulations of fulvestrant in particular. A search of available literature, in a time before internet access was common and academic journals routinely provided online access to their archives,

would not have returned information about any of the formulations disclosed in McLeskey. Instead, at most, a researcher would have received the title or abstract of McLeskey only as a search result. Ex. 2042 (AACR Journals Online) (showing that only the abstract of Clinical Cancer Research from 1998 was searchable online); Ex. 2125 (Affidavit of Internet Archive).

5) McLeskey Described Fulvestrant As A "Treatment Failure"

200. The skilled formulator reading McLeskey would be taught away from the claimed inventions, because McLeskey described fulvestrant as a failure. Specifically, the title of McLeskey declares that the tumors studied were "cross-resistant [] in vivo to the antiestrogen ICI 182,780." Ex. 1008 at 1. The abstract explains that the fulvestrant formulations "did not slow estrogen-independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice." Ex. 1008 at 1. Figure 1 demonstrates, and the figure caption explains, that "[g]rowth of FGF-transfected MCF-7 cells in ovariectomized nude mice is not inhibited by treatment with [fulvestrant]." Ex. 1008 at 5. McLeskey concluded that ICI 182,780 was a "treatment failure." Ex. 1008 at 10. McLeskey disparaged the results of fulvestrant administration in Howell 1996 as showing "only about 30-40% of such patients have a positive response to subsequent [fulvestrant]." Ex. 1008 at 2 (emphasis added). Therefore, instead of antiestrogens like fulvestrant, McLeskey concluded that agents "directed

against the autocrine or paracrine effects of FGFs" should be tried. Ex. 1008 at 12-13.

201. McLeskey concluded that the hormone-independent pathways under investigation were important for tamoxifen resistance, and a promising avenue for future study: "these data provide evidence for a mechanism by which FGF-stimulated estrogen-independent growth bypasses the ER signal transduction pathway . . . . [O]ur studies implicate direct action by FGFs in the estrogen-independent growth produced by transfection of either FGF-4 or FGF-1 into MCF-7 cells . . . Thus, it is likely that FGF receptor-mediated signaling is operative in a significant proportion of ER-positive breast tumors. Therefore, the model described in this report might be pertinent to a number of clinical cases of tumor growth that is refractory to therapy with antiestrogens." Ex. 1008 at 12.

202. That fulvestrant blocked estrogen receptors in cell culture, does not change these conclusions. That says nothing about whether any McLeskey ***formulation*** could be used successfully to treat hormone dependent disease of the breast. In cell culture, the compound is simply added to the culture medium; a formulation is not necessary. "Following transfection, each well was washed twice with PBS and incubated for 48 h in medium containing vehicle (0.01% ethanol), 10^{-9} M estradiol, 10^{-7} M [fulvestrant], a combination of E_2 and [fulvestrant], 10 ng/ml FGF-1 plus 10 μg/ml heparin, or a combination of FGF, heparin, and

[fulvestrant]." Ex. 1008 (McLeskey) at 4; *see also* Ex. 1008 (McLeskey) at Fig. 4 ("Treatment concentrations were as follows: vehicle, 0.1% ethanol; [fulvestrant], 10^{-7} M; estradiol, 10^{-8} M.").

C) The Skilled Formulator Would Not View The Castor Oil-Based Formulation Of McLeskey As "Matching" Howell

203. Howell states that the formulation was administered as a "monthly i.m. injection (5 ml)" in human breast cancer patients that previously failed on tamoxifen, and endocrine treatment. Ex. 1007 (Howell 1996) at 2. McLeskey does not match this description. McLeskey studied a model of estrogen-independent growth, and not the claimed hormonal dependent benign and malignant diseases of the breast and reproductive tract. Ex. 1008 at 2 ("We therefore sought to determine the sensitivity of the estrogen-independent tumor growth of FGF-transfected MCF-7 cells to [fulvestrant]."). McLeskey administered the castor oil-based formulation to cell cultures and mice, not humans, as in Howell. Ex. 1008 at 2-3. McLeskey administered the formulation subcutaneously, not as Howell does by intramuscular injection. Ex. 1008 at 2 ("ICI 182,780 . . . was administered s.c."); Ex. 1007 (Howell 1996) at 1. McLeskey administered the formulation weekly, not monthly as in Howell. Ex. 1008 at 2 ("ICI, 182,780 . . . was administered . . . every week.").

204. As noted above, the skilled formulator would recognize that the fulvestrant formulation used in Howell 1996 was simply an experimental

formulation: "[t]he aims of the study reported here were to assess the long-term efficacy and toxicity of the specific anti-oestrogen ICI 182780" (Ex. 1007 at 1); "we have assessed the pharmacokinetics, pharmacological and anti-tumour effects of the specific steroidal anti-oestrogen ICI 182780" (Ex. 1007 at 1); "administration of ICI 182780 was associated with a lower than expected incidence of side effects" (Ex. 1007 at 1). Thus, there is no basis for Dr. Burgess' argument that, after reading Howell 1996, "the primary goal of the formulator would have been to develop a formulation that successfully solubilized fulvestrant in castor oil at 50 mg/ml." Ex. 1012 (Burgess Decl.) at ¶ 174. In any event, McLeskey does not give any information on the solubility of fulvestrant in the formulation nor does McLeskey match the intramuscular administration method or monthly duration of action of Howell 1996.

205. A skilled formulator would recognize that the formulations of the other drugs used in McLeskey were research formulations, not clinical formulations, and therefore would assume that the fulvestrant formulations, like those other formulations, were specifically designed for efficiency in research with small animals and were not suitable for human use. For instance, McLeskey used "tamoxifen pellets" for subcutaneous implantation purchased from Innovative Research of America, a company that specializes in only animal formulations. Ex. 2044 (Innovative Research) at 13 ("All products in this catalog are sold for

investigational use in laboratory animals only and are not intended for diagnostic or drug use."). But, tamoxifen for human use was marketed in oral tablet form. Ex. 2045 (PDR 1999 Nolvadex®) at 4. Similarly, letrozole used in McLeskey was administered in a liquid vehicle of 0.3% hydroxypropyl cellulose via gavage—letrozole marketed for humans was administered as oral tablets containing ferric oxide, microcrystalline cellulose, and magnesium stearate. Ex. 2046 (PDR 1999 Femara®) at 12. In McLeskey, the 4-OHA, also known as formestane, was also administered in an aqueous vehicle of 0.3% hydroxypropyl cellulose by subcutaneous injection once daily, six days a week—for humans, formestane was approved in Europe as an intramuscular injection administered every two weeks. Ex. 1054 (Santen) at 8.

206. Dr. Burgess argues that a "it is well known that depot injections are typically given subcutaneously in mice because mice lack large enough muscles for intramuscular injection." Ex. 1012 (Burgess Decl.) at ¶ 210. In fact, the skilled artisan would have known that mice can receive intramuscular injections. See e.g.: Ex. 2128 (Skougaard) at 2; Ex. 2129 (Eagle) at 1; Ex. 2130 (Levine) at 3; Ex. 2131 (Yarinsky) at 1. Regardless, this argument completely fails to support that the McLeskey formulation was in fact intended for humans, let alone for intramuscular use instead of subcutaneous. As the tamoxifen pellets demonstrate, preformulated

subcutaneous formulations specially made for animal research are often used for convenience.

207. Dr. Burgess ignores the critical differences between the administration method in Howell 1996 and in McLeskey, which would suggest to a skilled formulator that the references should not be combined. The chart below demonstrates these differences. For instance, the castor oil-based formulation used in McLeskey was administered weekly by subcutaneous injection, while the Howell formulation was administered monthly by intramuscular injection. The method of McLeskey would not be one suitable for humans—requiring large volumes to be administered by subcutaneous administration once a week and there would be no reason to expect it would work if administered to humans as in Howell 1996. In fact, a formulator would expect it would not work given the significant differences. *See infra* ¶¶ 213-242.

Parameter	**Howell (1996)**	**McLeskey (1998)**
Frequency	**Monthly**	**Weekly**
Injection	**Intramuscular**	**Subcutaneous**
Excipients	**Castor oil and ?**	**Ethanol, benzyl benzoate, benzyl alcohol,** castor oil

208. To reach the Howell formulation from the McLeskey disclosure, one would have to make the following changes: change the method from investigation

of hormonal-independent pathways to hormone-dependent breast cancer; change the method from administration to experimental research animals to humans; change the route of administration from subcutaneous to intramuscular; change the dosing regimen from weekly to monthly; and change the volume administered. Dr. Burgess provides no reason to expect that these changes would result in physiological effects that matched Howell's.

D) Other Prior Art Formulations Were Closer To Howell Than McLeskey

209. Even if the skilled formulator wanted to find a prior art formulation with an administration like that used in Howell, the formulator would have been more interested in Example 3 of Dukes 1989 than the castor oil-based formulation in McLeskey.

210. Dukes 1989 would have met every one of Dr. Burgess' and Dr. Elder's criteria. Dr. Burgess asserts that a skilled artisan "would have been motivated to develop a formulation that would solubilize fulvestrant at the same concentration as Howell, *i.e.*, 50 mg/ml." Ex. 1012 (Burgess Decl.) at ¶ 173; *see also* Petition at 45. Under Dr. Burgess' criteria of a "high concentration of solvents," she would assume that the Example 3 formulation in Dukes 1989 was a solution at 50 mg/ml. *See* Ex. 1012 (Burgess Decl.) at ¶ 200. Dr. Burgess speculates that "a person of skill in the art would have thought or at least would have had a reasonable expectation that the McLeskey castor oil-based formulation

was the same formulation used in the Howell 1996 study," because McLeskey identifies the castor oil formulation as supplied by Zeneca and at a 50 mg/ml concentration of fulvestrant. Ex. 1012 (Burgess Decl.) at ¶ 183. There is nothing in the literature to support this speculation. Example 3 of Dukes 1989 ***satisfies these criteria***. The formulation in Example 3 is castor oil based, uses a 50 mg/ml concentration of fulvestrant, Dukes was an employee of AstraZeneca and the patent is assigned to Zeneca, AstraZeneca's predecessor. Ex. 1047 (Dukes 1989) at 11:6-11. And, in fact, the art therefore demonstrates that there were multiple castor oil fulvestrant formulations being used at Zeneca/AstraZeneca.

211. But, Dukes would have been a better choice using Dr. Burgess' and Elder's reasoning, because, compared to McLeskey, Dukes 1989 was closer to Howell. For instance, InnoPharma explains that Dukes 1989 "described a formulation that taught the same concentration of fulvestrant (50 mg/ml) and many of the same excipients (castor oil, benzyl alcohol)." Petition at 13. Like Howell, Example 3 of Dukes 1989 used a castor oil-based solution formulation. Like Howell, the Dukes 1989 formulation was administered intramuscularly, whereas the McLeskey formulations were administered subcutaneously. Additionally, Example 3 of Dukes 1989 administered the formulation biweekly, which is closer to the monthly administration used in Howell. Importantly, Example 3 of Dukes 1989 found "that at all doses tested the compound selectively inhibits the action of

the animals' endogenous oestrogen." Ex. 1047 at 10:43-44. On the other hand, McLeskey called fulvestrant administration a "treatment failure." Ex. 1008 at 10.

212. Further, Example 3 of Dukes 1989 would have suggested that the ingredients in McLeskey would be unsuccessful if one were trying to match Howell. The Example 3 formulation of Dukes 1989 contained benzyl alcohol and castor oil and was administered every two weeks—which indicates that the formulation had twice the duration of McLeskey. Ex. 1047 at 11:11-13. However, in addition to benzyl alcohol, McLeskey contained ethanol and benzyl benzoate, but was administered more frequently, once per week. Ex. 1008 at 2. The comparison of Dukes 1989 to McLeskey would suggest that the addition of benzyl benzoate and/or ethanol apparently increases the rate of release of fulvestrant from the formulation. Accordingly, if the skilled formulator wanted to duplicate the administration method and results of Howell and obtain a longer duration of release of fulvestrant, benzyl benzoate and/or ethanol and formulations in the art that contained benzyl benzoate and/or a combination of two alcohols as cosolvents would be avoided.

213. Dr. Burgess argues that one of ordinary skill "would have rejected the Dukes '814 patent formulation because of the high amount of benzyl alcohol used," citing the Gellert Declaration. Ex. 1012 (Burgess Decl.) at ¶ 181. But, what Dr. Gellert actually explained was that "the skilled formulator would have been

concerned with using such a high alcohol content," and that would have similarly applied to the McLeskey formulation with 20% total alcohols. Ex. 1012 (Gellert Decl.) at ¶ 21.

E) The Combination Of Howell 1996 And McLeskey Could Not Have Been Expected To Result In The Claimed Inventions.

214. In my view, even if an ordinary formulator would have been motivated to combine McLeskey and Howell, which they would not have been, that ordinary formulator could not have reasonably expected the physiological results of the invention. Dr. Burgess does not provide scientific reasoning as to such a reasonable expectation.

215. As discussed above, Dr. Burgess proposes that the skilled artisan "would have thought or at least would have had a reasonable expectation that the McLeskey castor oil-based formulation was the same formulation used in the Howell 1996 study." Ex. 1012 (Burgess Decl.) ¶ 183. Dr. Burgess bases this unsupported speculation on AstraZeneca's alleged sponsorship of the Howell study and the statement in McLeskey attributing a castor oil-based formulation to B.M. Vose of Zeneca. Ex. 1012 (Burgess Decl.) at ¶ 183. Dr. Burgess also notes that "[b]oth the Howell and McLeskey formulations were castor oil-based solutions with identical fulvestrant concentrations." Ex. 1012 (Burgess Decl.) at ¶ 183. This speculation is not supported by anything in the prior art.

216. Further, what the references actually say is that there are several critical differences between the administration method in Howell 1996 and in McLeskey, which would have taught the skilled artisan that the formulations were likely to be different. For instance, the castor oil-based formulation used in McLeskey was administered weekly by subcutaneous injection, while the Howell 1996 formulation was administered monthly by intramuscular injection. The skilled formulator would not have been able to administer the McLeskey formulation in an entirely different way with a reasonable expectation of success.

1) McLeskey Used Experimental Animal Formulations That Would Not Be Viewed As Suitable For Human Use

217. McLeskey disclosed experimental formulations for use in animals—not clinical formulations for human use. *See supra* ¶¶ 55-57. Dr. Burgess admits that a formulation that "was designed for short-term animal testing" would not be considered for clinical use. Ex. 1012 (Burgess Decl.) at ¶ 206. The formulator would have viewed the McLeskey formulations as consistent with the knowledge that many early stage formulations are meant to be "exaggerated" dosage forms, containing high concentrations of drug in order to administer high doses of drug to the animal model, or are formulated for the needs of the animal research containing high content of excipients known to be toxic or irritating to humans. Ex. 2118 (Litchfield 1961) at 5. Ironically, InnoPharma's expert, Dr. Burgess accuses Dr.

Sawchuk and myself of "ignor[ing] . . . the differences between administering drugs to mice and humans." Ex. 1012 (Burgess Decl.) at ¶ 252.

2) No Approved Product Used The Same Combination Of Excipients As McLeskey

218. A formulator, with familiarity of the relevant scientific literature, commercial marketed formulations, and the solvents and excipients typically used, would not have expected the formulation of the claimed inventions—including the specific proportions of ethanol, benzyl alcohol, benzyl benzoate, and castor oil—to have succeeded.

219. Dr. Burgess has not cited any previously marketed product that contains the claimed combination of excipients, and I am not aware of any. In fact, Dr. Burgess has not even cited another marketed intramuscular injection that contains ethanol and benzyl alcohol as cosolvents. Regarding benzyl alcohol, existing injection formulations used much lower concentrations than the formulation of the claimed inventions. The prior art taught the use of benzyl alcohol as a preservative at a low concentration of up to 5%, or, rarely, as high as 10% of total volume. *See, e.g.*, Ex. 1105 (Powell) at 7-9; Ex. 1102 (Nema) at 3; Ex. 1018 (Avis Ch. 5) at 29.

220. Dr. Burgess provides no reason to expect the McLeskey formulation to work other than that McLeskey used it. But, McLeskey says that fulvestrant was a "treatment failure." Ex. 1008 at 10.

3) Making The McLeskey Formulation Would Introduce Additional Unpredictability

221. The McLeskey reference does not explain how to combine the ingredients to create the formulation, much less provide the order in which they must be added. In contrast, the specification of the '122 Patent provides the following instructions for the order of mixing: the fulvestrant is mixed with alcohol and benzyl alcohol; benzyl benzoate is added; the remaining amount is added as castor oil. Ex. 1001 at 11:55-59. But a skilled formulator at the time of the claimed inventions would not have had access to this information in the specification. Order of mixing is important; without instructions on how to mix the different components, the components would not necessarily be miscible and the active ingredient would not necessarily dissolve.

222. The castor oil formulation in McLeskey was described as "50 mg/ml preformulated drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil." Ex. 1008 at 2. Hence, McLeskey does not indicate whether the components are in percent weight per volume (% w/v) or percent volume per volume (% v/v). However, a person of ordinary skill in the art could assume that the units were % v/v, because the formulation was a liquid and it was common practice to express concentrations in a liquid composition as volume percentages. A skilled formulator would be familiar with compositions described in % v/v. *See supra* at ¶¶ 63-64.

4) The McLeskey Formulation Would Not Be Expected To Work When Administered Monthly Instead Of Weekly

223. McLeskey administered a castor-oil based fulvestrant formulation weekly, while Howell administered a fulvestrant formulation monthly. The skilled artisan would not believe that a formulation, like that in McLeskey, that is intended for weekly administration, would sustain the intended fulvestrant plasma levels for four times as long.

224. Example 3 of Dukes 1989 does not contain benzyl benzoate and is administered biweekly, whereas the castor oil-based formulation in McLeskey contains benzyl benzoate but is administered weekly. Similarly, the Parczyk formulation cited by Dr. Burgess contain benzyl benzoate and was administered 6 days per week. Ex. 1048 (Parczyk) at 1. Comparisons of these formulations to Dukes 1989 would suggest that the addition of benzyl benzoate and/or ethanol apparently increases the rate of release of fulvestrant from the formulation. Accordingly, if the skilled formulator wanted to duplicate the administration method and results of Howell and obtain a longer duration of release of fulvestrant, benzyl benzoate and formulations in the art that contained benzyl benzoate and/or a combination of two alcohols as cosolvents would be avoided.

225. On the other hand, certain types of excipients and dosage forms had been used for extended-release formulations. A formulator interested in developing an extended-release formulation would first pursue the known

techniques available in the literature, and would not expect a formulation administered weekly to be appropriate for long-term, monthly use.

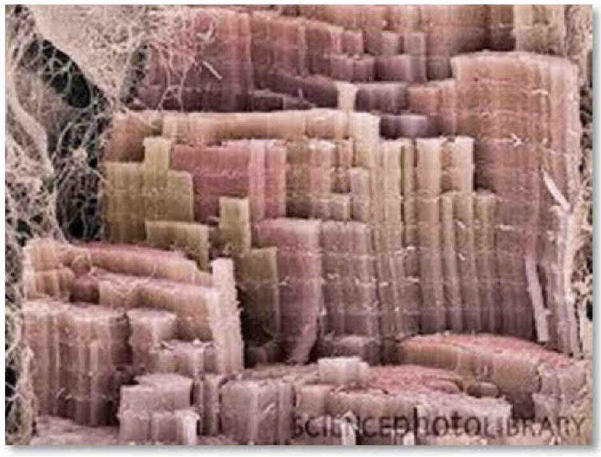
5) The McLeskey Formulation Would Not Be Expected To Work When Administered Intramuscularly Instead Of Subcutaneously

226. InnoPharma argues that "the far more reasonable expectation of success was with the previously successful IM route," based on Howell using "that ***exact*** route of administration." Petition at 32-33 (emphasis in original). But, McLeskey administered both fulvestrant formulations subcutaneously, not intramuscularly.

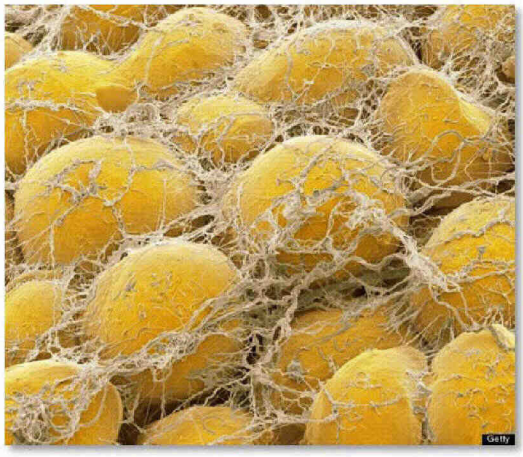
227. In fact, the skilled formulator would not expect a formulation administered subcutaneously to work as intended when administered intramuscularly. Specifically, the local environment a drug would encounter following an *intramuscular* injection is very different from the environment the same drug would encounter, following a *subcutaneous* injection. Intramuscular injections are directed into the layer of striated muscle fibers situated under the subcutaneous layer. The intramuscular environment comprises mostly muscle fibers (85%) and connective tissue (15%). The muscles are organized and largely shaped by the connective tissue, composed of collagen, reticular, and elastin fibers of varying proportions. The muscles are interspersed with blood capillaries. Ex. 1094 (Tse I) at 8 ("Intramuscular injections are made deep into the skeletal muscles, preferably far away from major nerves and blood vessels."); Ex. 2106

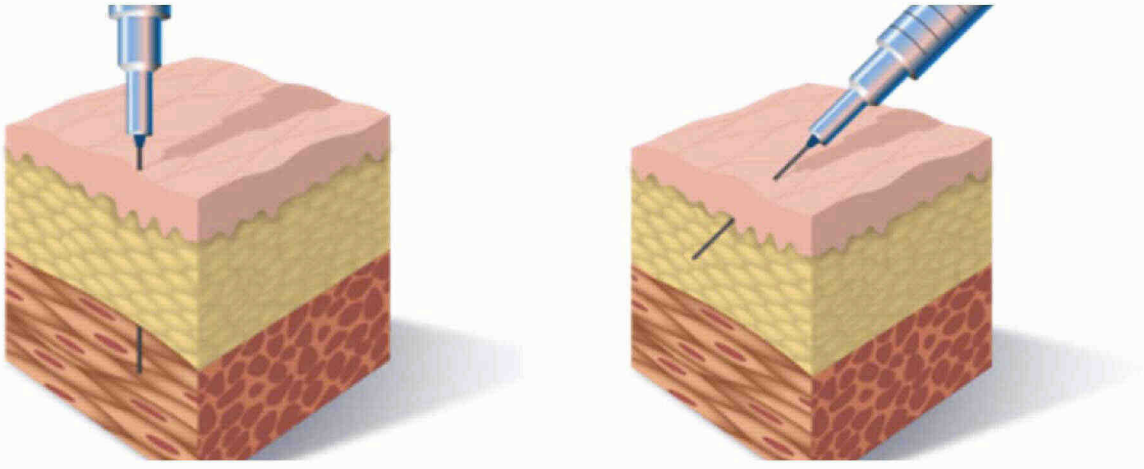
(Ansel Ch. 14) at 9 ("[Subcutaneous] injection of a drug beneath the surface of the skin is usually made in the loose interstitial tissues of the outer surface of the upper arm, the anterior surface of the thigh, and the lower portion of the abdomen."); *see also* Ex. 1091 (Ansel Ch. 4) at 30 ("The subcutaneous (hypodermic) administration of drugs involves their injection through the layers of skin into the loose subcutaneous tissue"). Furthermore, the subcutaneous tissue contains adipose tissue (fat cells), blood capillaries and lymph vessels. The pictures below show the differences between the subcutaneous and intramuscular environments.

Intramuscular



Subcutaneous





228. "The blood supply to the site of injection is an important factor in considering the rate of drug absorption, consequently the more proximal capillaries are to the site of injection, the more prompt will be the drug's entrance into circulation. Also, the more capillaries, the more surface area for absorption, and the faster the rate of absorption" Ex. 1091 (Ansel Ch. 4) at 30. In general, the concentration of blood capillaries is higher in the muscle tissue than in the subcutaneous tissue. Lymphatic circulation is more important for absorption in the subcutaneous space. Hence, the rate of absorption would be expected to be different between the two injection sites. Ex. 1111 (Tse II) at 1-5.

229. On one hand, many references taught that substances administered by *subcutaneous* injection were more quickly absorbed, and quicker to act, with a shorter T_{max} as compared to administration by intramuscular injection. *See, e.g.,* Ex. 2086 (Groves Ch. 2) at Figure 4 (showing that subcutaneous injection gives a higher rate of absorption and a shorter T_{max} compared to intramuscular injection);

Ex. 2120 (Lifschitz 1999) at 6 (disclosing total plasma concentration to T_{max} as higher for subcutaneous administration); Ex. 2121 (Lavy 1999) at 1 ("The s.c. route appears to be superior to the i.m. route in terms of local tolerance and serum drug level[.]").

230. In contrast, many other references taught that substances administered by *intramuscular* injection were more quickly absorbed, and quicker to act, with a shorter T_{max} as compared to a subcutaneous injection. *See, e.g.,* Ex. 2107 (Avis Ch. 2) at 12, 17 ("The intramuscular route is preferred over the subcutaneous route when a rapid route of absorption is desired."); Ex. 1111 (Tse II) at 2 ("Absorption of drugs which are given subcutaneously is generally slower than after intramuscular administration because of less efficient regional circulation."); Ex. 2113 (Avis Ch. 3) at 50-51 ("These results suggested that accidental i.m. injection in the thigh will considerably increase the variability of insulin absorption and may thus impair glycemic control"); Thus, the skilled formulator would believe that changing from subcutaneous to intramuscular injections would have an effect on the release profile and resulting pharmacokinetics.

231. In addition to the differences between the subcutaneous and intramuscular environments within the same species, there were also significant differences in the subcutaneous and intramuscular local environments in humans and rodents. *See, e.g.,* Ex. 2122 (Chu 1960) at 8, 10; Ex. 1091 (Ansel Ch. 4) at 30.

232. As discussed above, the biological activity of a drug depends on many factors, including absorption, distribution, metabolism, and excretion, all of which affect the changing environment of the active ingredient. *See supra* ¶¶ 176-185. For instance, precipitation of the active ingredient in the tissue could cause pain and tissue damage and also lead to the accumulation of active ingredient at the injection site, and a poor release profile. Ex. 2117 (Greenblatt 1978) at 6-7. How the McLeskey formulation would behave after injection in the muscle could not be predicted, and McLeskey, which administers the formulation subcutaneously, gives no information on behavior in the muscle or blood plasma fulvestrant concentrations.

233. Dr. Burgess characterizes the intramuscular and subcutaneous routes as "similar," because the "same factors affecting intramuscular drug absorption also govern drug bioavailability following subcutaneous doses." Ex. 1012 (Burgess Decl.) at ¶ 253. But, in the very next sentence Dr. Burgess acknowledges that "subcutaneous administration generally provides a slower release profile." Ex. 1012 at ¶ 253; *see also* Ex. 1012 at ¶ 68 ("The body absorbs intramuscular injections more rapidity as muscle tissue has a greater blood supply.").

6) The Concentration/Castor Oil Theory Of Dr. Burgess Is Contradicted By The Literature

234. It is well established that guesses as to in vivo bioavailability are not accurate, even when based on dissolution data: "[i]n the absence of in vivo data, it

is generally impossible to make valid conclusions about bioavailability." Ex. 2162 (Applied Biopharmaceutics) at 28. *See also* Ex. 1091 (Ansel Ch. 4) at 21 ("[T]wo seemingly 'identical' or 'equivalent' products, of the same drug, in the same dosage strength and in the same dosage form type, but differing in formulative materials or method of manufacture, may vary widely in bioavailability and thus in clinical effectiveness."); Ex. 2081 (Remington's Ch. 75) at 5 ("In some instances, the bioavailability of a drug formulation represents a quality parameter of enormous proportion. It is a matter of record that with certain drugs, depending on the formulation, the rate at which the drug substance becomes available can vary significantly from very high to none at all.").

235. Despite the well-known unpredictability of *in vivo* release rates, particularly from intramuscular formulations, Dr. Burgess argues that "the person skilled in the art would appreciate that because both the Howell 1996 formulation and the McLeskey 1998 formulation comprise a solution of fulvestrant at the same concentration (50 mg/ml), both using castor oil as the base of the vehicle, the McLeskey 1998 castor oil-based formulation would be expected to achieve the same day-28 results as reported in Howell 1996." Ex. 1012 (Burgess Decl.) at ¶ 187.

236. Dr. Burgess argues that "one skilled in the art would expect the other cosolvents to quickly dissipate from the injection site, leaving a fulvestrant/castor

oil depot, resulting in the same day-28 minimum serum concentrations that were shown in Howell 1996." Ex. 1012 (Burgess Decl.) at ¶ 194.

237. As a basic assumption, Dr. Burgess argues that the skilled artisan would believe that all castor oil-based formulations administered by intramuscular injection would achieve the same plasma levels. This is not true under general pharmacokinetics principles. Ex. 2114 (Zuidema 1994) at 14 ("Many factors may affect the release from an intramuscular or subcutaneous injection site."); Ex. 2114 (Zuidema 1994) at 1 ("Many variables are known to affect drug release after intramuscular or subcutaneous injection."). Such factors include "**properties of the vehicle in which the drug is formulated**." Ex. 2114 (Zuidema 1994) at 1-2 (emphasis added). For example, "cosolvents such as propylene glycol, glycerol and polyetheylene glycol 400 have been reported contradictorily to diminish and to enhance absorption rate of model compounds." Ex. 2114 (Zuidima 1994), at 7; *see also* Ex. 1099 (Aulton Ch. 21) at 7 ("However, formulation, coupled with variation in the site of administration may affect markedly the biopharmacy of drugs."); Ex. 2107 (Avis Ch. 2) at 21 ("Many factors affect the rate of drug absorption from an intramuscular injection."); Ex. 2107 (Avis Ch. 2) at 31-32 (listing factors that affect absorption, including solubility of the drug, partition coefficient of the drug, rate of blood flow at the injection site, degradation of the drug at the injection site, particle size of the drug, and formulation ingredients); Ex. 2107 (Avis Ch. 2) at 32

("Such effects may be manifested in diverse ways, such as complexation, which reduces the rate of drug dissolution, and as increased viscosity, which retards the transport of the drug from injection site to the systematic circulation."). In fact, Dr. Burgess admits as much, saying that "[e]xcipients can . . . . affect[] the release rate of the active ingredient." Ex. 1012 (Burgess Decl.) at ¶ 61.

238. Dr. Burgess argues that "castor oil is the rate limiting factor in the McLeskey castor oil-based formulation." Ex. 1012 (Burgess Decl.) at ¶ 187. Dr. Burgess cites to no McLeskey-specific information for this but bases this assertion on a supposed general proposition that "[i]t was known that the rate-liming step for the pharmacokinetics of an oily depot injection is the release of the active drug from the oil." Ex. 1012 (Burgess Decl.) at ¶ 188. The references that Dr. Burgess cites do not support this broad argument. For instance, Dr. Burgess quotes a reference on antipsychotics that "[o]nce the drug (administered as an ester dissolved in oil) is injected into the muscle, it is slowly released from the depot site." Ex. 1012 (Burgess Decl.) at ¶ 188. But, this reference explains that, "[t]he time to reach peak plasma concentrations is very different from one preparation to another," and that "it is however, difficult to understand which are the main factors governing the pharmacokinetics of these depot preparations." Ex. 1097 (Balant-Gorgia) at 7. Dr. Burgess quotes a reference as stating that the "rate-limiting step is the liberation of drug from the oil depot." Ex. 1012 at (Burgess Decl.) ¶ 188.

However, the formulation in this abstract has no other excipients ("etofenamate dissolved in oil"), and the rest of the abstract cited by Dr. Burgess notes that zero order kinetics "is directly related to the liberation of drug from the galenical ***formulation***." Ex. 1076 (Kohler) at 1 (emphasis added). As another example, the Jorgensen reference cited by Dr. Burgess refers to the "oil depot," not just the oil, and, moreover, relates to sesame seed oil and not castor oil. Ex. 1077 (Jorgensen) at 5.

239. Dr. Burgess cites nothing to suggest that the release of an active ingredient from a formulation with several excipients, like McLeskey, would depend entirely on only one of those excipients. To the contrary, the Tse I reference notes that "[t]he absorption rates vary widely depending on the type of ***preparation*** used, as well as on other biopharmaceutical factors." Ex. 1094 (Tse I) at 10 (emphasis added). The skilled formulator could not have foreseen the effect of particular excipients on the release rate without in vivo data on the specific formulation. References note that "[v]alidation of sustained release product designs can be achieved only by in vivo testing." Ex. 2134 (Lachman's) at 23.

240. Dr. Burgess argues that "the cosolvents would be expected to quickly dissipate from the injection site," and that this means that all castor-oil based formulations would produce the same release rate. Ex. 1012 (Burgess Decl.) ¶ 189. However, Dr. Burgess also argues that the cosolvents were needed to keep

the fulvestrant in solution in the castor oil, meaning that that after the other excipients "quickly dissipated" (according to Dr. Burgess), one would expect the fulvestrant to precipitate into muscle, potentially adversely affecting the rate by leading to poor or erratic release. In fact, the patent specification describes this issue of "dissipation of the cosolvents" and explains that the release rates of the invention are therefore surprising. After experimentation, the inventors found that benzyl alcohol "dissipates rapidly from the injection site and is removed from the body within 24 hours of administration," and, consequently, they hypothesized "that ethanol w[ould] dissipate at least as quickly, if not more rapidly, from the injection site." Ex. 1001 at 8:47-53. Based on the metabolism of benzyl benzoate, the inventors further hypothesized that "it is unlikely that benzyl benzoate, when used, is present at the injection site during the whole of the extended release period." Ex. 1001 at 8:57-60. The inventors noted that surprisingly, "despite the rapid elimination of the additional solubilizing excipients, i.e. the alcohol and pharmaceutically-acceptable non-aqueous ester solvent, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period can still [be] achieved by the formulation of the invention." Ex. 1001 at 8:61-67. In contrast, the inventors explained that aqueous suspensions caused "extensive local tissue irritation at the injection site as well as a poor release profile" due to "the

presence of fulvestrant in the form of solid particles," i.e., precipitation. Ex. 1001 at 8:38-42.

241. In fact, contrary to Dr. Burgess' suggestion, and as described in more detail above, release and absorption from an intramuscular injection depend on many factors that in turn depend on the formulation and change in the formulation composition over time. Physical properties such as the shape and the area of deposition and the distribution of the injection in the area of deposition influence the release and absorption of the drug, as do chemical factors such as solubility in the formulation, solubility in the intercellular environment and permeability of biological membranes. Ex. 2115 (Ballard 1968) at 1-2 ("The local distribution of solutions injected subcutaneously or intramuscularly is of interest, because the penetration rate of the drug depends in part upon the geometry and the resulting area of the depot exposed to the tissue."); Ex. 2116 (Hirano 1981) at 12-13 ("However, if the drug can hardly be released from the oil vehicle or if the vehicle exerts some local effect, additional factors such as absorption or metabolism of the vehicle itself and physiological changes at the injection site should be taken into consideration in attempting to understand the drug absorption phenomena.") Ex. 1099 (Aulton Ch. 21) at 11 ("The maximum prolongation effect is obtained from the depot if it is spherical and, therefore, absorption is probably more rapid from the less viscous ester preparations because of their greater tendency to spread and

offer a larger surface to the tissue fluid."); Ex. 2082 (Aulton Ch. 1) at 11 ("Solubility can also be important in the absorption of drugs already in solution in liquid dosage forms since precipitation . . . can occur and bioavailability [be] modified."); Ex. 2113 (Avis Ch. 3) at 10 ("The rate of passage of a drug through a biological membrane by passive diffusion is affected by several physicochemical factors, such as concentration gradient, partition coefficient, ionization, macromolecular binding, and osmolality, in addition to differences in physical form of the medication.").

242. There was no information on any of these factors for the castor oil formulation of the invention in the prior art cited by Dr. Burgess. And, McLeskey states nothing to predict what would be the resulting pharmacokinetics of the once weekly subcutaneous formulation for mice that it described. McLeskey does not provide any fulvestrant plasma concentrations or profiles. Moreover, McLeskey does not show antiestrogen activity of any formulation of fulvestrant. McLeskey does not teach any information about the fulvestrant release profile, dose-response, or the toxicity and acceptability of any formulation. Without this information, even a formulation that showed antiestrogen activity (which the formulation in McLeskey did not) would be of little help to the skilled formulator in developing a formulation of fulvestrant for administration to humans via a different route

(intramuscular v. subcutaneous), different duration (administration once a month v. once a week) in a different amount. Ex. 1008 (McLeskey) at 5.

243. A skilled formulator could not predict *in vivo* performance, i.e., the fulvestrant plasma levels and the fulvestrant release profile of a particular formulation, without experimentation. When plasma levels are not provided for a specific formulation, the skilled formulator could not predict whether the fulvestrant would be released immediately in a burst, precipitate out in the muscle, show no release at all, be released erratically, most of the dose be released in the first few days and little thereafter, or be released extremely slowly. The claims require "satisfactory release of fulvestrant over an extended period of time" which is specifically delineated in blood plasma levels over time. In sum, for all of the reasons discussed above, I disagree with Dr. Burgess' argument that a skilled formulator would expect that the castor oil formulation used in McLeskey could be used with a reasonable expectation of success as an intramuscular injection for administration to humans to achieve the desired extended plasma profile.

F) The Gellert Declaration And The Sawchuk Declaration Are Consistent And Both Support The Patentability Of The Challenged Claims

244. The Gellert and Sawchuk declarations are written from different perspectives. Dr. Gellert is explaining that even with the inventors' invention research, the invention was surprising. Dr. Sawchuk is reviewing the art from the perspective of one of ordinary skill, without the benefit of the invention research.

245. Dr. Burgess argues that Dr. Gellert "specifically opined that suspensions such as those disclosed in Wakeling were inferior and not useable." Ex. 1012 (Burgess Decl.) at ¶¶ 38, 204. But, Dr. Gellert actually said that "a reasonable ***starting point*** would have been to investigate intramuscular injection of an aqueous or oil suspension of fulvestrant." Ex. 1020 (Gellert Decl.) at 13 (emphasis added). Dr. Sawchuk's declaration from the perspective of the skilled artisan without this information states that the Wakeling suspension would have been "among the most favored formulations to select for further development." *See* Petition at 16; Ex. 1019 (Sawchuk Decl.) at ¶ 41. It was only after the inventors' extensive work (not publicly known) that Dr. Gellert could report on the failures of suspensions. Ex. 1020 (Gellert Decl.) at ¶ 13.

246. Dr. Burgess misleadingly states that Dr. Gellert and Dr. Sawchuk have contradictory positions on whether the skilled artisan would consider castor oil formulations. Ex. 1012 at ¶¶ 37, 204; *see also* Petition at 16. Dr. Sawchuk correctly states that the McLeskey reference does not indicate a preference for either the peanut oil or the castor oil fulvestrant formulation over the other one. Ex. 1019 (Sawchuk Decl.) at ¶¶ 31-36. Dr. Sawchuk also says, noting McLeskey was a "treatment failure" that "judging solely on the basis of efficacy, the *McLeskey* castor oil composition would have been among the least favored compositions to select for further development." Ex. 1019 (Sawchuk Decl.) at ¶41.

On the other hand, Dr. Gellert explains that the inventors chose castor oil to pursue further based on "the fulvestrant solubility date from the preformulation screen (such as reported in Table 2 of the Evans Application)," in other words, the invention research. Ex. 1020 (Gellert Decl.) at ¶ 17. Dr. Gellert never addresses McLeskey. Thus, Dr. Gellert and Dr. Sawchuk are addressing entirely different questions.

247. Dr. Burgess quotes Dr. Sawchuk's statement that "McLeskey provides no information that would have led one of ordinary skill in the art to have a preference for either the peanut oil or the castor oil fulvestrant composition over the other one." Ex. 1012 (Burgess Decl.) at ¶ 204. Dr. Burgess misleadingly asserts that Dr. Gellert contradicted this by noting the "higher solubility of fulvestrant in castor oil relative to the other oils tested." Ex. 1012 (Burgess Decl.) at ¶ 204. However, on its face, Dr. Sawchuk's quote is limited to information ***in McLeskey***, and McLeskey contains ***no solubility information*** for castor oil, arachis oil, or any other oil or formulation. McLeskey never mentions the word "soluble." Additionally, Dr. Sawchuk's statement is consistent with O'Regan which uses the peanut oil formulation despite citing Howell and its castor oil formulation.

248. Dr. Burgess disputes Dr. Sawchuk's statement that "one of ordinary skill in the art had other choices besides the *McLeskey* castor oil composition with respect to potential fulvestrant formulations." Ex. 1019 at ¶ 40. In particular, Dr.

Burgess disputes that the Dukes formulation was an option. She states that "the propylene glycol formulation described in the Dukes '814 patent was not designed for clinical use" but for "short-term animal testing." Ex. 1012 (Burgess Decl.) at ¶ 206. This argument by Dr. Burgess applies equally to the McLeskey formulation (administered to mice on a weekly basis).

249. Dr. Burgess also argues that "the solution comprising 40% benzyl alcohol and castor oil [from Example 3 of Dukes 1989], was specifically considered by Dr. Gellert and rejected," based on "the very high amount of alcohol used." Ex. 1012 (Burgess Decl.) at ¶ 208, 38; *see also* Petition at 46. Dr. Gellert actually only says that "the skilled formulator would have been concerned with using such high a alcohol content"—for administration "to a human." Ex. 1020 (Gellert Decl.) at ¶ 21. But, Dr. Gellert's declaration explained that benzyl benzoate would not have been expected to help reduce alcohol content from the Dukes formulation. Dr. Sawchuk's Declaration simply lists castor oil-based formulation from Dukes 1989 as an alternative option—particularly given that the Dukes formulation included data demonstrating in vivo effect of the formulation on intramuscular injection while the McLeskey article indicated only a "treatment failure" on subcutaneous injection.

250. Dr. Burgess admits that McLeskey does not "contain clinical data," but considers this "irrelevant," because "[t]he skilled formulator would recognize

that the castor oil-based formulation disclosed in McLeskey 1998 would produce the same results as Howell 1996 if 5 ml of the formulation was administered intramuscularly to a patient." Ex. 1012 (Burgess Decl.) at ¶ 209. For all the reasons stated above, the skilled formulator would not make this assumption.

XV) NON-OBVIOUSNESS OVER HOWELL COMBINED WITH MCLESKEY AND O'REGAN (GROUND THREE)

251. InnoPharma's third ground attempts to combine Howell and McLeskey with O'Regan. Petition at 58.

A) O'Regan Does Not Fill the Fatal Gaps In InnoPharma's Combination Of Howell And McLeskey

252. Dr. Burgess argues that "[o]ne skilled in the art following the teachings of O'Regan would understand that the castor oil-based formulation disclosed in McLeskey 1998 would be administered intramuscularly to humans," and so "the person of skill in the art would have had a reasonable expectation of success in administering the castor oil-based formulation disclosed in McLeskey 1998 to human patients by intramuscular injection to achieve the results disclosed in Howell." Ex. 1012 (Burgess Decl.) at ¶ 256.

253. In particular, Dr. Burgess quotes O'Regan that "[c]linically, [fulvestrant] must be given by depot intramuscular injection because of low oral potency." Ex. 1012 (Burgess Decl.) at ¶ 255. But, O'Regan provides no citation for this statement. After this statement, O'Regan goes on to describe the research

from Howell 1996. O'Regan does not comparatively evaluate formulations of fulvestrant, nor include any data on oral bioavailability of fulvestrant. O'Regan does not identify a fulvestrant formulation to be administered intramuscularly, nor does it suggest that any particular formulation would successfully deliver fulvestrant intramuscularly. Certainly, having not cited McLeskey at all, or any pharmacokinetic results relating to intramuscular injection, O'Regan does not suggest that the McLeskey formulation administered intramuscularly would produce the results in Howell.

254. Dr. Burgess admits that the research in O'Regan "was conducted using subcutaneous injections of fulvestrant into mice." Ex. 1012 (Burgess Decl.) at ¶¶ 96, 265. In fact, O'Regan used a peanut oil formulation for subcutaneous administration like McLeskey, another example of a special animal research formulation. Additionally, I note that O'Regan uses a special animal formulation to administer tamoxifen and toremifene orally to her mouse model: "[t]amoxifen and toremifene were each suspended in a solution of 90% CMC (1% carboxymethylcellulose in double-distilled water) and 10% PEG 400/Tween 80 (99.5% polyethylenegly[c]ol 400 and 0.5% Tween 80)." Ex. 1009 (O'Regan) at 2.

XVI) UNEXPECTED RESULTS

A) The Unexpected Results Of The Claimed Inventions

255. The unexpected results of the claimed method of treatment, including the formulation of the inventions, are described in the specification. "Fulvestrant shows, along with other steroidal based compounds, certain physicochemical properties which make formulation of these compounds difficult." Ex. 1001 at 2:46-48. In particular, "[f]ulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$." Ex. 1001 at 2:48-51. In fact, the inventors found that it was "not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate." Ex. 1001 at 5:25-30. However, the inventors "surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 $mgml^{-1}$." Ex. 1001 at 5:48-51. This was surprising because "the solubility of fulvestrant in non-aqueous ester solvents . . . is significantly lower than the solubility of fulvestrant," in both the alcohol and the castor oil. Ex. 1001 at 5:52-57. The inventors included a table that shows the lower solubility of fulvestrant in benzyl

benzoate (6.15 $mgml^{-1}$) than in ethanol (> 200 $mgml^{-1}$), benzyl alcohol (>200 $mgml^{-1}$), and castor oil (20 $mgml^{-1}$). Ex. 1001 at Table 2.

256. Thus, "[t]he invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing [fulvestrant]." Ex. 1001 at Abstract; Ex. 1001 at 1:1-9. One advantage of the claimed inventions is that the inventors "surprisingly found . . . after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time." Ex. 1001 at 8:29-32. This was surprising because aqueous suspension formulations caused "extensive local tissue irritation" as well as "a poor release profile." Ex. 1001 at 8:36-40. Moreover, the inventors reported that benzyl alcohol "dissipates rapidly from the injection site" and "is removed from the body within 24 hours of administration." Ex. 1001 at 8:47-50. Similarly, the inventors considered it "unlikely that benzyl benzoate, when used, is present at the injection site during the whole of the extended release period." Ex. 1001 at 8:57-60. Nevertheless, the inventors found that "despite the rapid elimination of the additional solubilizing excipients, i.e. the alcohol and pharmaceutically-acceptable non-aqueous ester solvent, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period can still [be] achieved by the formulation of the invention." Ex. 1001 at 8:61-67.

257. Importantly, the inventors explained that "[s]imply solubilising fulvestrant in an oil based liquid formulation **is not predictive** of a good release profile or lack of precipitation of drug after injection at the injection site." Ex. 1001 at 9:20-22 (emphasis added). Indeed, Table 4 of the specification shows the "[e]ffect of formulation on precipitation of fulvestrant at the injection site," and Figure 1 shows differences in release profiles. Ex. 1001, Table 4; Figure 1. The inventors found that "the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site." Ex. 1001 at 10:52-55. This castor oil formulation comprised "fulvestrant (5%), ethanol [96%](10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil." Ex. 1001 at 10:15-21.

258. To dispute unexpected results, Innopharma argues that "[a]queous suspensions, however, are not an appropriate comparison because 'suspensions . . . were ***not*** an acceptable option for fulvestrant.'" Petition at 66. No prior art suggests that. Indeed, Dr. Gellert suggested that a skilled person would start with aqueous and/or oil suspensions and not castor oil-based solutions: "[b]ecause of the extremely low solubility of fulvestrant in water, a reasonable starting point would have been to investigate intramuscular injection of an aqueous or oil ***suspension*** of fulvestrant." Ex. 1020 (Gellert Decl.) at ¶ 13. In any case, Dr. Burgess argues

inconsistently that "none of the challenged claims requires a solution." Ex. 1012 (Burgess Decl.) at ¶ 196.

259. Dr. Burgess argues that unexpected results requires comparing the invention to the "closest prior art, the castor oil-based formulation disclosed in McLeskey 1998." Ex. 1012 (Burgess Decl.) at ¶ 284. For all the reasons explained above, McLeskey is not close prior art to the claimed invention. *Supra* ¶¶ 51-72.

260. I address Dr. Burgess' unsupported arguments related to solubility above. *Supra* ¶¶ 169-172.

261. I also address Dr. Burgess' argument that "castor oil is the key component determining the long-term release profile and ultimate pharmacokinetics of the formulation" above. *Supra* ¶¶ 233-242.

B) The Superior Solubility Of Fulvestrant In The Claimed Formulation Was Unexpected And Not Suggested By The Prior Art

262. As described above, the formulation of the claimed method achieves an unexpectedly superior solubility because the addition of benzyl benzoate to the claimed formulation *increases* the solubility of fulvestrant, despite the poor solubility of fulvestrant in benzyl benzoate alone. This poor solubility would have taught a skilled formulator at the time of invention that the addition of benzyl benzoate would lead to an undesirable reduction of overall solubility.

263. Attempting to diminish the unexpected increase of fulvestrant solubility from benzyl benzoate, Dr. Burgess argues that "[i]t is well known that combining multiple co-solvents can have a ***synergistic*** effect, *i.e.*, a mixture of solvents can have a greater solubilizing power than the sum of its parts," citing to Chien. Ex. 1012 (Burgess Decl.) at ¶ 116 (emphasis in original). I address these positions above. But, I note here that Dr. Burgess cites no reference that suggests that the increase in solubility with benzyl benzoate would be expected.

264. Dr. Burgess' assertions regarding the ability of a formulator to predict an increase in solubility based on the molecular character of the solvents and active ingredient contradict typical formulation practice and completely ignore the necessary step of a *pre-formulation screen*. *See* Ex. 1012 (Burgess Decl.) at 117-120. The solubility and other characteristics of an active ingredient would have to be explored individually for each proposed excipient. An experienced formulator would conduct a pre-formulation screen of each proposed excipient, separately measuring the solubility of fulvestrant in a range of pure solvents, including the proposed solvents and any co-solvent candidates:

> The activities necessary to develop a parenteral product can be placed into the following three broad areas: pre-formulation, formulation, and scale-up. While there are alternative development perspectives, all development ultimately needs to accomplish the same activities. ***Preformulation includes the***

characterization of the bulk drug plus initial screening for excipient compatibility with the drug.

Ex. 2123 (Gupta Ch. 17) at 14 (emphasis added).

265. "Preformulation studies" were said to "provide fundamental data and the experience necessary to develop formulations for a specific compound," including a determination of "[s]olubility" in "[s]elected solvents." Ex. 2123 (Gupta Ch. 17) at 14-15. "Significant formulation activities begin with initial pre-formulation data and knowledge of the specific route of administration," and "include the identification and selection of a suitable vehicle (aqueous, nonaqueous, or cosolvent system)." Ex. 2123 (Gupta Ch. 17) at 17, 14. In other words, a pre-formulation screen to assess solubility of the active ingredient in each component is a "fundamental" first step in pharmaceutical product development.

266. Pre-formulation work would have revealed that fulvestrant has a much lower solubility in benzyl benzoate than other steroids, for example. Where other, typical steroids have solubilities of about 200-400 mg/mL in benzyl benzoate, fulvestrant is about 50-100 times *less* soluble in benzyl benzoate than those typical steroids. Ex. 2124 (Huber) at 2:49-3:50 (dissolving typical steroids in benzyl benzoate at 200-400 mg/ml). Thus, this pre-formulation work would lead a skilled formulator to *discard* formulations with benzyl benzoate, and instead try formulations with *other* excipients.

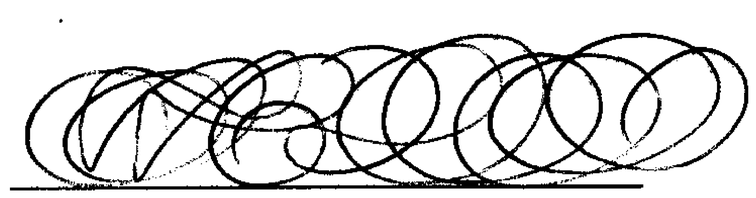
XVII)CONCLUSION

267. For the foregoing reasons, it is my opinion that InnoPharma has not shown a reasonable likelihood that claims 1, 2, 5, and 9 of the '122 Patent are unpatentable.

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

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

Dated: May 16, 2016



Lisbeth Illum, Ph.D.

EXHIBIT A

CURRICULUM VITAE

L ILLUM MPharm, PhD, DSc

Date of Birth: 30 March 1947

EDUCATION AND EDUCATIONAL QUALIFICATIONS

1966	General Certificate from Horsens Statsskole, Horsens.
1972	MPharm, First Class Honours Degree, Royal Danish School of Pharmacy.
1978	PhD, Department of Pharmaceutics, Royal Danish School of Pharmacy.
1987	DSc, Department of Pharmaceutics, Royal Danish School of Pharmacy.
1989	Docent, Department of Pharmaceutics, Royal Danish School of Pharmacy.
1990	Special Professor, Department of Pharmaceutical Sciences, University of Nottingham.

POSITIONS HELD

1972-1975	Lecturer, Department of Pharmaceutics, Royal Danish School of Pharmacy.
1975-1978	Postgraduate Scholarship, Department of Pharmaceutics, Royal Danish School of Pharmacy.
1978 - 1990	Senior Lecturer in Pharmaceutics, Department of Pharmaceutics, Royal Danish School of Pharmacy.
July 1981	Visiting Research Fellow, Pharmacy Department, University of Nottingham (NATO Science Fellowship).
Nov-Dec 1981	Visiting Research Fellow, Pharmacy Department, University of Nottingham.

Nov 1982 - Oct 1985	Senior Research Fellowship, Department of Pharmaceutics, Royal Danish School of Pharmacy.
Jan 1983 - Apr 1984	Visiting Research Fellow, Pharmacy Department, University of Nottingham.
May 1987-May 1990	Visiting Research Fellow, Pharmacy Department, University of Nottingham.
May 1990 -	Special Professor, Department of Pharmaceutical Sciences, University of Nottingham.
May 1989–April 1998	Managing Director, DanBioSyst UK Ltd, Nottingham, UK.
April 1998–Aug 1999	Managing Director, West Pharmaceutical Services Drug Delivery and Clinical Research Centre Ltd, Nottingham, UK.
Aug 1999 – Sept 2002	Chief Scientist, West Pharmaceutical Services Drug Delivery and Clinical Research Centre Ltd, Nottingham, UK.
Sept 2002 -	Director IDentity, Nottingham, UK
Jan. 2003 - 2005	Managing Director, Phaeton Research Ltd., Nottingham, UK
Febr. 2007 – Oct. 2011	CEO, Critical Pharmaceuticals Ltd.
October 2008 -	Special professor, Department of Chemistry, University of Nottingham

RESEARCH STUDENTS:

Have supervised or co-supervised about 50 post-grad students

PRESIDENT ELECT Controlled Release Society:

2007-2008

PRESIDENT Controlled Release Society:

2008-2009

PAST PRESIDENT Controlled Release Society:

2010-2011

EDITORIAL BOARDS:

Am or have been on the editorial board of the following journals:
J. Pharm. Sci.
Am. J. Drug Del.
Pharm. Res.
Int. J. Pharm.
Eur. J. Pharm. Sci.

J. Drug Target.
Drug Devel. Ind. Pharm.
J. Drug Delivery
J. Control. Rel.
J. Drug Del. Translational Res.
Pharm. Nanotech.

FELLOWSHIPS: Fellow of AAPS
Fellow of CRS

EXPERT WITNESS IN LEGAL CASES:

- 2005: Case between Photogen Technologies (now IMCOR Pharmaceuticals Co.), Alliance Pharmaceuticals Corp. and Molecular Biosystems INC against Amersham Health INC on perfluorcarbon gas microbubbles. Produced expert report.

- 2008: Case between Aventis and Sun Pharmaceuticals on docetaxel injectable formulation. Produced expert report.

- 2008/2009: Expert for PriceWaterHouseCooper for evaluation of Irish company's oral drug delivery portfolio. Produced expert report.

- 2009: EPO deposition for Eli Lilly Corp on nasal PTH patent. Produced expert report.

- 2009/2010: US litigation case between Department of Justice (US Tax Office) and Proctor & Gamble Company (Case No. 1:08-CV-608) on colonic delivery systems. Expert witness for plaintiffs. Deposed by defendants. Case was settled.

- 2011/2012: US antitrust litigation case concerning Wellbutrin XL between GlaxoSmithKline/Biovail Corp./Biovail Laboratories and a range of health and welfare funds ie Plumbers and Pipefitters Local 572 Health and Welfare fund (Civil Action No. 08-cv-2433-MAM), IBEW-NECA Local 505 Health and Welfare Plan (Civil Action No. 08-cv-2686-MAM), Painters District Council No.30 Health and Welfare funds (Civil Action No. 08-cv-2688-MAM), Mechanical Contractors-United Association Local 119 Health and Welfare Plan (Civil Action No. 08-cv-2712-MAM), Bricklayers and Masons Local Union No. 5 Ohio Health and Welfare Fund (Civil Action No. 08-cv-03404-MAM), Meijer, Inc. and Meijer Distribution, Inc. (Civil Action No. 08-cv-2433-MAM) and Rochester Drug Co-operative, Inc. (Civil Action No. 08-cv-02462-BWK). Expert witness for defendants. No deposition. Case was settled.

- 2012/2013 US litigation case concerning Fentora® (Effervescent Buccal tablets) between Cephalon Inc and CIMA Laboratories (Plaintifs) and Mylan Pharmaceuticals Inc and Mylan Inc. (Defendants). Produced expert reports (infringement and validity) for Plaintiffs, was deposed by Defendants and appeared in court March 2013 as main Plaintiff expert. Court ruling in August 2013 in favour of plaintiff.

- 2013/2014 Australian litigation case concerning Nasonex® (nasal spray) between Merck Sharp & Dohme & Anor v Apotex pty Ltd. in Australia. Produced scientific expert report. Case settled summer 2014.

- 2013/2014 US antitrust litigation case concerning Doryx between Mylan Pharmaceuticals, Inc, Rochester Drug Co-operative, Inc., Meijer, Inc, Meijer Distribution, Inc., Americal Sales Company, LLC, Walgreen Co, Safeway INC, Supervalu INC and HEB Grocery Co LP et al for Plaintiffs and Warner Chilcott Public Limited Company et al for Defendants. Engaged by Defendant and produced expert report. Was deposed by Plaintiffs in Nov 2013, Court granted summary judgment on all counts in Warner-Chilcott's favor in April 2015.

- 2014/2015 US litigation case concerning Saphris® between Forest Laboratories, Inc. and a number of generic drug manufacturers. Engaged as expert witness for plaintiff.

- 2014/2015 US litigation case concerning Faslodex® between AstraZeneca Inc and Sandoz Inc, Sagent Pharmaceuticals Inc and Glenmark Generics Inc. Engaged as an expert witness for plaintiff. Deposed by defendants for claim construction.

PRESENTATIONS AT SCIENTIFIC MEETINGS

"Tekniske og farmaceutiske aspekter vedrorende partikler i vaesker til parenteralt brug".
Industrifarmaceutforeningen, IFU-gruppe, Copenhagen, Denmark, November 1976.

"Partikelteknologiske og kliniske aspekter af partikelkontaminering i paranterale vaesker fra emballage of medicinske utensilier".
Molnlycke-Steritex A/S, symposium, Vedbaek, 1978.

"Medicinske utensilier af plast - partikelafgiftsproblemer". Centralsteriliseringsklubben, Bella Centret, Copenhagen, Denmark, October 1979.

"Partikelafgift fra medicinske utensilier".
Nordisk R^3 - forening, Symposium, Ronne, May 1980.

"Characterisation of particulate contamination released by application of parental solutions".
2nd International Conference on Pharmaceutical Technology, Paris, France, June 1980.

"Clinical and technological aspects of infusion fluid contaminated with particulate matter".
Nottingham University, Nottingham, UK, Seminar, September 1980.

"Particulate contamination of parenteral products".
Boot's Company Ltd, seminar, Nottingham, UK, September 1980.

"Particulate contamination of intravenous fluids".
Seminar, Kentucky University, Kentucky, USA, November 1980.

"Nature, types and sources of particulate matter".
Particulate Matter Monitoring Workshop, Amsterdam, Holland, April 1981.

"Clinical significance of particulate matter".
Particulate Matter Monitoring Workshop, Amsterdam, Holland,April 1981.

"Sorption of drugs by plastic infusion bags".
FIP Wien, September 1981.

"Gamma Scintigrafi i Drug delivery research".
Industrifarmaceutforeningen, IFU-gruppe, Copenhagen, Denmark April 1982.

"The targeting of drugs using microspheres".
19th International Pharmaceutical Research Conference of Japan, Sangane, July 1982,

"Shedding of Particles from Infusion sets".
Molnlycke-Steritex Seminar, Espergaerde, September 1982.

"Microspheres and nanoparticles in drug targeting".
C D Searle & Co, Chicago, Ill, USA, November 1982.

"Drug targeting with microspheres".
Amsterdam University, Pharmacy Department, May 1983.

"Drug targeting using monoclonal antibodies and nanoparticles".
FIP Montreux, September 1983.

"Drug targeting using monoclonal antibody-coated nanoparticles".
Microspheres and Drug Therapy Meeting, Amsterdam, Holland, October 1983.

"Passive and Active drug targeting".
Pharmacy Department, Nottingham University, Nottingham, UK, February 1984.

"Colloidal particles for active and passive drug targeting".
The Upjohn Company Kalamazoo, USA, March 1984.

"The kinetics of uptake and organ distribution of colloidal drug carrier particles".
2nd European Congress of Biopharmaceutics and Pharmacokinetics, Salamanca, April 1984.

"Passive and Active targeting using colloidal drug carrier systems".
Drug targeting meeting, Nyon, October 1984.

"Polymers as drug targeting systems".
Nordiske Polymerdage, Copenhagen, Denmark, May 1985.

"Polymer coated colloids and liver uptake".
NATO Advanced Study Institute "Targeting of drugs with Synthetic Systems".
24 June to 5 July 1985, Cape Sounion Beach , Greece.

"Directed delivery using colloidal carriers".
8 August 1985, Syntex Research Palo Alto, California.

"Colloidal carriers in passive and active site specific drug targeting".
14 August 1985, SmithKline and French, Philadelphia, USA.

"Microspheres as carriers in selective drug therapy".
British Pharmaceutical Conference, 11 September 1985.

"Microspheres as a novel drug delivery system".
Pharmacia, Uppsala, Sweden, 10 January 1986.

"Surface coated microspheres to minimise capture by the reticuloendothelial system".
American Chemical Society Meeting, New York, 13-18 April 1986.

"Colloidal carriers for drug targeting".
Alza Corporation, Palo Alto, California, 18 April 1986.

"Controlled Release System for Nasal Delivery".
Temadag om Nasal Administering av Lakemedel, Malmo, Sweden, 24 September 1986.

"Microspheres as a potential nasal drug delivery system".
NATO Advanced Research Workshop on Advanced Drug Delivery Systems for Peptides and Proteins, Copenhagen, Denmark, 28 May-1 June 1986.

"Drug delivery systems for nasal application".
3rd International Pharmaceutical Technology Symposium.
Ankara, Turkey, 9-11 September 1986.

"Nasal Applikation af laegemidler" Novo Industri A/S.
Copenhagen, Denmark, 10 October 1986.

Naesen som administrationsvej", Biofarmacisektionen.
Copenhagen, Denmark, 10 November 1986.

"Microspheres and Drug Targeting".
Danish Society for Polymer Technology,
Copenhagen, Denmark, 19-20 November 1986.

"Mikrosfaerer som malrettede missiler",
Annual address at the Assembly of the Royal Danish School of Pharmacy,
Copenhagen, Denmark, 5 December 1986.

"Microspheres and site specific delivery".
Department of Organic Chemistry, Gent University, Gent, 12 December 1986.

"Microspheres for drug targeting".
Leo Pharmaceuticals, Helsingborg, Sverige, 21 January 1987.

"Mikrosfaerer som transportsystem".
ATV-meeting, Royal Danish School of Pharmacy,
Copenhagen, Denmark, 22 January 1987.

"Particulate Systems; Possibilities and challenges".
3rd European Congress of Biopharmaceutics and Pharmacokinetics,
Freiburg, FGR, 21 April 1987.

"Colloidal carriers and Drug Targeting".
Johnson & Johnson annual Symposium on Drug Delivery, New Brunswick,
New Jersey, USA, 13 October 1987.

"Nasal delivery of peptides and proteins: Biopharmaceutical considerations".
Nasal Administration of peptide and protein drugs, Princeton,
New Jersey, USA, 15-16 October 1987.

"Microspheres and site specific delivery".
Aston University, 15 February 1988.

"Microspheres for nasal drug delivery".
Ciba Geigy, Horsham, 21 June 1988.
"Site specific delivery using microspheres".
Gent University, Belgium, 27 June 1988.

"Targeting to the vasculature and the bone marrow using colloidal carriers".
"ORIS", Paris, France, 5 July 1988.

"Colloidal particles for drug delivery".
Third International conference on drug absorption.
Edinburgh, UK, 27-30 September 1988.

"Nasal delivery of peptide and protein drugs".
Cold Spring Harbor Meeting, Cold Spring Harbor.
23-26 October 1988.

"Targeting of colloidal carriers to the bone marrow".
Amersham Award Presentations, Nuclear Medicine Society Meeting.
London, UK, 12 April 1989.

"Nasal delivery systems for peptides".
Second International Symposium on Disposition and Delivery of Peptide Drugs.
Leiden, 1-3 September 1989.

"Targeted Microspheres".
Harden Conference on Cellular Barriers and Drug Targeting.
Wye College, Kent, UK, 10-15 September 1989.

"New Nasal Drug Delivery Systems".
IBC Meeting, "Drug Delivery and Targeting Systems".
London, UK, 30 November - 1 December 1989.

"Nasal Delivery of Peptides and Proteins".
Roche Pharmaceuticals, 7 February 1990.

"Nasal Drug Delivery Systems", Drug Delivery Workshop.
Davos, Switzerland, 18-23 March 1990.

"Nasal Delivery of Peptides and Proteins".
Technologie Farmaceutiche Innovative.
Montecatini Terme, Italy, 8-10 May 1991.

"Nasal Delivery of Drugs - Factors of Importance".
FIP Washington, USA, 2-6 September 1991.

"Transmucosal Delivery of Drugs".
Pfizer, Groton, USA, 3 September 1991.

"Microspheres for Nasal Delivery".
European Symposium on Buccal and Nasal Administration as an Alternative to Parenteral Administration.
Paris, France, 10-11 December 1991.

"Nasal delivery systems".
Nasal and Pulmonary Delivery of Peptides and Protein Drugs.
Pharmaceutical, Clinical and Marketing Considerations.
Donaueschingen, Germany, 7-9 April 1992.

"Nasal and vaginal delivery of peptides and proteins".
2nd Jerusalem Conference on Pharmaceutical Sciences and Clinical Pharmacology.
Jerusalem, Israel, 24-29 May 1992.

"Parenteral administration of drug delivery systems: Problems and opportunities for optimal function".
NATO ASI: Targeting of drugs: Advances in systems construct.
Cape Souinion Beach, Greece, 24 June-5 July 1993.

"Nasal route of drug delivery: Problems and Future Potential".
Methods to overcome biological barriers in drug delivery.
Kuopio, Finland, 26-28 August 1993.

"Vaginal drug delivery".
AAPS.
Lake Buena Vista, Florida, 14-18 November 1993.

"Nasal delivery systems for peptide drugs".
2nd International Symposium Innovations in Pharmaceutical Sciences and Technology,
Thaltej, Ahmedabad, India, 25-27 February 1994.

"Transmucosal absorption of peptides and proteins".
New Drug Delivery Systems, Management Forum.
London, UK, 20 May 1994.

"Challenges in Nasal Drug Delivery".
Eastern AAPS.

New Brunswick, USA, 5-8 June 1994.

"Alternative Routes to Drug Delivery - Nasal Rectal, Vaginal systems".
Gordon Conference on Medicinal Chemistry.
New London, USA, 7-12 August 1994.

"Nasal delivery of peptides and proteins".
ACS Conference on Formulations and Drug Delivery.
Boston, Massachusetts, USA, 10-13 October 1995.

"Transmucosal delivery of challenging drugs".
UK CRS, 2nd Symposium on Controlled Drug Delivery: Current Perspectives and Future Trends.
London, UK, 8 January 1996.

"New approaches to the oral delivery of challenging molecules".
CRS Conference on Advances in Controlled Delivery.
Baltimore, Maryland, USA, 19-20 August 1996.

"Improved therapy through nasal drug delivery".
IIR Drug Delivery Systems.
The Madison, Washington DC, USA, 23-25 October 1996.

"Improved therapy through nasal drug delivery".
IIR Drug Delivery Systems.
The Park Hyatt, Philadelphia, PA, USA, 14-16 May 1997.

"The nasal route for delivery of polypeptides".
The Alfred Benzon Symposium no. 43.
Peptide and Protein Delivery.
Copenhagen, Denmark, 17-21 August 1997.

"Polysaccharides as nasal delivery systems".
Polysaccharide Biotechnology.
University of Nottingham, Nottingham, UK, 3-5 September 1997.

"Animal models for the prediction of nasal absorption in man".
Nasal and Pulmonary Conference V.
Stockholm, Sweden, 29 September-1 October 1997.

"Nasal administration of peptides and proteins: How far can we go?"
Nasal Drug Delivery Focus Group.
AAPS, Boston, USA, 5 November 1997.

"Aspects of Development of nasal formulations for peptides and proteins".
Nasal Drug Delivery Symposium ,Management Forum.
London, UK, 7-8 April 1998.

"Nasal delivery of peptides".
GlaxoWellcome Symposium on delivery of peptides.
Ware, UK, 8 September 1998.

"Nasal delivery of drugs".
J & J Symposium.
Princeton, NJ, USA, 29 September 1998.

"Powders as nasal delivery systems".
Nasal Drug Delivery Symposium Management Forum.
London, UK, 25-26 March 1999.

"Intranasal Drug Delivery"
Perioperative Care 2000
RUH, Bath 6th December 1999

"Novel approaches for the nasal delivery of vaccines"
Novel Vaccine Formulations and delivery systems
UKI-CRS Meeting
Dublin, 6-7th January 2000

"Nasal bioadhesive drug delivery systems"
Bioadhesion – Fact or Fiction?
Management Forum Meeting
London, 17th January 2000

"Examining recent advances in nasal drug delivery to determine its commercial potential"
Protein & Peptide Drug Delivery
IIR Ltd
London, UK, 19-20th July, 2000

"Current and future developments in nasal delivery"
British Pharmaceutical conference 2000
Birmingham, 10-13 September 2000, UK

"The immune response of nasally administered influenza vaccine is enhanced by the polysaccharide chitosan"
Options for the control of influenza IV
Hersonissos, Crete, Greece, 23-28 September 2000

"Nasal delivery systems for morphine"
New approaches to pain management
Management Forum
London, Uk, 12-13 October, 2000

"Transmucosal (nasal) Delivery of Vaccine"
Symposium on Transmucosal Systems
AAPS, Indianapolis, USA, 29 October – 2 November, 2000

"Applications for the improved nasal delivery of drugs, vaccines and DNA"
RACI Meeting on Delivery of Peptide Drugs
Victoria College of Pharmacy, Melbourne, AUS, 14 November, 2000

"Nasal drug delivery, - From nose to brain,- Animal models and predictions in man"
Symposium on "The nasal route for systemic drug delivery"
AstraZeneca R & D, Lund, Sweden, 28-29 November, 2000

"What's new in nasal drug delivery"
Nasal Drug Delivery Meeting
Management Forum
London, 26/27th March, 2001

"Intranasal morphine for pain management"
Brain/Pain Research: From molecules to mind
The Fourth Military Medical University
Xian, China, 30th April-2nd May 2001.

"Pain Management- Nasal Deliver"
SMI Conference on Drug Delivery
London, UK, 1-2nd October 2001

"Nasal drug delivery – From nose to brain"
Medical University of Lubeck
Lubeck, Germany, 9th November 2001

"Nasal delivery of problem drugs-Polar drugs, peptides, vaccines and DNA"
APSA Conference
Melbourne, Australia, 9-12 December 2001

"Nasal drug delivery"
Otago University, Department of Pharmacy
Dunedin, New Zealand, 14th December 2001

"Recent advances in nasal drug delivery"
6th US-Japan Drug Delivery Meeting
Maui, Hawaii, USA, 16 – 21 December 2001

"The significamce of animal models in the investigation of respiratory therapies"
Practical approaches to nasal and pulmonary drug delivery
Paris, 24-25th January,2002

"Nasal delivery of insulin"
Diabetes Management – New Developments
Management Forum, London 28th February – 1st March, 2002

"Nasal drug delivery – possibilities, problems and solutions"
7th European Symposium on Controlled Drug Delivery
Noordwijk aan Zee, Holland, 3-5th April, 2002

"Nasal delivery of insulin"
Diabetes Management – New Developments
Controlled Release Society Workshop
Seoul, Korea, 20-21 July 2002

"Nasal drug delivery"
Dept. of Pharmaceutics and Biotechnology
Vienna University, 7th November, 2002

"Drug Delivery: An Overview"
Commercial Issues in Drug Delivery 2002
SMI
London, UK, 23-24th September 2002
"Nose to brain drug delivery"
Access of Therapeutics to the Brain
CRS
Belfast, UK, 10th January, 2003

"Advantages and issues for intranasal delivery"
Opinion Leaders Meeting
Ionix
Windsor, UK, 3-4 March, 2003

"Innovation in drug technology and delivery"
Migraine Innovators
AstraZeneca Meeting
Bruges, Belgium, 15-16th March 2003

"Important considerations in nasal drug delivery"
Nasal Drug Delivery
Management Forum
London, UK, 24-25 March, 2003

"Formulation strategies for challenging drugs – Novel concepts for improved therapeutic benefits"
Drug Research Academy summer meeting 2003
Cromwell, Middelfart, 28-29 August 2003

"Nasal drug Delivery"
BPC 2003
Harrogate, UK, 15-17 September 2003

"Physiology of the olfactory mucosa and pathways involved in nose to brain delivery"
Symposium on "***Intranasal Delivery for CNS Disorders***", AAPS 2003
Salt Lake City, Utah, USA, 26th – 30th October 2003.

"Case studies: Nasal delivery"
IIR symposium on "Protein and peptide formulation for drug delivery"
London, 17th-19th November 2003

"Challenges in oral drug delivery with special emphasis on peptide and protein delivery"
IBC 4th International Conference on " Formulation & Drug Delivery Strategies for Biopharmaceuticals"
Munich, Germany, 17th –18th February, 2004.

"Nose-to-brain delivery"
Barnett Int. Symposium Nasal Drug Delivery
Philadelphia, USA, 26-27th February, 2004

"Nasal absorption enhancers"
Nasal Drug Delivery
Management Forum
London, UK, 29-30 March, 2004

"Is bioavailability the most important consideration in nasal delivery ?"
EUFEPS 2004 - 8th European Congress of Pharmaceutical Sciences
Brussels, October 17-20, 2004

"Nasal clearance in Health and Disease"
ISAM
Perth, Australia, 14th-18th March, 2005

"Is nasal delivery of biopharmaceuticals a reality ?"
IBC, BioProcess International ,
12-13 April 2005, Hotel Palace, Berlin, Germany

"Absorption enhancers for nasal sprays: Major options and their toxicological characteristics"
RDD Europe 2005
25-27 May 2005, Paris, France

"Bioadhesive Polymers as Novel Drug Delivery Systems
Novozymes
25th August 2005, Copenhagen, Denmark

"Novel Approaches for the Nasal Delivery of Vaccines
- are nanoparticles the answer ?
iNano Summer school
7th October 2005, Aebeltoft, Denmark

"Nanoparticulate systems for nasal delivery of drugs
- a real improvement over simple systems ?"
Nastech Pharmaceuticals
15th February 2006, Bothwell, Washington, USA

"In Vitro and in Vivo Animal Models for Nose-to-Brain Drug Delivery"
Alza Pharmaceuticals
17th February 2006, Palo Alto, California, USA

"Nasal Delivery - Pain Management
Auriga Pharmaceuticals
18th October 2006, Atalnta, Georgia, USA

"Meeting the Unmet Needs in nasal drug delivery
Drug Delivery To The Lungs, 2006
30th November-1st December 2006, Edinburgh

"Nose-to-Brain Drug Delivery"
Roche
15th December 2006, Basel, Switzerland

"A passionate affair with Chitosan"
CRS
8th-11th July 2007, Long Beach, California, USA

"Nasal drug delivery of biopharmaceuticals"
PBP World Meeting
Valletta, Malta, 8-11 March, 2010

"Have nanoparticles got a role in nasal drug delivery ?"
Management Forum
Nasal Drug Delivery, London, UK, 14-15 April, 2010

"Nasal delivery of peptides and proteins – Are we there yet ?"
CRS
Portland, Oregon, 10-14 July, 2010

"Fundamental principles of nose to brain delivery "
AAPS/Pharmaceutical Sciences World Congress
New Orleans, Louisiana, USA, 14-18 November, 2010

"Nasal delivery of peptides and proteins – Are we there yet"
Marcus Evans Peptide Forum
Vienna, Austria, 2 – 3 December 2010

"Nasal delivery of macromolecules – Are we there yet?"
SMI Controlled Release
London, March 30 – 31 2011

"Injectable sustained release of proteins"
SMI Controlled Release
London, March 30 – 31 2011

"Nose to brain delivery of drugs – A mist in the air ?"
ULLA European Summer School
From Brain to Drugs and Back
Parma, Italy, July 2, 2011

"A nose of the future ?"
8th LTS Symposium
New Horizons in Drug Delivery
Konigswinter, Germany, September 29-30, 2011

"Nasal delivery of biologics – Where are we ?"
Groupe de Metabilisme et de Pharmacocinetique
Maison Internationale, Cite Universitaire de Paris,
Paris, France, 10-11 October, 2011

"Nasal Systemic Delivery"
Management Forum
Nasal & Buccal Drug Delivery
London, April 25-26th, 2013

PARTICIPATION IN SCIENTIFIC MEETINGS

Nordisk symposium for Renlighedsteknik og Rene Rum, Hamar.
24-25 April 1974.

12 Nordiske Apoteker - og farmaceutmode, Copenhagen.
9-12 June 1974.

Skandinavisk Symposium i partikelstorrelsesmåling og måling of specifik overflade samt porevolumen, Malmo.
4-5 December 1974.

IV Nordisk Symposium for Farmacilaerere, Helsingfors.
26-27 May 1975.

3rd International Symposium on Contamination Control.
Copenhagen, 29 August-2 September 1976.

Nordisk Symposium for Renlighedsteknik og Rene Rum, Gothenburg.
25-26 May 1977.

5th Nordiske Symposium for Farmacilaerere, Copenhagen.
23-24 May 1977.

Nordisk Symposium for Renlighedsteknik og Rene Rum, Oslo.
11-12 April 1978.

Nordisk Symposium for Renlighedsteknik og Rene Rum, Hensingfors.
21-23 May 1979.

Plastics in Medicine and Surgery, International Conference, Twente, Holland.
21-22 June 1979.

Nordisk Symposium for Renlighedsteknik og Rene Rum, Ronne.
18-21 May 1980.
*Member of organising committee.

2nd International Conference on Pharmaceutical Technology, Paris, France.
3-5 June 1980.

5th International Symposium on Contamination Control, Munich.
15-17 September 1980.

British Pharmaceutical Conference, Newcastle upon Tyne, UK.
18-19 September 1980.

29th Meeting of Academy of Pharmaceutical Sciences.
San Antionia, Texas, 9-13 November 1980.

Nordisk Symposium for Renlighedsteknik og Rene Rum, Gothenburg.
4-6 May 1981.

41st International Congress of Pharmaceutical Science, Wien.
7-11 September 1981.

British Pharmaceutical Conference.
Brighton 14-18 September 1981.

19th International Pharmaceutical Research Conference of Japan, Sangane.
12-14 July 1982.
*Invited speaker.

British Pharmaceutical Conference.
Edinburgh, 13-17 September 1982.

33rd Meeting of Academy of Pharmaceutical Sciences, San Diego, California.
14-18 November 1982.

43rd International Congress of Pharmaceutical Sciences of FIP, Montreux.
5-9 September 1983.

Microspheres and Drug Therapy Symposium, Amsterdam.
October 1983.
*Member of organising committee.

2nd European Congress of Biopharmaceuticals and Pharmacokinetics.
Salamanca, April 1984.

Macromolecules as Drugs and as Carriers for Biologically Active Materials.
New York Academy of Sciences Conferences.
New York, 26-28 March 1984.

Drug targeting symposium.
Nyon, Switzerland, October 1984.
*Invited speaker.

Nordiske Polymerdage.
Copenhagen, 29-30 May 1985.
*Invited speaker.

NATO Advanced Study Institute, "Targeting of Drugs with Synthetic Systems".
24 June to 5 July 1985, Cape Sounion Beach, Greece.

British Pharmaceutical Conference.
Leeds, 9-12 September 1985.
*Invited speaker.

American Chemical Society Meeting.
I International Symposium on Polymeric Drugs.
*Invited speaker.

II Recent Advances in Controlled Release Technology.
*Invited speaker.
New York, USA, 13-18 April 1986.

Nasal administering av Lakemedel, Sektionen Galenisk Farmaci og Biofarmaci.
*Invited speaker.
Lund, Sweden, 24 April 1986.

NATO Advanced Research Workshop on Advanced Drug Delivery Systems for Peptides and Proteins.
Copenhagen, 28 May-1 June 1986.
*Member of organising committee.

3rd International Pharmaceutical Technology Symposium.
*Invited speaker.
Ankara, Turkey, 9-11 September 1986.

Drug Delivery Systems - Controlled Release.
Danish School for Polymer Technology.
*Invited speaker.
Copenhagen, 19-20 November 1986.

3rd European Congress of Biopharmaceutics and Pharmacokinetics (FIP).
*Invited speaker.
Freiburg, FGR, 21-24 1987.

Xth International Congress of Pharmacology.
*Invited speaker.
Sydney, Australia, 23-28 August 1987.

Nasal Administration of Peptide and Protein Drugs.
*Invited speaker.
Princeton, New Jersey, USA, 15-16 October 1987.

Johnson & Johnson's Annual Symposium on Drug Delivery.
*Invited speaker.
New Brunswick, New Jersey, USA, 13 October 1987.

3rd International Conference on Drug Absorption.
*Invited speaker.
Edinburgh, UK, 27-30 September 1988.

Therapeutic Peptides and Proteins: Formulation, Delivery and Targeting.
*Invited speaker.
Banbury Center of Cold Spring Harbor Laboratory, 23-26 October 1988.

Peptide Drug Delivery Colloquium.
*Invited speaker.
Charing Cross and Westminster Medical School, UK, 19 December 1988.

2nd International Symposium on Disposition and Delivery of Peptide Drugs (FIP Satellite Symposium).
*Invited speaker.
Leiden, 1-3 September 1989.

NATO Advanced research Workshop on Cell Cultures in Drug Transport.
*Member of Organising Committee.
Bandol, France, 4-8 September 1989.

The Biochemical Society - Harden conference on Cellular Barriers and Drug Targeting.
*Invited speaker.
Wye College, Kent, UK, 10-15 September 1989.

"Drug Delivery and Targeting Systems".
IBC Technical Meetings.
*Invited speaker.
London, UK, 30 November-1 December 1989.

Drug Delivery Workshop.
*Invited speaker.
Davos, Switzerland, 18-23 March 1990.

Technologie Farmaceutiche Innovative.
*Invited speaker.
Montecatini Terme, Italy, 8-10 May 1991.

FIP.
*Invited speaker and Symposium organiser.
Washington DC, USA, 2-6 September 1991.

Eur. Symp. Buccal and Nasal Administration as an alternative to Parenteral Administration.
*Invited speaker.
Paris, France, 10-11 December 1991.

Nasal and Pulmonary Delivery of Peptide and Protein Drugs.
Pharmaceutical, Clinical and Marketing Considerations.
*Invited speaker.
Donaueschingen, Germany, 7-9 April 1992.

2nd Jerusalem Conference on Pharmaceutical Sciences and Clinical Pharmacology.
*Invited speaker.
Jerusalem, Israel, 24-29 May 1992.

NATO ASI: Targeting of Drugs: Advances in system constructs.
*Invited speaker.
Cape Sounion Beach, Greece, 24 June-5 July 1993.

Methods to overcome biological barriers in drug delivery.
*Invited speaker.
Kuopio, Finland, 26-28 August 1993.

AAPS.
*Invited speaker.
Lake Buena Vista, Florida, 14-18 November 1993.

2nd Int. Symposium Innovations in Pharmaceutical Sciences and Technology.
*Invited speaker.
PERD Centre, Thaltej, Ahmedabad, India, 25-27 February 1994.

New Drug Delivery Systems.
*Invited speaker.
Management Forum, London, UK. 20 May 1994.

Eastern AAPS Meeting.
*Invited speaker.
New Brunswick, USA. 5-8 June 1994.

Gordon Conference on Medicinal Chemistry.
*Invited speaker.
New London, USA, 7-12 August 1994.

ACS Conference on Formulations and Drug Delivery.
*Invited speaker.
Boston, Massachusetts, USA, 10-13 October 1995.

UK CRS, 2nd Symposium on Controlled Drug Delivery.
Current Perspectives and Future Trends.
*Invited speaker.
London, UK, 8 June 1996.

Henry Stewart Conference Studies.
The DNA Vaccine Revolution.
London, UK, 11 July 1996.

CRS Conference on Advances in Controlled Delivery.
*Invited speaker.
Baltimore, Maryland, USA, 19-20 August 1996.

IIR Drug Delivery Systems.
*Invited speaker.
The Madison, Washington DC, USA, 23-25 October 1996.

IIR Drug Delivery Systems.
*Invited speaker.
The Park Hyatt, Philadelphia, PA, USA, 14-16 May 1997.

The Alfred Benzon Symposium no. 43.
*Invited speaker.
Peptide and Protein Delivery.
Copenhagen, Denmark, 17-21 August 1997.

Polysaccharide Biotechnology.
*Invited speaker.
University of Nottingham, Nottingham, UK, 3-5 September 1997.

Nasal and Pulmonary Conference V.
*Invited speaker.
Stockholm, Sweden, 29 September-1 October 1997.

Nasal Drug Delivery Focus Group.
*Invited speaker.
AAPS, Boston, USA, 5 November 1997.

Nasal Drug Delivery Symposium.
*Invited speaker.
Management Forum.
London, UK, 7-8 April 1998.

RDD 6.
Hilton Head, USA, 4-7 May 1998.

CRS
Las Vegas, USA, 21-25 June 1998.

GlaxoWellcome Symposium on delivery of peptides.
*Invited speaker
Ware, UK, 8 September 1998.

J & J Symposium
*Invited speaker.
Princeton, NJ, USA, 29 September 1998.

Vaccine Delivery.
Delhi, India, 2-5 November 1998.

AAPS.
San Francisco, California, USA, 16-19 November 1998.

Nasal Vaccine Symposium.
*Invited speaker.
London, UK, 21-22 January 1999.

Nasal Drug Delivery Symposium Management Forum
*Invited speaker
London, UK, 25-26 March 1999.

"Perioperative Care 2000"
*Invited speaker
RUH, Bath, UK, 6th December 1999

"Novel Vaccine Formulations and delivery systems"
*Invited speaker
UKI-CRS Meeting
Dublin, Ireland, 6-7th January 2000

"Bioadhesion – Fact or Fiction?"
*Invited speaker
Management Forum Meeting
London, UK, 17th January 2000

"Nasal Drug Delivery"
Management Forum
London, UK, 23-24 March 2000

Millennial World Conference of Pharmaceutical Sciences
San Francisco, Cal., USA, 16-20 April, 2000

The Third Annual Conference on Vaccine Research
Washington, USA, April 30 – May 2, 2000

Osteoporosis Therapies: Strong Bones For Life
SMI Pharmaceutical Conference
London, UK, 7-8 June, 2000

The 27th Int. Symposium on Controlled Release of Bioactive Materials
Paris, France, July 10 – 13th, 2000

"Protein & Peptide Drug Delivery"
*Invited speaker
IIR Ltd
London, UK, 19-20th July, 2000

British Pharmaceutical conference 2000
*invited speaker
Birmingham, 10-13 September 2000, UK

Options for the control of influenza IV
Hersonissos, Crete, Greece, 23-28 September 2000

New approaches to pain management
*invited speaker
Management Forum

London, UK, 12-13 October, 2000

Symposium on Transmucosal Systems
* invited speaker
AAPS, Indianapolis, USA, 29 October – 2 November, 2000

RACI Meeting on Delivery of Peptide Drugs
* invited speaker
Victoria College of Pharmacy, Melbourne, AUS, 14 November, 2000

Symposium on "The nasal route for systemic drug delivery"
* invited speaker
AstraZeneca R & D, Lund, Sweden, 28-29 November, 2000

Meeting on Nasal Drug Delivery
* invited speaker
Management Forum, London 26/27th March 2001

Brain/Pain Research: From molecules to mind
* invited speaker
The Fourth Military Medical University
Xian, China, 30th April-2nd May 2001.

Conference of the European Chitin Society
Ancona, Italy, 6-10th May, 2001

Workshop on "Transmucosal Vaccine Delivery"
*Workshop organiser and Chairman
CRS Meeting
San Diego, Califormia, USA, 23-24th June 2001

SMI Conference on Drug Delivery
* invited speaker
London, UK, 1-2nd October 2001

APSA Conference
* invited speaker
Melbourne, Australia, 9-12 December 2001

6th US-Japan Drug Delivery Meeting
- invited speaker

Maui, Hawaii, USA, 16 – 21 December 2001

Practical approaches to nasal and pulmonary drug delivery
Valois Symposium
* invited speaker
Paris, 24-25th January,2002

Diabetes Management – New Developments
- Invited speaker
- Chairman and organiser

Management Forum, London 28th February – 1st March, 2002

Nasal drug delivery
Management Forum, London, 21-22nd March, 2002

7th European Symposium on Controlled Drug Delivery
* invited speaker
Noordwijk aan Zee, Holland, 3-5th April, 2002

Diabetes Management – New Developments
Controlled Release Society Workshop
* Invited speaker
* Chairman and organiser
Seoul, Korea, 20-21 July 2002

Commercial Issues in Drug Delivery 2002
SMI
* Invited speaker
London, UK, 23-24th September 2002

Nasal drug delivery
Dept. of Pharmaceutics and Biotechnology
* Invited speaker
Vienna University, 7th November, 2002

Access of Therapeutics to the Brain
CRS
* Invited speaker
Belfast, UK, 10th January, 2003

Opinion Leaders Meeting
Ionix
*Invited speaker
Windsor, UK, 3-4 March, 2003

Migraine Innovators
AstraZeneca Meeting
*Invited speaker
Bruges, Belgium, 15-16th March 2003

Nasal Drug Delivery
Management Forum
*Invited speaker
London, UK, 24-25 March, 2003

Drug Research Academy summer meeting 2003
*Invited speaker

Cromwell, Middelfart, 28-29 August 2003

BPC 2003
Science Symposium, Drug delivery
* Invited speaker
Harrogate, UK, 15-17 September 2003

AAPS 2003
Symposium on "***Intranasal Delivery for CNS Disorders***"
* Invited speaker
Salt Lake City, Utah, USA, 26th – 30th October 2003.

IIR symposium on "Protein and peptide formulation for drug delivery"
* Invited speaker
London, 17th-19th November 2003

IBC 4th International Conference on " Formulation & Drug Delivery Strategies for Biopharmaceuticals"
* Invited speaker
Munich, Germany, 17th –18th February, 2004.

Barnett Int. Symposium Nasal Drug Delivery
*Invited speaker
Philadelphia, USA, 26-27th February, 2004

Management Forum
Nasal Drug Delivery
* Invited speaker
London, UK, 29-30 March, 2004

EUFEPS 2004
* Invited speaker
Brussels, 17-20 October 2004.

ISAM
* Invited speaker
Perth, Australia, 14th-18th March, 2005

IBC, BioProcess International ,
* Invited speaker
12-13 April 2005, Hotel Palace, Berlin, Germany

RDD Europe 2005
* Invited speaker
25-27 May 2005, Paris, France

Drug Delivery to The Lungs, 2006
* Invited speaker
30th November-1st December 2006, Edinburgh

CRS
*Invited speaker
8th-11th July 2007, Long Beach, California, USA

CRS
13th – 16th July 2008, New York, NY, USA

EUCHIS 2009
23 – 26 May 2009, Venice, Italy

CRS
July 2009, Copenhagen, Denmark

APV 7th World Meeting
*Invited speaker
8-11 March 2010, Malta

Management Forum
Nasal Drug Delivery
14-15 April 2010, London, UK

CRS
*Invited speaker
11- 14th July 2010, Portland, Oregon, USA

AAPS/Pharmaceutical Sciences World Congress
*Invited speaker
New Orleans, Louisiana, USA, 14-18 November, 2010

Marcus Evans Peptide Forum
*Invited speaker
Vienna, Austria, 2 – 3 December 2010

SMI Controlled Release
*Invited speaker
London, March 30 – 31 2011

ULLA European Summer School
*Invited speaker
From Brain to Drugs and Back
Parma, Italy, July 2, 2011

8th LTS Symposium
*Invited speaker
New Horizons in Drug Delivery
Konigswinter, Germany, September 29-30, 2011

Groupe de Metabilisme et de Pharmacocinetique
*Invited speaker
Maison Internationale, Cite Universitaire de Paris,

Paris, France, 10-11 October, 2011

Management Forum
*Invited speaker
Nasal & Buccal Drug Delivery
London, April 25-26th, 2013

FUNDING AND AWARDS

"Statens laegevidenskabelige Forskningsråd" (MRC), 15,525 Dkr for project on "Partikelkontaminering af parenterale vaesker", 1977.

"Statens laegevidenskabelige Forskningsråd" (MRC), 16,590 Dkr for project on "Partikelkontaminering of parenterale vaesker", 1978.

"Statens laegevidenskabelige Forskningsråd" (MRC) 5,950 Dkr for study tour to USA 1980.

"Erik Horslevs Fond" 4,000 Dkr for study tour to USA 1980.

"British Concil" 3,500 Dkr for study tour to England 1980.

"NATO Science Fellowship" 9,955 Dkr for study at University of Nottingham, July-August 1981.

"Otto Mullers Efts's Legat" 4,000 Dkr for study visit at University of Nottingham, November-December 1981.

"British Council" 1,300 Dkr for study visit at University of Nottingham, November-December 1981.

"NATO Science Fellowship" 8,700 Dkr for study visit at University of Nottingham, 1982.

"Statens laegevidenskabelige Forskningsråd" 8,300 Dkr for Professor S S Davis research stay 1982.

"Apoteker Julius Waels og cand Pharm Helga Waels legat" 3,000 Dkr for study tour to Japan, July 1982.

"Tegnes Mindelegat" 7,000 Dkr for study tour to Japan, July 1982.

"Erik Horslevs Fond" 4,460 Dkr for study tour to Japan, July 1982.

"NATO Science Foundation", Double Jump Program, 18,000 Dkr, 1983.

"NATO Science Foundation", Double Jump Program, 45,000 Dkr, 1984.

"Statens laegevidenskabelige Forskningsråd" (MRC) 33,000 Dkr, June 1984.

"Statens laegevidenskabelige Forskningsråd" (MRC) 27,085 Dkr, June 1984.

"NATO Science Foundation" Double Jump Program, 45,000 Dkr, 1985.

"NATO Science Foundation", support for a meeting on Modern Aspects of Drug Delivery, 135,000 Dkr, 1985.

"Fisons Pharmaceuticals", Project on nasal delivery, 200,000 Dkr, 1985.

"Statens laegevidenskabelige Forskningsråd" (MRC) 37,000 Dkr, August 1985.

"Statens laegevidenskabelige Forskningsråd" (MRC) 16,000 Dkr, August 1985.

"Ciba-Geigy", Horsham, Project on drug delivery (with Nottingham University) £20,000 August 1985.

"Statens laegevidenskabelige Forskningsråd" (MRC) 32,500 Dkr, July 1986.

"Statens laegevidenskabelige Forskningsråd (MRC) 17,000, August 1986.

Novo Industry A/S 75,000 Dkr to project on nasal drug delivery, August 1986.

Novo Industry A/S 225,000 Dkr to project on nasal drug delivery, October 1986.

"The Amersham Award", £2,000 for work on targeting of colloidal carriers to the bone marrow, April 1987.

Alza Corporation, $165,000 for project on buccal and vaginal delivery, April 1987.

"Statens laegevidenskabelige Forskningsråd" (MRC) 57,000 Dkr, April 1987.

Glaxo Research, 60,000 Dkr to a project on nasal delivery, September 1987.

Nordisk Gentofte A/S 137,000 Dkr to project on Nasal delivery of peptide drugs, September 1987.

Sandoz Research £20,000 to project on Targeting of drugs to the bone marrow, September 1987.

"Statens laegevidenskabelige Forskningsråd" (MRC) 36,000 Dkr, April 1988.

"Marie Longgaard's Award", 80,000 Dkr, September 1988.

"NATO Science Foundation", support for a meeting on Cell Cultures for Drug Absorption Studies, £10,500, 1988.

"Statens laegevidenskabelige Forskningsråd" (MRC), 36,000 Dkr, April 1989.

"BRITE/EURAM Award" about £600,000 for project on "Drug Targeting" in Collaboration with colleagues from Belgium, France, Italy and England, August 1989.

I have not kept yhis one up to date. But I have received 4 SMART awards and 2-3 other large European grants.

Eurand Carreer Achievement Award, 9th July 2007

Wellcome Trust Grant, 12th June 2009, £ 1.5 mill

PUBLICATIONS

1. L Illum and N Moller: Surface area stability of micronized steroids stabilised by irradiation, Arch, Pharm, Chemi., Sci. Ed **2**, 1974, 167-174.

2. L Illum: Applicability of the Silting Index method to the evaluation of Particulate contamination in aqueous fluids. Arch. Pharm. Chemi., Sci Ed. **4**. 1976, 81-90.

3. L Illum, V Gauno Jensen & N Moller: Characterisation of particulate contamination released by application of parenteral solutions I. Particulate matter from administration sets. Arch. Pharm. Chemi., Sci. Ed. **6**, 1978, 93-108.

4. L Illum, V Gauno Jensen & N Moller: Characterisation of particulate contamination released by application of parenteral solutions. II. Particulate matter from cannulae. Arch. Pharm. Chemi., Sci. Ed. **6**, 1978, 169-178.

5. L Illum, V Gauno Jensen & N Moller: Influence of blood plasma on size distribution of particulate contamination in parenteral solutions. Arch. Pharm. Chemi., Sci. Ed. **6**. 1978, 179-183.

6. L Illum: Partikelkontaminering of vaesker til parenteralt brug. Partikelteknologiske og kliniske aspekter af partikelkontaminering fra emballage og medicinske utensilier. Danmarks farmaceutiscke Hojskole, November 1978 (PhD thesis).

7. L Illum: Characterisation of particulate contamination released by application of parenteral solutions. III Particulate matter from Syringes. Arch. Pharm. Chemi., Sci Ed. **8**. 1980, 109-119.

8. L Illum, V Gauno Jensen & N Moller: Characterisation of particulate contamination released by application of parenteral solutions. Proceedings from 11th Nordic Symposium on Contamination Control, Ronne, 18-21 May 1980.

9. L Illum, V Gauno Jensen & N Moller: Characterisation of particulate contamination released by application of parenteral solutions. Proceedings from 2nd International Conference on Pharmaceutical Technology, Paris, 3-5 June 1980.

10. L Illum: Nature, types and sources of particulate matter. Proceedings from Particulate Matter Monitoring Workshop, Amsterdam, April 9-11, 1981.

11. L Illum: Clinical Significance of particulate matter. Proceedings from Particulate Matter monitoring Workshop, Amsterdam, April 9-11, 1981.

12. L Illum & H Bundgaard: Sorption of drugs by plastic infusion bags. J Pharm. Pharmacol. **33**, 1981, Suppl. 102P.

13. L Illum & H Bundgaard: Sorption of drugs by plastic infusion bags. Int. J Pharm. **10**, 1982, 339-351.

14. L Illum & S S Davis: Cellulose microspheres as a sustained released system for parenteral administration. Int. J Pharm. **11**, 1982, 323-327.

15. L Illum, S S Davis, C G Wilson, N Thomas, M Frier and J G Hardy: Blood clearance and organ deposition of intravenously administered colloidal particles: the effects of particle size, nature and shape. Int. J. Pharm. **12**, 1982, 135-147.

16. L Illum & S S Davis: The targeting of drugs parenterally by use of microspheres. J Parent. Sci. Tech. **36**, 1982, 232-248.

17. L Illum & S S Davis : Specific intravenous delivery of drugs to the lungs using ion-exchange microspheres. J. Pharm. Pharmacol. **34**, 1982, Suppl., 89P.

18. L Illum, J G Hardy, C G Wilson & S S Davis : Gamma ray detection probe for the evaluation of blood activity-time profiles. J. Pharm. Pharmacol. **34**, 1982, Suppl. 90P.

19. L Illum & S S Davis: Effect of non-ionic surfactant on the fate and deposition of polystyrene microspheres following intravenous administration, J Pharm. Sci. **72**, 1983, 1086-1089.

20. H Bundgaard & L Illum: Kinetics and mechanisms of sorption of various drugs by plastics. Acta. Pharm. Suec. Suppl. **3**, 1983, 68-75.

21. L Illum, H Bundgaard & S S Davis: A constant partition model for examining the sorption of drugs by plastic infusion bags. Int. J. Pharm. **17**, 1983, 183-192.

22. L Illum, P D E Jones, J Kreuter, R W Baldwin & S S Davis: Absorption of monoclonal antibodies to polyhexylcyanoacrylate nanoparticles and subsequent immunospecific binding to tumour cells in vitro. Int. J. Pharm. **17**, 1983, 65-76.

23. S S Davis & L Illum: Drug Delivery Systems. The Practitioner **227**, 1983, 1537-1543.

24. S S Davis & L Illum: The targeting of drugs using polymeric microspheres. British Polymer Journal **15**, 1983, 160-164.

25. L Illum, P D E Jones, R W Baldwin & S S Davis: Tissue distribution of poly (hexyl-2-cyanoacrylate) nanoparticles coated with monoclonal antibodies in mice bearing human tumour xenografts. J. Pharmacol, Exp. Ther. **230**. 1984, 733-736.

26. S J Douglas, L Illum, S S Davis & J Kreuter: Particle size and size distribution of poly (butyl 2-cyanoacrylate) nanoparticles. I. Influence of physicochemical factors. J Colloid Interface Sci. **101**, 1984, 149-158.

27. L Illum & S S Davis: The organ uptake of intravenously administered colloidal particles can be altered using a non-ionic surfactant (Poloxamer 338). FEBS Letters **167**, 1984, 79-82.

28. L Illum, P D E Jones & S S Davis: Drug targeting using monoclonal antibody coated nanoparticles. In S S Davis , L Illum, J G McVie & E Tomlinson (Eds), Microspheres and Drug Therapy, Elsevier Biomedical press, Amsterdam, 1984, p353-364.

29. S S Davis, L Illum, J G McVie & E Tomlinson (Eds): Microspheres and Drug Therapy, Elsevier Biomedical Press, Amsterdam, 1984.

30. L Illum & S S Davis: The kinetic of uptake and organ distribution of colloidal drug carrier particles delivered to rabbits. Proceedings from 2nd European Congress of Biopharmaceutics and Pharmacokinetics, Salamanca, Vol, II **97**, 1984.

31. L Illum: In search of Polysomes. Pharm. Inter. **5**, 1984, 185-186.

32. S J Douglas, L Illum & S S Davis: Particle size and size distribution of poly (butyl 2-cyanoacrylate) nanoparticles. II. Influence of stabilizers. J Colloid Interface Sci. **103**, 1985, 154-163.

33. L Illum & P D E Jones: Attachment of monoclonal antibodies to microspheres. In K J Widder and R Green (Eds), Drug and Enzyme Targeting, Academic Press, New York, 1985, p67-84.

34. H Jorgensen & L Illum: Design and evaluation of a microsphere drug delivery system for the controlled release of drug to the nose. Scholar student report. Royal Danish School of Pharmacy, DK-Copenhagen, 1985.

35. K Jacobsen & L Illum: Albumin nanopartikler. Udvikling og anvendelse. Scholar student report. Royal Danish School of Pharmacy, DK-Copenhagen, 1985.

36. S S Davis, J G Hardy, L Illum & C G Wilson: Nuclear Medicine Techniques for the Development of Pharmaceutical Formulations. In P H Cox (Ed), Yearbook of Radiopharmacy and Radiopharmacology, Gordon and Breech, 1985, p1-34.

37. L Illum & S S Davis: Passive and active targeting using colloidal drug carrier systems. In P Buri and A Gumma (Eds), Drug Targeting, Elsevier Science Publishers, Amsterdam, 1985, p65-80.

38. S S Davis, I M Hunneyball, L Illum, J H Ratcliffe, A Smith & C G Wilson: Recent advances in the use of microspheres for targeted therapy. Drug. Exptl. Clin. Res. XI, 1985, 633-640.

39. L Illum, J Huguet, M Vert & S S Davis: Accumulation in the lung of ^{75}Se-norcholestenol administered intravenously in a globular partially quaternized poly thio-1-(N, 4N-diethyl amino-methylethylene carrier system. Int. J. Pharm. **26**, 1985, 113-121.

40. P E West, L Illum & S S Davis: An investigation into the in vivo fate of a commercial fat emulsion. Proceed. Intern. Symp. Control. Rel. Bioact. Mater. **12**, 1985, 134-135.

41. S S Davis & L Illum: Drug targeting using colloidal carriers. Proceed. Intern. Symp. Control. Rel. Bioact. Mater. **12**, 1985, 326-327.

42. L Illum: Drug targeting using colloidal carrier systems - will it work? Acta Pharm. Tech. **31**, 1985, 53-56.

43. S S Davis, M Frier & L Illum: Colloidal particles as radiodiagnostic agents. In P Guiot and P Couvreur (Eds), Polymeric Nanoparticles and Microspheres, CRC Press Inc, Boca Raton, Florida, USA, 1986, p175-197.

44. L Illum, N Thomas & S S Davis: The effect of selected suppression of the reticuloendothelial system on the distribution of model carrier particles. J Pharm. Sci. **75**, 1986, 16-22.

45. R H Muller, S S Davis, L Illum & E Mak: Charge reduction of colloidal carriers for drug targeting by coating with polymers. Proceedings APV 32nd Annual Congress, Amsterdam, 1986.

46. E Mak, S S Davis, L Illum & R H Muller: Determination of the surface hydrophobicity of colloidal drug carriers using a rose bengal binding method. Proceedings APV 32nd Annual Congress, Amsterdam, 1986.

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List of patent families.
Each patent family have granted patents in different countries

1. Pharmaceutical composition including sodium cromoglycate

Priority date: 29 Nov 1985
Patent numbers: US4847091 A, EP0248051A1, WO1987003197A1
Inventors: Lisbeth Illum
ABSTRACT
Pharmaceutical compositions comprising microspheres incorporating sodium cromoglycate, wherein the microspheres comprise material having ion-exchange properties.

2. Colloidal particles coated with hydrophilic compound

Priority date: 17 Jan 1986
Patent numbers: US4904479 A
Inventors: Lisbeth Illum
ABSTRACT
Particles of a drug are directed away from the reticuloendothelial system by the use of surface coating and surface grafting techniques which substantially prevent the take up of the composite particles by the liver.

3. A drug composition with microspheres and process for its preparation

Priority date: 10 Oct 1987
Patent numbers: PCT/GB1988/000836, EP0396549 B1, WO1989003207A1, US5204108
Inventors: Lisbeth Illum
ABSTRACT
A drug delivery composition comprising a plurality of microspheres and active drug associated with each microsphere, the drug being for systemic delivery and having a maximum molecular weight of 6000, and the composition being substantially free of an enhancer. The microspheres may be of starch, gelatin or albumin. Suitable drugs include peptides, such as insulin, and antigenic vaccine ingredients. The compositions are suitable for delivery across a mucosal surface such as the vagina, eye or nose

4. Enhanced uptake drug delivery system

Priority date: May 22, 1987
Patent numbers: PCT/GB1988/000396, WO1988009163 A1
Inventors: Lisbeth Illum
ABSTRACT

A drug delivery system including a plurality of microsphere particles containing an active drug and including a surfactant material associated with each particle which surfactant material has the property of enhancing the uptake of the active drug.

5. Adhesive drug delivery composition

Priority date: Nov 8, 1988
Patent numbers: PCT/GB1989/001317, WO1990004963
Inventors: Antony James Caston, Lisbeth Illum, Paul Williams
ABSTRACT
Adhesive material from the fimbriae (esp. Type 1) of bacteria or synthetic analogues or fragments thereof is combined with a drug to provide for attachment to the gut of a mammal, thereby prolonging the transit time of the drug through the gut. The 28kDa polypeptide from E. coly Type 1 fimbriae is the preferred adhesive material ("adhesin"). The drug is presented in a carrier such as albumin, a polylactide/glycolide copolymer or alginate microcapsules. The adhesin may be incorporated in the carrier during preparation thereof, adsorbed onto the carrier after preparation, or covalently linked thereto, for example with carbodiimide.

6. Drug delivery compositions

Priority date: 25 Feb 1989
Patent numbers: CA2045472 A1
Inventors: Lisbeth Illum
ABSTRACT
A composition for administration to the mucosa comprises a pharmacologically active compound and a polycationic substance. The polycationic substance is preferably DEAE-dextran or chitosan and the pharmacologically active compound is preferably insulin or calcitonin. The composition may be a solution, dispersion, powder or microspheres. Other enhancers, such as lysophosphatidylcholine, can be included if desired.

7. Pharmaceutical compositions

Priority date: 18 Aug 1989
Patent numbers: PCT/GB1990/001293, WO1991002545 A1
Inventors: Lisbeth Illum
ABSTRACT
Compositions for trans-mucosal delivery, e.g. intranasal, include a lysophosphatidyl-glycerol compound as the adsorption enhancer. The preferred compounds for delivery are insulin and calcitonin.

8. Small particle drug compositions

Priority date: 4 Nov 1989
Patent numbers: CA2060176 A1
Inventors: Lisbeth Illum

ABSTRACT
A drug delivery composition for intranasal delivery comprises a plurality of bioadhesive microspheres and active drug associated with each microsphere, at least:90 wt % of the microspheres having a diamete r in the range 0.1 .mu.m to 10 .mu.m. The microspheres may be of starch, gelatin, dextran, collagen or albumin. Suitable drugs include peptides, such as insulin, and antigenic vaccine ingredients. The composition may, additionally comprise an absorption enhancer. The microspheres are administered to the nasal cavity by a means such that the product of the square of the microsphe re diameter and the flow rate is greater than 2000 .mu.m2 litres/min

9. Diagnostic aid

Priority date: 19 Feb 1991
Patent numbers: GB2256183, WO1991GB00247
Inventors: Lisbeth Illum
ABSTRACT
Hollow (i.e. gas or vapour-filled) microcapsules, for example of albumin, are prepared by forming a shell around a solid or liquid core and subsequently removing the core. The core may be a volatile oil such as perfluorohexane. The shell may be made by simple or complex coacervation, oil/water/oil double emulsion, or MSIEP (minimisation of solubility at isoelectric point) methods, followed by chemical or heat hardening to render it water-insoluble. When the double emulsion method is used, the microcapsules have a honeycomb appearance with multiple gas-filled chambers. The microcapsules can be used for echocardiography.

10. Preparation of microparticles

Priority date: 1 Aug 1991
Patent numbers: PCT/GB1992/001421, CA2113901 C
Inventors: Lisbeth Illum, Olufunmiloyo L. Johnson
ABSTRACT
Solid microspheres or hollow (i.e. gas or vapour filled) microcapsules, for example of amylodextrin are prepared by forming a shell from a water-soluble starch derivative around a solid or liquid core and subsequently removing the core. The core may be a volatile oil such as perfluorohexane. The microspheres or microcapsules may be made by an oil/water/oil double emulsion followed by chemical or heat hardening to render them water-insoluble. The microspheres can be used for nasal delivery systems and the microcapsules for echocardiography.

11. Composition for nasal administration

Priority date: 5 Feb 1992
Patent numbers: PCT/GB1993/000228, CA2127805 C
Inventors: Lisbeth Illum
ABSTRACT
A composition for nasal administration of polar metabolites of opioid analgesics comprises a polar metabolite of an opioid analgesic and an absorption promoting agent. Preferred metabolites morphine-6-glucuronide and morphine-6-sulphate. A preferred absorption promoting agent is chitosan but other suitable agents include

cationic polymers, bioadhesive agents, surface active agents, fatty acids, chelating agents, mucolytic agents, cyclodextrin, microsphere preparations or combinations thereof.

12. Pharmaceutical compositions

Priority date: 13.Feb 1992
Patent numbers: GB2251188, WO9102545 A1
Inventors: Lisbeth Illum
ABSTRACT
Compositions for transmucosal delivery, e.g. intranasal, include a lysophosphatidylglycerol compound as an absorption enhancer. The preferred compounds for delivery are insulin and calcitonin.

13. Lymphatic delivery methods

Priority date: 28 Jul 1992
Patent numbers: PCT/GB1993/001596, WO1994002122 A1
Inventors: Nicola Christy, Stanley Stewart Davis, Lisbeth Illum, Moein Moghimi,
ABSTRACT
A composition for delivering an active agent to the lymphatic system comprises a plurality of colloidal particles and an active agent associated with each particle, wherein the surface of each particle has a hydrophobicity ratio as defined of less than 10, or wherein a modifying agent is adsorbed onto the surface of each particle such that the modifying agent gives an advancing contact angle as defined of less than 60° or wherein the adsorbed layer thickness as defined is less than 10 nm or the albumin uptake ratio is between 0.2 and 0.5. The composition may satisfy one or more of these requirements. Preferred modifying agents are non-ionic surfactants, in particular block copolymers containing polyethyleneglycol.

14. Lymphatic delivery composition

Priority date: 28 Jul 1992
Patent numbers: US5792475, PCT/GB93/01596 (divisional)
Inventors: Nicola Christy, Stanley Stewart Davis, Lisbeth Illum, Moein Moghimi,
ABSTRACT
A composition for delivering an active agent to the lymphatic system comprises a plurality of colloidal particles and an active agent associated with each particle, wherein the surface of each particle has a hydrophobicity ratio of less than 10 as defined by hydrophobic interaction chromatography.

15. Nasal drug delivery composition containing nicotine

Priority date: 20 May 1993
Patent numbers: PCT/GB1994/001092, CA2163089 A1
Inventors: Lisbeth Illum
ABSTRACT

The present invention provides a nasal drug delivery composition comprising nicotine or a pharmacologically-acceptable salt or derivative thereof wherein the composition is adapted to delivery a pulse of nicotine for rapid absorption and a controlled release of nicotine for subsequent sustained absorption. The controlled release phase can be achieved by providing an ion-exchange material which will form a complex with the nicotine. The ion-exchange material may be a polymeric material such as a polysaccharide, or may be in the form of bioadhesive ion-exchange microspheres. The pulse release can be achieved by overloading the ion-exchange material with nicotine so that the composition contains some excess nicotine forimmediate release and absorption. Alternatively, some nicotine may be associatedwith a non ion-exchange material which will release the nicotine immediately on contact with the nasal mucosa, for example non-ion-exchange bioadhesive microspheres.

16. A drug delivery composition for alpha-adreno receptor blocking agents

Priority date: 29 May 1993
PCT/GB1994/001158, CA2163340A1
Inventors: Nidal Faraj, Lisbeth Illum, Peter Watts

ABSTRACT

The invention provides an oral drug delivery composition comprising an .alpha.-adreno receptor blocking drug characterised in that the composition is adapted to release a first portion of the drug in the upper gastrointestinal tract and to release a second portion of the drug by sustained release in the terminal ileum and/or the colon. This composition provides a two phase release profile which maintains sufficient and steady plasma levels for therapeutic effect whilst minimising side effects by avoiding a high peak in plasma levels. The sustained release of the second and optionally the first portion of the drug is achieved by a controlled release system such as a hydrophilic gel matrix. The specific release of the second portion of the drug in the colon can be achieved by coating tablets containing the second portion with a pH or redox sensitive coating such as a polymethylmethacrylate.

17. Intranasal antimigraine composition

Priority date: 13 April 1994
Patent numbers: CN1995192535 19950410, CN1146151 (A), WO9528158 (A1)
Inventors: M K J Francois; R C A Embrechts; L Illum

ABSTRACT

The present invention relates to a composition comprising an antimigraine compound of formula (I) and chitosan, which is particularly suited for intranasal administration. Process for preparing said composition, its use as a medicine and a nasal spray device, especially a unidose nasal spray device containing said composition.

18. Intercellular Adhesion Molecule 1 (ICAM-1) and a bioadhesive

Priority date: 26 Jul 1994
Patent numbers: US20010053359 A1
Inventors: Peter Watts, Lisbeth Illum
ABSTRACT

A drug delivery composition for nasal administration is provided which comprises the antiviral agent ICAM-1 and a bioadhesive material. The bioadhesive material may be a chitosan solution, a liquid formulation comprising a polymeric material or a plurality of bioadhesive microspheres. The polymeric material is preferably gellan gum or alginate. The microspheres may comprise starch, chitosan, hyaluronic acid, or gelatin.

19. Drug delivery composition containing chitosan or derivative thereof having a defined z. potential

Priority date: 20 Aug 1994
Patent numbers: PCT/GB1995/001980, US5840341 A
Inventors: Lisbeth Illum, Peter James Watts
ABSTRACT

A drug delivery composition for administration to mucosa is provided. The composition includes a pharmacologically active compound and particles, preferably powder or microspheres, of chitosan or a chitosan derivative or salt wherein the particles are either solidified or partially cross-linked such that they have a zeta potential of +0.5 to +50 mV. Solidified particles are made by treating particles made from a water soluble chitosan salt with an alkaline agent such as sodium hydroxide in a non-acid containing water to render them insoluble.

20. Lipid vehicle drug delivery composition containing vitamin E

Priority date: 20 Jul 1995
US20020025337 A1, CA2224734A1, EP0839025A1,WO1997003651A1
Inventors: Lisbeth Illum, Simon Lawrence, Clive Washington, Peter Watts
ABSTRACT

The present invention provides a drug delivery composition comprising a lipid vehicle containing a drug and Vitamin E to enhance the solubility of the active drug in the lipid vehicle. The composition is particularly useful for drugs which are poorly soluble. The composition may be in the form of a liposome or an oil-in-water emulsion. The Vitamin E may be mixed with a pharmaceutically acceptable oil such as a marine oil or a vegetable oil.

21. Composition for enhanced uptake of polar drugs from the colon

Priority date: 8 Aug 1995
PCT/GB1996/001933, WO1997005903 A3
Inventors: Lisbeth Illum, Peter James Watts
ABSTRACT

The invention provides a drug delivery composition for colonic delivery comprising a polar drug, an absorption promoter which (a) comprises a mixture of a fatty acid having 6 to 16 carbon atoms or a salt thereof and a dispersing agent, or (b) comprises a mixture of mono/diglycerides of medium chain fatty acids and a dispersing agent, and means adapted to release the polar drug and absorption promoter in the colon following oral administration. A preferred fatty acid is capric acid or a salt thereof. Colon specific delivery can be achieved by providing the composition in a capsule, tablet or pellet which is coated with a material which dissolves in the small intestine or is degraded by the conditions in the colon.

22. Influenza vaccine compositions

Priority date: 1 Nov 1995
Patent numbers: PCT/GB1996/002680, CA2236538 C
Inventors: Steven Neville Chatfield, Lisbeth Illum
ABSTRACT
The invention provides a vaccine composition in the form of a kit comprising a first container containing an antigenic preparation comprising influenza antigen or antigens; and a second container containing an effective adjuvant amount of a chitosan. The antigenic preparation in the first container preferably comprises haemagglutinin and neuraminidase influenza antigens.

23. Vaccine compositions for intranasal administration comprising chitosan and use thereof

Priority date: 7 Dec 1995
Patent numbers: PCT/GB1996/003019, CA2237529 C
Inventors: Lisbeth Illum
ABSTRACT
There is provided vaccine compositions for intranasal administration, which compositions comprise one or more antigens and an effective adjuvant amount of a chitosan.

24. Polysaccharide microspheres for the pulmonary delivery of drugs

Priority date: 23 Mar 1996
Patent numbers: PCT/GB1997/000808, EP0895473 B1, WO1997035562A1
Inventors: Lisbeth Illum, Peter Watts
ABSTRACT
There is provided improved compositions for the delivery of pharmacological agents to the respiratory tract of a mammal to provide improved peripheral deposition and systemic uptake wherein a therapeutic agent is incorporated into a polysaccharide microparticle through a process of spray drying.

25. Composition for enhanced uptake of polar drugs from mucosal surfaces

Priority date: 6 Jul 1996
Patent numbers: PCT/GB1997/001852, WO1998001159 A3
Inventors: Lisbeth Illum, Peter James Watts
ABSTRACT
A composition for administration to a mucosal surface of a mammal comprising a non-metabolisable bile salt analogue and a therapeutic agent. Preferably the non-metabolisable bile salt analogue is a non-naturally occurring conjugate of cholic acid and an amino acid, and in particular cholylsarcosine. Preferably the therapeutic agent is a polar molecule.

26. Gene therapy delivery system for targeting to endothelia

Priority date: 10 Jul 1996
Patent numbers: PCT/GB1997/001860, WO1998001161 A3
Inventors: Lisbeth Illum
ABSTRACT
A composition comprising biodegradable microspheres that act as carriers for the delivery of DNA to the endothelial cells of a vascular bed, wherein the microspheres carry a net negative charge and to which is adsorbed positively charged particles of a smaller size, wherein such positively charged particles comprise a conjugate of DNA and a cationic compacting agent.

27. Compositions suitable for delivery of genes to epithelial cells

Priority date: 10 Jul 1996
Patent numbers: PCT/GB1997/001859, WO1998001160 A3
Inventors: Lisbeth Illum
ABSTRACT
A composition comprising a particulate complex of chitosan and DNA wherein the complex is between 10 nm and 1 μm in size and carries a surface charge.

28. Chitosan-gelatin a microparticles

Priority date: 14 Jan 1997
Patent numbers: PCT/GB1998/000108, CA2275717 C
Inventors: Peter James Watts, Lisbeth Illum
ABSTRACT
There is provided a pharmaceutical composition for use in the improved up--take of therapeutic agents across mucosal surfaces which comprises a mixture of chi-tosan and a type A, cationic, gelatin, together with a therapeutic agent. The composition is preferably in the form of microparticles, such as microspheres.

29. Improved delivery of drugs to mucosal surfaces

Priority date: 18 Apr 1997
Patent numbers: CA2282506 A1, US20070110677 A1
Inventors: Lisbeth Illum, Peter James Watts
ABSTRACT
Liquid pharmaceutical compositions for administration to a mucosal surface, comprising a therapeutic agent and a pectin with a low degree of esterification are

described. Such compositions gel, or can be adapted to gel, at the site of application in the absence of an extraneous source of divalent metal ions

30. Gastroretentive controlled release microspheres for improved drug delivery

Priority date: 24 May 1997
Patent numbers: PCT/GB1998/001513, EP0984774 B1, WO1998052547A1
Inventors: Lisbeth Illum, He PING
ABSTRACT
There is provided a drug delivery composition for the controlled release of an active agent in the stomach environment over a prolonged period of time which comprises a microsphere comprising an active ingredient in the inner core of the microsphere and (i) a rate controlling layer of a water insoluble polymer and (ii) an outer layer of a bioadhesive agent in the form of a cationic polymer.

31. Controlled release microsphere delivery system

Priority date: 9 Sep 1997
Patent numbers: PCT/GB1998/002692, WO1999012549 A3
Inventors: Cheng Yu-Hui, Davis Stanley Stewart, Illum Lisbeth, Watts Peter James
ABSTRACT
There is provided a pharmaceutical composition comprising polymeric microparticles including a drug and a fatty acid, which composition may be adapted to provide a release rate of drug that is approximately linear with time, and to provide no significant burst effect.

32. Compositions for nasal administration

Priority date: 2 Dec 1997
Patent numbers: PCT/GB1998/003572, CA2312839 C
Inventors: Lisbeth Illum, Peter James Watts
ABSTRACT
There is provided a composition for the nasal delivery of a drug suitable for the treatment of erectil dysfunction to a mammal wherein the composition is adapted to provide an initial rise in plasma level followed by a sustained plasma level of the drug.

33. Novel dosage form

Priority date: 22 Jan 1998
PCT/GB1999/000193, WO1999037290 A1, CA2318257A1, EP1059918A1
Inventors: Lisbeth Illum, Peter James Watts
ABSTRACT
The present invention provides an orally administrable pharmaceutical dose unit of a size greater than 7 mm comprising a drug and an outer coating which is adapted to prevent release of said drug into the stomach or the small intestine when the pharmaceutical dose unit is in the presence of food. The present invention further provides an orally administrable pharmaceutical dose unit of a size greater than 7 mm

which comprises a drug and an outer coating wherein the coating is made of a material that is soluble at pH values below 5.0 and is adapted to provide a separation of the pharmaceutical dose unit from co-administered food material. Preferably, the pharmaceutical dose unit is in the form of a coated tablet or capsule. Conveniently, the outer coating is a polymer. In addition, the invention relates to a method for separating an orally administrable pharmaceutical dose unit from co-administered food, and to the use of said pharmaceutical dose units in medicine.

34. O/W emulsion comprising an hydroxylated oil

Priority date: 24 Oct 1998
Patent numbers: WO0024373 (A1) ZA200102690 (A) US2001055569 (A1), PCT/GB1999/003489
Inventors: Stanley Stewart Davis, Lisbeth Illum
ABSTRACT

The present invention provides a composition comprising an oil-in-water emulsion and a drug dissolved in the emulsion. The oil phase comprises a hydroxylated oil, particularly a hydroxylated vegetable oil. The preferred hydroxylated vegetable oil is castor oil.

35. Water solubility

Priority date: 13 Oct 1998
Patent numbers: US20010051613 A1, PCT/GB1999/003396, WO0021510
Inventors: Lisbeth Illum, Peter Watts, Yu-Hui Cheng
ABSTRACT

The present invention provides a composition comprising (i) fexofenadine or a pharmaceutically acceptable salt thereof and (ii) a pharmaceutical excipient that increases the solubility of the fexofenadine or salt in water. The pharmaceutical excipient is preferably a cyclodextrin.

36. Composition for the administration of a D1-agonists

Priority date: 31 Dec 1998
Patent numbers: US6310089
Inventors: Peter James Watts, Lisbeth Illum
ABSTRACT

A composition for intranasal administration comprising a full or partial D!-agonist of the dopamine receptor

37. Nucleic acid or oligonucleotide and a positively charged, aminated ethylene oxide-propylene oxide block copolymer

Priority date: 2 Mar 1999
Patent numbers: US20020044972 A1
Inventors: Stanley Davis, Lisbeth Illum, Burhan Daudali
ABSTRACT

A composition is provided including: (a) a nucleic acid or an oligonucleotide; and (b) a block copolymer containing a hydrophilic block that carries functional groups that provide the block with a positive charge. These compositions may be used to deliver a nucleic acid or an oligonucleotide to a cell.

38. Compound

Priority date: 20 Oct 1999
Patent numbers: PCT/GB2000/004003, CA2388395 C
Inventors: Lisbeth Illum, Peter Watts, Alan Smith, Ian Lafferty
ABSTRACT
The methane sulphonate salt of morphine and compositions thereof are described. Also described is a composition adapted for nasal delivery comprising a methane sulphonate salt of an opioid analgesic

39. Oil-in-water emulsions comprising a benzodiazepine drug

Priority date: 30 June 2001
Patent numbers: WO03004015, GB20010016107
Inventors: Yu-Hui Cheng, Lisbeth Illum, John Bond, Peter Watts
ABSTRACT
There is provided oil-in-water emulsion compositions comprising a benzodiazepine drug, such as midazolam, that is dissolved in an oil phase that comprises 1 to 35% (w/w) vitamin E.

40. Pharmaceutical treatment process using chitosan or derivative thereof

Priority date: May 13, 2003
Patent numbers: US20100203119 A1
Inventors: Michael Leane, Alan Smith, Lisbeth Illum
ABSTRACT
The present invention provides a solid composition for oral administration comprising:

- (i) a drug compound;
- (ii) chitosan or a derivative thereof or a salt of chitosan or salt of a derivative of chitosan; and
- (iii) an organic acid.
  Preferably the drug compound is a polar molecule having a molecular weight of 1 KDa or less, a peptide, a protein or a polysaccharide. The compositions of the invention provide enhance absorption of the drug compound.

41. Chitosan containing solution

Priority date: 21 Feb 2004
Patent numbers: PCT/GB2005/000592, WO2005079749 A3

Inventors: Ann Margaret Dyer, Patricia Pastor, Lisbeth Illum
ABSTRACT
The invention provides a composition comprising (i) chitosan, a sait or derivative thereof or a sait of a derivative thereof, (ii) a polyol-phosphate or sugar-phosphate salt, (iii) a plasticizer, and (iv) a therapeutic agent. Typically, the composition is a solution or suspension at ambient temperature but forms a gel at physiological temperatures.

42. Intranasal administration of active agents to the central nervous system

Priority date: 31 Oct 2007
Patent numbers: PCT/US2008/081722, WO2009058957 A3, EP2207802A2
Inventors: Johanna Bentz, Beth Hill, Lisbeth Illum
ABSTRACT
Pharmaceutical compositions and methods for delivering a polypeptide to the central nervous system of a mammal via intranasal administration are provided. The polypeptide can be a catalytically active protein or an antibody, antibody fragment or antibody fragment fusion protein. The polypeptides are formulated with one or more specific agents.

43. Pharmaceutical composition containing surface-coated microparticles

Priority date: Jul 1, 2008
Patent numbers: PCT/JP2009/062053, WO2010001932 A1
Inventors: Katsuyuki Okubo, 大久保　勝之, Chieko Kitaura, 千枝子 北浦, Kenjiro Minomi, 憲二郎 味呑, Elizabeth Pearson, ピアソン、エリザベス, Clive J. Roberts, ジェイ．　ロバーツ、クライブ, Martyn C. Davies, シー．デイビス、マーティン, Snjezana Stolnik-Trenkic, ストルニックートレンキック、スネジャナ, Lisbeth Illum, イラム、リスベス,
ABSTRACT
Disclosed is a pharmaceutical composition which can be used for the administration of a low-molecular-weight substance or a high-molecular-weight substance such as a peptide and a protein by a means other than injection with high efficiency. Also disclosed is a method for producing the composition. Specifically disclosed is a pharmaceutical composition for transmucosal administration, which comprises (a) a substance which can carry a positive or negative electrical charge at a given pH value, (b) pharmaceutically acceptable microparticles, and (c) a pharmaceutically acceptable surface-coating polymer which can be electrically charged at the above-mentioned pH value. In the composition, the surface-coating polymer coats the surfaces of the microparticles, and the substance is immobilized on the surfaces of the microparticles through the surface-coating polymer. In the composition, the microparticles interact non-covalently with the surface-coating polymer and, at the same time, the surface-

coating polymer interacts electrostatically with the substance, thereby forming a complex.

44. Process for preparing microparticles

Priority date: 11 Jul 2008
Patent numbers: PCT/GB2009/001711, WO2010004287 A3
Inventors: Andrew Naylor, Andrew Lester Lewis, Lisbeth Illum,
ABSTRACT
A process for preparing microparticles comprising a biologically active material and a polymer and having a mean particle size expressed as the volume mean diameter (VMD) of from 10 to 500 μm, wherein the biologically active material is substantially insoluble in the polymer, which process comprises: a. contacting a mixture of the biologically active material or a precursor thereof, the polymer or a precursor thereof and a processing aid with a supercritical fluid which is capable of swelling the polymer under temperature and pressure conditions necessary to maintain the fluid in a supercritical state; b. allowing the supercritical fluid to penetrate and liquefy the polymer, whilst maintaining the temperature and pressure conditions so that the fluid is maintained in a supercritical state; c. releasing the pressure to precipitate microparticles comprising the biologically active agent and the polymer.

45. Composition

Priority date: 11 Jul 2008
Patent numbers: PCT/GB2009/001727, CA2730325 A1
Inventors: Andrew Naylor, Andrew Lester Lewis, Lisbeth Illum
ABSTRACT
The invention provides a composition comprising (i) a somatotrophic hormone, (ii) a biodegradable polymer component, and (iii) a release modifier A process for preparing, and the use of such a composition are also provided

46. Absorption of therapeutic agents across mucosal membranes or the skin

Priority date: Sep 12, 2008
Patent numbers: US20140072588 A1
Inventors: Lisbeth Illum, Faron Michael Jordan, Andrew Lester Lewis
ABSTRACT
Absorption of a therapeutic agent across a mucosal membrane or the skin can be enhanced using an absorption enhancer comprising a hydroxy fatty acid ester of polyethylene glycol.

47. Improvements in the absorption of therapeutic agents across mucosal membranes or the skin

Priority date: Sep 12, 2008
Patent numbers: PCT/GB2009/051188, CA2734381 A1
Inventors: Lisbeth Illum, Faron Michael Jordan, Andrew Lester Lewis
ABSTRACT

Absorption of a therapeutic agent across a mucosal membrane or the skin can be enhanced using an absorption enhancer comprising a hydroxy fatty acid ester of polyethylene glycol. This invention relates to the enhancement of absorption of therapeutic agents across mucosal membranes or the skin. In particular, the invention concerns the use of a hydroxy fatty acid ester of polyethylene glycol for enhancing transmucosal or transdermal delivery of a pharmaceutically active therapeutic agent. The invention also relates to compositions and methods for administration of a pharmaceutically active therapeutic agent to a mucosal membrane or the skin. Background of the Invention Administration of therapeutic agents to the mucosa is well known in the art. Therapeutic agents can be delivered to the nasal cavity, the vaginal cavity, pulmonarily, buccally, sublingually, rectally, orally and to the eye for the local treatment of diseases or for a systemic effect.

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1. S S Davis, L Illum, J G McVie & E Tomlinson (Eds): Microspheres and Drug Therapy, Elsevier Biomedical Press, Amsterdam, 1984.

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5. Editor Special issue J. Drug Targeting in honour of S. S. Davis, 2010

6. Editor Special issue Drug Delivery and Translational Research on Nasal Drug Delivery in collaboration with Prof. Elka Touitou, 2012

EXHIBIT B

PRIOR TESTIMONY OF LISBETH ILLUM, PH.D.

Cephalon Inc. et al. v. Mylan Pharmaceuticals Inc. et al., 1:11-cv-00164-SLR (D. Del. 2013) (testimony for Plaintiffs by deposition and at trial)

Mylan Pharmaceuticals Inc. et al. v. Warner Chilcott Public Limited Company et al., 2:12-cv-03824-PD (E.D. Pa. 2015) (testimony for Defendants by deposition)

AstraZeneca Pharmaceuticals LP et al. v. Sandoz Inc. et al., 14-cv-03547-RMB-KMW (consolidated) (D.N.J. complaint filed June 3, 2014) (testimony for Plaintiffs by deposition)

Forest Laboratories, LLC et al. v. Sigmapharm Laboratories, LLC, 14-cv-01119-SLR-SRF (D. Del. 2014) (testimony for Plaintiffs by deposition)

EXHIBIT C

MATERIALS CONSIDERED BY LISBETH ILLUM, PH.D. FOR DECLARATION OF LISBETH ILLUM Ph.D. IN SUPPORT OF PATENT OWNER'S PRELIMINARY RESPONSE

Exhibit	Description
2020	V. Craig Jordan, *The Strategic Use of Antiestrogens to Control the Development and Growth of Breast Cancer*, 70 CANCER 977 (Supp. 1992) ("Jordan Supp. 1992")
2042	AACR Journals Online
2043	Declaration of Sandra McLeskey, Ph.D. (Oct. 1, 2014) ("McLeskey Declaration")
2044	Innovative Research of America, Time Release Pellets for Biomedical Research, 2014 Product Catalog ("Innovative Research")
2045	PHYSICIAN'S DESK REFERENCE, 53rd ed., 3425-28 (1999) ("PDR 1999 Nolvadex®")
2046	PHYSICIAN'S DESK REFERENCE, 53rd ed., 2025-28 (1999) ("PDR 1999 Femara®")
2051	Adam Cohen et al., *What does the investigator need to know about the drug?*, *in* A GUIDE TO CLINICAL DRUG RESEARCH, Ch. 3 (1995) ("Cohen")
2052	Stephanie Sweetana et al., *Solubility Principles and Practices for Parenteral Drug Dosage Form Development*, 50 PDA J. PHARM. SCI. & TECH. 330 (1996) ("Sweetana")
2054	Suzanne C. Beyea et al., *Administering IM Injections The Right Way*, 96 A. J. NURSING 34 (1996) ("Beyea")
2079	Wolfgang Klement, *Pain, Irritation, and Tissue Damage with Injections*, *in* INJECTABLE DRUG DEVELOPMENT: TECHNIQUES TO REDUCE PAIN & IRRITATION, Ch. 2 (Pramod K. Gupta et al. eds., 1999) ("Gupta Ch. 2")
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")
2081	Louis J. Ravin et al., *Preformulation*, *in* REMINGTON'S PHARMACEUTICAL SCIENCES, Ch. 75 (Alfonso Gennaro ed., 18th ed. 1990) ("Remington's Ch. 75")
2082	P. York, *The design of dosage forms*, *in* PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN, Ch. 1 (M.E. Aulton ed., 1988) ("Aulton Ch. 1")

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Exhibit	Description
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2086	Michael J. Groves, *Perspectives on the Use and Essential Requirements of Parenteral Products, in* PARENTERAL TECHNOLOGY MANUAL, Ch. 2 (2d ed. 1989) ("Groves Ch. 2")
2087	Michael J. Akers, *Challenges in the Development of Injectable Products*, *in* INJECTABLE DRUG DEVELOPMENT: TECHNIQUES TO REDUCE PAIN & IRRITATION, Ch. 1 (Pramod K. Gupta et al. eds., 1999) ("Gupta Ch. 1")
2089	VIDAL® 1999 LE DICTIONNAIRE (75th ed. 1999) ("Vidal 1999")
2090	VIDAL® 1997 LE DICTIONNAIRE (73rd ed. 1997) ("Vidal 1997")
2091	ABPI Compendium of Data Sheets and Summaries of Product Characteristics (1999-2000) ("ABPI 1999-2000")
2092	Declaration of Laird Forrest, Ph.D. in Support of Petition for *Inter Partes Review*, *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, Case IPR2016-01325, Ex. 1003 (P.T.A.B. June 29, 2016) ("Forrest Mylan Decl.")
2093	Edward Rudnic et al., *Oral Solid Dosage Forms*, *in* REMINGTON'S PHARMACEUTICAL SCIENCES, Ch. 89 (Alphonso R. Gennaro ed., 18th ed. 1990) ("Remington's Ch. 89")
2094	J.I. Wells et al., *Preformulation*, *in* PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN, Ch. 13 (M.E. Aulton ed., 1988) ("Aulton Ch. 13")
2095	Howard C. Ansel et al., *Capsules and Tablets, in* PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS, Ch. 7 (7th ed. 1999) ("Ansel Ch. 7")
2096	Howard C. Ansel et al., *Solutions, in* PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS, Ch. 12 (7th ed. 1999) ("Ansel Ch. 12")
2097	Howard C. Ansel et al., *Disperse Systems, in* PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS, Ch. 13 (7th ed. 1999) ("Ansel Ch. 13")
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Exhibit	Description
2099	B.E. Jones et al., *Capsules*, *in* PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN, Ch. 19 (M.E. Aulton ed., 1988) ("Aulton Ch. 19")
2100	Shen Gao et al., *In vitro percutaneous absorption enhancement of a lipophilic drug tamoxifen by terpenes*, 51 J. CONTROLLED RELEASE 193 (1998) ("Gao 1998")
2101	THE MERCK INDEX (12th ed. 1996) ("Merck Index")
2102	Howard C. Ansel et al., *Transdermal Drug Delivery Systems*, *in* PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS, Ch. 10 (7th ed. 1999) ("Ansel Ch. 10")
2103	Sol Motola et al., *Preformulation Research of Parenteral Medications*, *in* 1 PHARMACEUTICAL DOSAGE FORMS: PARENTERAL MEDICATION, Ch. 4 (Kenneth E. Avis et al. eds., 2d ed. 1992) ("Avis Ch. 4")
2104	J.B. Kayes, *Disperse Systems*, *in* PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN, Ch. 6 (M.E. Aulton ed., 1988) ("Aulton Ch. 6")
2105	Arturo G. Porras et al., *Pharmacokinetics of Alendronate*, 36 CLIN. PHARMACOKINET. 315 (1999) ("Porras")
2106	Howard C. Ansel et al., *Parenterals, in* PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS, Ch. 14 (7th ed. 1999) ("Ansel Ch. 14")
2107	Richard J. Duma et al., *Parenteral Drug Administration: Routes, Precautions, Problems, Complications, and Drug Delivery Systems*, *in* 1 PHARMACEUTICAL DOSAGE FORMS: PARENTERAL MEDICATION, Ch. 2 (Kenneth E. Avis et al. eds., 2d ed. 1992) ("Avis Ch. 2")
2109	George N. Wade et al., *ICI 182,780 antagonizes the effects of estradiol on estrous behavior and energy balance in Syrian hamsters*, 265 AM. J. PHYSIOL. R1399 (1993) ("Wade 1993")
2110	Scott G. Lundeen et al., *Characterization of the Ovariectomized Rat Model for the Evaluation of Estrogen Effects on Plasma Cholesterol Levels*, 138 ENDOCRINOLOGY 1552 (1997) ("Lundeen 1997")
2112	Robert G. Strickley, *Parenteral Formulations of Small Molecules Therapeutics Marketed in the United States (1999)—Part I*, 53 PDA J. PHARM. SCI. & TECH. 324 (1999) ("Strickley I")

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Exhibit	Description
2113	Sol Motola, *Biopharmaceutics of Injectable Medication*, *in* 1 PHARMACEUTICAL DOSAGE FORMS: PARENTERAL MEDICATION, Ch. 3 (Kenneth E. Avis et al. eds., 2d ed. 1992) ("Avis Ch. 3")
2114	J. Zuidema et al., *Release and absorption rates of intramuscularly and subcutaneously injected pharmaceuticals (II)*, 105 INT'L J. PHARMACEUTICS 189 (1994) ("Zuidema 1994")
2115	Berton E. Ballard, *Biopharmaceutical Considerations in Subcutaneous and Intramuscular Drug Administration*, 57 J. PHARM. SCI. 357 (1968) ("Ballard 1968")
2116	Koichiro Hirano et al., *Studies on the Absorption of practically Water-insoluble Drugs following Injection. I. Intramuscular Absorption from Water-immiscible Oil Solutions in Rats*, 29 CHEM. PHARM. BULL. 519 (1981) ("Hirano 1980")
2117	D.J. Greenblatt et al., *Absorption of Oral and Intramuscular Chlordiazepoxide*, 13 EUR. J. CLIN. PHARMACOL. 267 (1978) ("Greenblatt 1978")
2118	John T. Litchfield, *Forecasting Drug Effects in Man from Studies in Laboratory Animals*, 177 J. AM. MED. ASS'N 34 (1961) ("Litchfield 1961")
2120	A. Lifschitz et al., *Ivermectin disposition kinetics after subcutaneous and intramuscular administration of an oil-based formulation to cattle*, 86 VET. PARASITOLOGY 203 (1999) ("Lifschitz 1999")
2121	E. Lavy et al., *Pharmacokinetics of clindamycin HCl administered intravenously, intramuscularly, and subcutaneously to dogs*, 22 J. VET. PHARMACOL. THER. 261 (1999) ("Lavy 1999")
2122	C. H. U. Chu, *A Study of the Subcutaneous Connective Tissue of the Mouse, with Special Reference to Nuclear Type, Nuclear Division and Mitotic Rhythm*, 138 ANATOMICAL RECORD 11 (1960) ("Chu 1960")
2123	Larry A. Gatlin et al., *Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parenteral Products*, *in* INJECTABLE DRUG DEVELOPMENT: TECHNIQUES TO REDUCE PAIN & IRRITATION, Ch. 17 (Pramod K. Gupta et al. eds., 1999) ("Gupta Ch. 17")

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Exhibit	Description
2124	U.S. Patent No. 3,164,520, Raymond Huber, *Injectable steroid compositions containing at least 75% benzyl benzoate* ("'520 Patent")
2125	Affidavit of Internet Archive (Oct. 2016) ("Affidavit of Internet Archive")
2126	PHYSICIAN'S DESK REFERENCE, 53rd ed., 3404-6 (1999) ("PDR 1999 Arimidex®")
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2128	M.R. Skougaard et al., *Comparative effectiveness of intraperitoneal and intramuscular ^{3}H-TDR injection routes in mice*, 45 EXP. CELL RES. 158 (1966) ("Skougaard")
2129	Harry Eagle et al., *The serum concentration of penicillin G in mice, rabbits, and men after its intramuscular injection in aqueous solution*, 57 J. BACTERIOL. 119 (1949) ("Eagle")
2130	H.B. Levine et al., *Immunologic impairment in mice treated intravenously with killed Coccidioides immitis spherules: suppressed response to intramuscular doses*, 97 J. IMMUNOL. 297 (1966) ("Levine")
2131	A. Yarinsky et al., *The Uptake of Tritiated Hycanthone by Male and Female Schistosoma mansoni Worms and Distribution of the Drug in Plasma and Whole Blood of Mice following a Single Intramuscular Injection*, 42 BULL. WORLD HEALTH ORGAN. 445 (1970) ("Yarinsky")
2132	Werner Lowenthal, *Metrology and Calculation*, *in* REMINGTON'S PHARMACEUTICAL SCIENCES, Ch. 9 (Alphonso R. Gennaro ed., 18th ed. 1990) ("Remington's Ch. 9")
2133	Declaration of Ronald J. Sawchuk, Ph.D. in Support of Patent Owner's Preliminary Response in *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, Case IPR2016-01325, Ex. 2003 (P.T.A.B. Oct. 5, 2016) ("Sawchuk Mylan Decl.")
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")
2135	Declaration of Lisbeth Illum, Ph.D. in Support of Patent Owner's Preliminary Response in *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, Case IPR2016-01325, Ex. 2001 (P.T.A.B. Oct. 6, 2016) ("Illum Mylan Decl.")

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Exhibit	Description
2136	Declaration of John F.R. Robertson, M.D. in Support of Patent Owner's Preliminary Response in *Mylan Pharmaceuticals Inc. v. AstraZeneca AB*, Case IPR2016-01325, Ex. 2002 (P.T.A.B. Oct. 6, 2016) ("Robertson Mylan Decl.")
2157	Arlene McDowell et al., *Anatomy and Physiology of the Injection Site: Implications for Extended Release Parenteral Systems*, *in* LONG ACTING INJECTIONS & IMPLANTS, Ch. 4 (Jeremy C. Wright et al. eds., 2012) ("Wright Ch. 4")
2158	Robert G. Strickley, *Parenteral Formulations of Small Molecules Therapeutics Marketed in the United States (1999) Part II*, 54 PDA J. PHARMACEUTICAL SCI. & TECH. 69 (2000) ("Strickley II")
2159	Celine Martel et al., *Comparison of the Effects of the New Orally Active Antiestrogen EM-800 with ICI 182 780 and Toremifene on Estrogen-Sensitive Parameters in the Ovariectomized Mouse*, 139 ENDOCRINOLOGY 2486 (1998) ("Martel 1998")
2160	Hung T. Huynh et al., *Insulin-like Growth Factor I Gene Expression in the Uterus Is Stimulated by Tamoxifen and Inhibited by the Pure Antiestrogen ICI 182780*, 53 CANCER RES. 5585 (1993) ("Huynh 1993")
2161	S. Chatterjee et al., *Contrasting Action of Antiestrogen (ICI-182780) for Preventing Initiation of Embryo Implantation by Estradiol or Epidermal Growth Factor (EGF)*, 53 LIFE SCIENCES 1625 (1993) ("Chatterjee")
2162	Leon Shargel et al., *Biopharmaceutic Considerations in Drug Product Design*, *in* APPLIED BIOPHARMACEUTICS & PHARMACOKINETICS, Ch. 6 (4th ed. 1999) ("Applied Biopharmaceutics")
2163	Vincent A. Dipippo et al., *Tamoxifen and ICI 182,780 Interactions with Thyroid Hormone in the Ovariectomized-Thyroidectomized Rat*, 281 J. PHARMACOL. & EXP. THER. 142 (1997) ("Dipippo")
2164	Jean D. Sibonga et al., *Effect of the High-Affinity Estrogen Receptor Ligand ICI 182,780 on the Rat Tibia*, 139 ENDOCRINOLOGY 3736 (1998) ("Sibonga 1998")
2165	H.Y. Al-Matubsi et al., *Oestrogenic effects of ICI 182,780, a putative anti-oestrogen, on the secretion of oxytocin and prostaglandic $F_{2\alpha}$ during oestrous cycle in the intact ewe*, 51 ANIMAL REPROD. SCI. 81 (1998) ("Al-Matubsi")