UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.

Petitioner

v.

ASTRAZENECA AB

Patent Owner

Case IPR2016-01325

U.S. Patent 8,329,680

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 (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. In addition, I was the founder and Managing Director of Phaeton Research Ltd. (2003-2005) and the CEO of Critical Pharmaceuticals Ltd, a drug delivery company based in BioCity in Nottingham from 2007-2011. I am also Director of Eurocage Ltd., a drug delivery consultancy company.

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, 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 ~ 57. I have co-edited four books related to drug delivery, drug therapy, and drug transport. I am the inventor on nearly fifty patent family applications on novel drug delivery systems.

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. I have lectured 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 Mylan Pharmaceuticals Inc. filed a Petition requesting Inter Partes Review ("Petition") of U.S. Patent No. 8,329,680 (the '680 Patent"), which issued to John R Evans and Rosalind U Grundy on December 11, 2012 and is assigned to AstraZeneca AB. I have reviewed the Petition, and understand that it alleges that claims 1-20 of the '680 Patent are unpatentable over McLeskey (Ex. 1005) and, alternatively, over the combination of Howell 1996 (Ex. 1006) with McLeskey (Ex. 1005).

IV) MY OPINIONS AND THEIR BASES

13. I have been asked to give my opinion on whether Mylan has shown a reasonable likelihood that a person of ordinary skill in the art ("POSA") would understand claims 1-20 of the '680 Patent to be rendered obvious by: (1) McLeskey (Exhibit 1005); or (2) the combination of Howell 1996 (Ex. 1006) with McLeskey (Ex. 1005).

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 '680 Patent claims priority.

15. For the reasons explained below, in my opinion, Mylan has not shown that there is a reasonable likelihood that it would prevail in an *inter partes* review of claims 1-20 of the '680 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 ¶ 24, below.

VI) THE '680 PATENT SPECIFICATION AND CLAIMS

17. I have been informed that the priority date of the '680 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 '680 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 '680 Patent "surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 $mgml^{-1}$." Ex. 1001 at 6:9-13. 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 6:13-18. 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 9:42-44.

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 8:59-60. The specification of the '680 Patent states that "[b]y use of the term 'therapeutically significant levels' we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient." Ex. 1001 at 9:24-27. Further, the specification describes "extended release" as "at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved." Ex. 1001 at 9:29-31. 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 10:49-51.

21. Independent claim 1 of the '680 Patent is provided below.

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

22. Independent claim 9 of the '680 Patent is provided below.

> 9. A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment a formulation consisting essentially of:
>
> about 50 $mgml^{-1}$ of fulvestrant;
>
> about 10% w/v of ethanol
>
> about 10% w/v of benzyl alcohol;
>
> about 15% w/v of benzyl benzoate; and

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

23. Dependent claims limit claims 1 and/or 9 to a method: wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$ (claims 2 and 10); wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer (claims 3, 6, 11, and 14); wherein the method comprises administering intramuscularly to a human in need of such treatment 5 mL of the formulation (claims 4, 7, 12, and 15); wherein the method further comprises once monthly administration of the formulation (claims 5, 8, 13, and 16); wherein the formulation is administered in a divided dose (claims 17-20).

VII) PERSON OF ORDINARY SKILL IN THE ART

24. 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 patents-in-suit 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.

25. As considered from the perspective of the formulator member of that team, the inventions of the asserted claims are novel, and not obvious, for the following reasons.

VIII) LEGAL PRINCIPLES

26. 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.

27. I understand that to institute an Inter Partes Review Mylan 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 IPR is instituted, Mylan must show unpatentability by a preponderance of the evidence, and preponderance of the evidence means "more probable than not."

28. 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.

29. 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."

30. 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.

31. 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.

32. 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

33. In independent claims 1 and 9, the term "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks" is a claim limitation entitled to patentable weight. Independent claims 1 and 9 do 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 claims 1 and 9 to an amount of fulvestrant that achieves and maintains 2.5 $ngml^{-1}$ for at least four 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.

34. The formulator would understand "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks" to mean that the blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ is achieved and maintained for at least four weeks. The plain meaning of the words "achieves" and "at least" indicate to the

formulator that the patient's blood plasma level must remain at or above 2.5 or 8.5 for the entire specified time period. 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. 1011 (Order by Judge Bumb of the District of New Jersey).

35. 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 5:54-58. 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 9:42-24. Thus, the inventors faced the problem not only of dissolving a sufficient amount of fulvestrant in a formulation but also determining 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.

36. 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 6:9-12. 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 8:59-60. 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 10:49-51.

37. Despite Dr. Forrest's claims, *see* Ex. 1003 at ¶¶ 40, the blood plasma limitations of the '680 Patent, including the term "wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least four weeks," are critical to the invention, as discussed further below. In addition, Dr. Forrest provides no explanation or support for reading an average concentration limitation into the claims. *See* Ex. 1003 at ¶ 42. Indeed, there is no support in the claims or specification for such an interpretation.

X) STATE OF THE RELEVANT ART

A) Formulation Background

38. "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.

39. 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. 2083 (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

40. The skilled formulator would know that the release profile of a drug from the formulation and its absorption into the blood stream are critical factors influencing the action of the drug on the patient. Ex. 2083 (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.").

41. 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.

42. The inventors surprisingly discovered a treatment method that combined a specific pharmacokinetic profile (fulvestrant blood plasma levels 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 four 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

43. 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.

44. 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.

45. "Drugs may be administered by a variety of dosage forms and routes of administration." Ex. 2083 (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. 2083 (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.

46. 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. 2083 (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. 2085 (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.").

47. 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. 2083 (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.

48. 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.

49. 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 been previously used in approved commercial products. *See* Ex. 2088 (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. 1043 (Powell) (listing over 140 excipients used in marketed parenteral formulations)

XI) REFERENCES CITED IN THE PETITION AND FORREST DECLARATION

50. In the Petition, Mylan selects a specific and limited set of references, all describing studies with fulvestrant and, in one case, other steroids, as showing the scope of prior art at the time of the invention. Petition at 18-28. 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 Forrest 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.

51. 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 ¶¶ 139-143, 180-181), there were many experimental formulations of fulvestrant known in the art, other than those discussed by Dr. Forrest. Dr. Forrest ignores the broad range of disclosures in the art; instead, using knowledge of the inventions' formulation, he selects, without providing any reason or motivation, a short list of references closest to the claimed inventions. Ex. 1003 at ¶¶ 60-92.

A) McLeskey (Ex. 1005)

52. 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. 1005 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. 1005 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. 1005 at 1-2.

53. In putting forward the McLeskey reference, Dr. Forrest totally ignores the negative findings of the study. In fact, the title of McLeskey declares that the tumors studied were "Cross-Resistan[t] *in Vivo* to the Antiestrogen ICI 182,780." Ex. 1005 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. 1005 at 1. And, McLeskey concluded that ICI 182,780 was a "treatment failure." Ex. 1005 at 10. Dr. Forrest does not explain why the skilled artisan would prefer McLeskey over other references that did show fulvestrant activity. *See, e.g.*, Ex. 1007 (Dukes 1989) at 9 ("[A]t all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen."); Ex. 1008 (Wakeling 1991) at 6 (reporting "excellent antiuterotropic action achieved without affecting body weight and gonadotropin secretion").

54. Dr. Forrest describes McLeskey as "the type of publication the ordinarily skilled artisan would look to in order to effectively solubilize a drug." Ex. 1003 at ¶ 64. Dr. Forrest cites absolutely ***no support*** for this claim. To the contrary, if McLeskey contained solubility information on fulvestrant, Dr. Forrest would not have needed to include the section of his declaration that attempted to show "that the Formulation in McLeskey was a Solution." Ex. 1003 at ¶¶ 74-76. In that section, Dr. Forrest cites to ***other*** fulvestrant publications, not McLeskey, for solubility information. Ex. 1003 at ¶ 75. For the same reason, the skilled artisan would not have focused on McLeskey in order to obtain fulvestrant solubility information. Furthermore, if the aim, according to Dr. Forrest, was to find a formulation similar to Howell 1996, neither Howell 1995 nor Howell 1996 disclose whether the long acting castor oil-based formulation is a solution or a suspension formulation. Howell is silent on this point.

55. In fact, 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. 1005 at 2. Thus, 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.

56. In order to argue McLeskey is relevant art, Dr. Forrest focuses on the broad group of publications "that administer drug formulations to a living organism." Ex. 1003 at ¶ 64. But, a PubMed search for publications that mention fulvestrant reveals over 250 hits by 2000. Dr. Forrest's criteria of administering fulvestrant to "a living organism" fails to distinguish McLeskey from the vast majority of other fulvestrant publications. In fact, many of the references cited by Dr. Forrest administer fulvestrant to "living organisms" but use different formulations than that of McLeskey. *See* Ex. 1007 (Dukes 1989) at 9 (castor oil with benzyl alcohol), Ex. 1008 (Wakeling 1991) at 2 (arachis oil), Ex. 1009 (Wakeling 1992) at 2 (arachis oil), Ex. 1013 (O'Regan 1998) at 2 (peanut oil), Ex. 1027 (DeFriend 1994) at 2 (propylene glycol).

57. Dr. Forrest claims that all publications administering fulvestrant to "rodents, primates, and dogs" would be "highly relevant to the formulation of that drug in a human in the clinical setting." Ex. 1003 at ¶ 64. On the contrary, a skilled formulator would recognize that the drug formulations in McLeskey were not suitable for human use. For example, McLeskey used "tamoxifen pellets" from Innovative Research of America, which are a research formulation only. Ex. 2044 (Innovative Research) at 9 ("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, also 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. 2047 (Santen) at 8.

58. Dr. Forrest next argues that "Zeneca Pharmaceuticals (predecessor to AstraZeneca) first provided Dr. McLeskey with fulvestrant in a solid form," and "then provided McLeskey with fulvestrant preformulated." Ex. 1003 at ¶ 66. However, McLeskey is completely silent on the order in which Zeneca provided the fulvestrant material. In any case, no preference is expressed for one fulvestrant formulation over the other; in fact, it is clear from the paper, and in particular Figure 1, that the peanut oil and castor oil formulations were treated as interchangeable for the purposes of the research study. Ex. 1005 at 2, 5.

59. 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.

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

60. Dr. Forrest incorrectly claims that McLeskey discloses the "exact excipients and exact formulation" of claims 1 and 9 of the '680 patent. Ex. 1003 at ¶¶ 107, 134; *see also* Ex. 1003 at ¶¶ 15, 138, 176. 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. 1005 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.

61. 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%

62. The reference that Dr. Forrest cites in support of his argument, itself supports that liquid components are typically described in % v/v. 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. 1021 (Remington's Ch. 9) at 6.

63. Dr. Forrest argues that "[t]he POSA would have understood that the unit or percent basis should be determined based on the character of the active pharmaceutical ingredient." Ex. 1003 at ¶ 71. He cites no support for this, and the art showed otherwise. The excipients in the description of the formulation in McLeskey are all liquids, and 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). In addition, Dr. Forrest's own reference, Riffkin (Ex. 1022) at Tables IV, V, and VI describes components in percentages that add up to 100%, and therefore must be volume per volume and not weight per volume; e.g., the first formulation listed in Table VI is

described as 20 mg/ml active ingredient in castor oil 78%, benzyl benzoate 20%, and benzyl alcohol 2%.

64. Dr. Forrest argues that "[w]eight is a more precise indicator of an amount of a solid material than is volume because weight accounts for density differences. Consider, for example, a recipe calling for one cup of brown sugar. A loosely packed cup of sugar and a firmly packed cup of sugar are volumetrically the same, but represent a different weight of brown sugar" Ex. 1003 at ¶ 70. However, the same is not true for liquids. Moreover, 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. Dr. Forrest's citation to Powell as disclosing a "standard convention" is unwarranted. Ex. 1003 (Forrest Declaration) at ¶ 72. Powell does not say that and indeed cites a number of instances where % v/v is the measurement. And, Powell is a compendium of marketed products, and not lab scale, animal research formulations, like those used in McLeskey.

65. Dr. Forrest relies on hindsight for his assertion that a skilled formulator "would have known" that the McLeskey castor oil formulation was described in % w/v. *See* Ex. 1003 at ¶¶ 95, 107, 134. As discussed above, Dr. Forrest's reliance on Ex. 1021 (Remington's Ch. 9) itself demonstrates that the formulation at issue was properly understood to be described in % v/v. Dr. Forrest ignores the many examples of liquid excipients in liquid formulations disclosed in

% v/v. *See, e.g.*, Ex. 2088 (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. 1022 (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.

2) McLeskey Does Not Disclose Any Solubility Information

66. Dr. Forrest argues that "[t]he claims of the '680 patent do not require that the administered pharmaceutical formulation be a solution (rather than a suspension)." Ex. 1003 at ¶ 74. But, the specification makes clear that the inventions contemplate a solution formulation: "[t]he invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound [fulvestrant] . . . ***in solution*** in a ricinoleate vehicle." Ex. 1001 at Abstract; Ex. 1001 at 5:3-10. In the '680 Patent, the inventors stated 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." Ex. 1001 at

5:54-58. However, the inventors discovered 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 6:9-12. Additionally, the inventors noted problems with previous attempts to develop a suspension formulation: "[w]e have found extensive local tissue irritation at the injection site as well as a poor release profile." Ex. 1001 at 8:64-65.

67. Regardless, McLeskey provides no indication whether fulvestrant in either formulation, peanut oil-based or castor oil-based, is in solution. Dr. Forrest implies that, because other references disclosed castor oil-based formulations of fulvestrant in solution, the formulator would assume that all castor oil-based formulations of fulvestrant were solutions. *See* Ex. 1003 at ¶ 75 ("Because castor oil was known to form a solution when solubilizing fulvestrant . . . the POSA would have understood that this [McLeskey] formulation was in the form of a solution."). But, no formulation of fulvestrant described in the art as a solution contained the excipients used in the castor oil-based formulation of McLeskey, and the skilled artisan would recognize that changes in excipients will affect solubility. Furthermore, although no solubility data for fulvestrant in castor oil had been published, the castor oil-based solution formulation in Example 3 of Dukes 1989

contained a considerable amount of benzyl alcohol (40%), assumed to enable the dissolution of fulvestrant.

68. The '680 Patent specification states 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 5:54-58. The skilled formulator would have expected that the excipients are critical to fulvestrant's solubility in oils. And, 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." Ex. 1001 at 6:9-12.

69. Dr. Forrest argues that "[t]he POSA would have also expected that the McLeskey formulation would effectively solubilize fulvestrant, due to . . . the POSA's ability to perform routine predictive solubility calculations." Ex. 1003 at ¶ 134. While citing to general references related to solubility parameters, Dr. Forrest does not even attempt to perform such a "routine" calculation for fulvestrant, nor does Dr. Forrest cite any such calculation that predicts the surprisingly increased solubility of fulvestrant in castor oil-based formulations with benzyl benzoate. *See* Ex. 1003 at ¶¶ 174-175. The most that Dr. Forrest even alleges is "the widespread availability of solubility parameter methods to design

optimal dosage forms." Ex. 1003 at ¶ 175. If Dr. Forrest cannot even use those parameters today to perform "routine" calculations of fulvestrant solubility, it is difficult to understand how a skilled formulator would rely on the availability of such parameters in 2000 to predict the surprising results of the claimed inventions.

70. Dr. Forrest cites publications by Hancock, Hansen, and Hildebrand as describing the solubility parameter. Ex. 1003 at ¶ 174. The references cited by Dr. Forrest support that, at most, the solubility parameter provides high-level information about whether two liquids are likely miscible; no reference cited by Dr. Forrest explains how to determine the precise effect of adding a co-solvent, such as benzyl benzoate, to a complex system of other co-solvents on the solubility of a solid, such as fulvestrant. *See* Ex. 1045 (Hansen) at 3 ("[I]t has been assumed that if each of the solubility parameter components for one liquid are, respectively, close to corresponding values for another liquid, then by similarity, the process of their mixing should occur readily . . . . [N]o precise calculations have been attempted, since there is no detailed theory for this interpretation of the solubility parameter."); Ex. 1045 (Hansen) at 3 ("Since the parameters assigned to the solvents are not precise, their present use in detailed calculations may be questioned."); Ex. 1045 (Hansen) at 3 ("These broad and general statements are typical of the type of observation one makes when considering a situation from a solubility parameter point of view."); Ex. 1049 (Hancock) at 18 ("The use of

solubility parameter theory to predict interactions is usually described for two component mixtures, however, given that mixtures of miscible materials show intermediate solubility parameters it should be possible to use multi-dimensional solubility parameter maps to determine the compatibility of multi-component mixtures."). Indeed, as recently as 2006, the introduction to an eBook co-authored by Dr. Hansen stated that "remarkably few of us use [Hansen Solubility Parameters] as a routine part of our working lives." Ex. 2092 (Abbott & Hansen) at 6.

71. Dr. Forrest further argues that "[e]ven if the McLeskey formulation was an oil suspension, the POSA would have known that the two types of formulations would have behaved similarly in a human patient." Ex. 1003 at ¶ 76. The only references cited for fulvestrant suspensions are not in human patients at all, but in animals. Further, no cited reference compares suspensions to solutions. In fact, although the Davy Reference cited by Dr. Forrest was not a direct comparison, it noted several potential differences in release profiles of suspension compared to solution preparations. Ex. 1052 (Davy 1985) at 2 ("***In contrast*** [to the suspension], IM administration of bleomycin saline solution is reported with peak levels obtained after one hour, a mean half-life of 2.6 h, and no detectable levels in serum after 24 h."). Moreover, the prior art taught that oily solutions can have different release rates than oily suspensions. For oily suspensions, "[d]rug

particles must first dissolve in the oil phase and then partition into the aqueous medium." Ex. 2080 (Remington's Ch. 91) at 16. As a result, "the duration of action obtained from oil suspensions is longer than that from oil solutions." Ex. 2080 (Remington's Ch. 91) at 17. Moreover, larger particles in suspensions "sediment quickly, cause more pain on injection and tend to block syringe needles." Ex. 2085 (Aulton Ch. 21) at 15.

72. The inventors indicated in the patent specification that aqueous suspensions had resulted in "extensive local tissue irritation at the injection site as well as a poor release profile. It is believed that the tissue irritation/inflammation was due to the presence of fulvestrant in the form of solid particles." Ex. 1001 at 8:64-67. This demonstrated that, at least for fulvestrant, such an assumption would not be true.

B) Howell 1995 (Ex. 1012)

73. Howell 1995 is an early stage clinical study, seeking to investigate fulvestrant's biological activity. Howell 1995 discloses preliminary results from 19 patients with advanced breast cancer who were tamoxifen-resistant. Ex. 1012 at 1.

74. In terms of formulation, the patients in Howell 1995 received a long-acting formulation of fulvestrant in a castor oil-based vehicle by monthly intramuscular injections. Ex. 1012 at 1. Howell 1995 fails to disclose any further details about the fulvestrant formulation.

75. Of the 19 patient treated, 7 had partial responses, 6 showed no change and 6 showed progression of the tumor. Ex. 1012 at 1. Howell 1995 concludes: "[o]ur study suggests that [fulvestrant] may improve rate and duration of response when used as first-line treatment for advanced breast cancer, since it has no demonstrable agonist activity." Ex. 1012 at 2. 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.

76. Because Howell 1995 does not disclose the specific details of the formulation used, it teaches the ordinary researcher nothing regarding what results would be obtained using any given fulvestrant formulation. Howell 1995 also fails to disclose any pharmacokinetic data regarding, e.g., blood plasma fulvestrant concentrations during any period of treatment.

C) Howell 1996 (Ex. 1006)

77. Howell 1996 reports further results from the same 19-patient study described in Howell 1995. Again, 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. 1006 at 7.

78. Regarding the formulation, the authors of Howell 1996 say 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. 1006 at 2. 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. Hence, nothing in Howell 1996 would have taught the skilled formulator to focus on finding "a castor oil-based formulation that would solubilize fulvestrant." *See* Ex. 1003 at ¶ 131. The authors do not suggest that the formulation used in the study is the final (marketable) version of the formulation for treatment of humans.

79. Although a dose of 250 mg fulvestrant was used in the 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. 1006 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. 1006 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.

80. 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. 1006 at 6. In their "Discussion" section, the authors 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. 1006 at 7. The skilled artisan would recognize that Howell 1995 and Howell 1996 are reports of an early-stage clinical trial, given the limited number of patients, advanced disease, and lack of controls.

D) Wakeling 1991 (Ex. 1008)

81. Wakeling 1991 reports the sustained antiestrogen effects of fulvestrant in rats and monkeys after subcutaneous injection in a peanut oil suspension. In terms of formulation, Wakeling 1991 teaches only research formulations prepared immediately before use and administered to animals. Stock solutions of tamoxifen, a metabolite of tamoxifen (ICI 164,384), and fulvestrant (ICI 182,780) were

"prepared in ethanol, stored at 4°C, and diluted as required." Ex. 1008 at 1. Immediately before use, fulvestrant was "prepared for administration by diluting an ethanol stock solution into the required volume of arachis oil with gentle warming (60°C)." Ex. 1008 at 2. This "oil suspension" formulation was administered by subcutaneous injection to mice and rats. Ex. 1008 at 3; Ex. 1008 at Figure 3; Ex. 1008 at Figure 9.

82. Notably, Wakeling 1991 also investigates the effect of oral administration of fulvestrant to rats, and finds that the anti-uterotropic activity was qualitatively similar to that after fulvestrant given by the subcutaneous route, but with a reduced potency (about 10%). Ex. 1008 at 2-3. Thus, Wakeling 1991 disclosed that oral administration of fulvestrant was a viable (though challenging) option, and hence given this incentive encouraged further formulation work on oral administration.

E) Wakeling 1992 (Ex. 1009)

83. Wakeling 1992, like Wakeling 1991, investigates the biological activity of the fulvestrant compound in rats. The authors also investigate the activity of various anti-estrogenic compounds in tissue culture, rats, pigtail monkeys, and xenografts of two types of cancer cells in mice. Wakeling 1992 is not a formulation paper, but a basic research paper.

84. Similar to Wakeling 1991 and Wakeling 1993 (below), Wakeling 1992 finds that a bolus dose of fulvestrant as a suspension in arachis oil, administered *subcutaneously*, achieved anti-oestrogenic *activity* for in excess of one month in both mice, rats and monkeys. Ex. 1009 at 1-2. Importantly, the studies only measure pharmacological activity and do not state that blood plasma levels were continuous over one month. Wakeling 1992 treats fulvestrant as a research tool, saying it "provides the opportunity to evaluate clinically the potential therapeutic benefits of complete blockade of oestrogen effects in endocrine-responsive human breast cancer" and "will be used to test" whether or not the category of pure antiestrogens have a place in breast cancer treatment, showing that fulvestrant's role in human cancer treatment was uncertain. Ex. 1009 at 1, 4.

F) Wakeling 1993 (Ex. 1028)

85. This review article discusses both fulvestrant and the pure antiestrogen, ICI 164,384, and summarizes the ongoing animal research into the safety and effectiveness of pure antiestrogens for cancer treatment. Wakeling 1993 notes the risk of using a pure antiestrogen as a breast cancer treatment: "[o]ne predicted undesirable action of pure antiestrogens in therapeutic use may be a tendency to reduce bone density and hence to precipitate or exacerbate osteoporosis." Ex. 1028 at 7.

86. Wakeling 1993 cites to Wakeling 1991, which teaches the use of a subcutaneously administered peanut oil suspension of fulvestrant, to suggest that fulvestrant could achieve anti-estrogenic activity in rats over a long period of time (1 month) with a single injection. Ex. 1028 at 10. All three Wakeling publications (1991, 1992, and 1993) are early work evaluating the action of the fulvestrant compound in animal models, and not papers about the development of formulations for fulvestrant. The review also states that "[a]nimal toxicology and human volunteer studies have recently been successfully completed as a prelude to therapeutic studies with the oil depot formulation of ICI 182,780 in patients." Ex. 1028 at 10. The only sustained release oil formulation discussed in Wakeling 1991 and 1992 is the peanut oil formulation.

G) Osborne 1995 (Ex. 1018)

87. The Osborne publication is a report on basic science research, where the authors implanted human, estrogen receptor positive, breast cancer cells (MCF-7) into athymic nude mice (i.e., mice that would not reject the tumor cells). Ex. 1018 at 1-2. The authors report fulvestrant's effects against tamoxifen-resistant cancer growth in this experimental, modified animal model.

88. In terms of formulation of fulvestrant, Osborne reports that a castor oil formulation of ICI 182,780, administered subcutaneously once weekly, suppressed

tumor growth and tumorigenesis in this experimental model. Ex. 1018 at 2. No further details are provided regarding the castor oil formulation.

89. The Osborne paper is related to the use of a particular modified mouse model for experimental investigation of tamoxifen-resistant cancer growth, and not related to development of fulvestrant formulations.

H) Dukes 1992 (Ex. 1025)

90. Dukes 1992 reports an animal study that investigated the effects of fulvestrant on the uterus of overiectomized, oestrogen-treated monkeys. Ex. 1025 at 1. In essence, this is a study using an MRI imaging protocol in monkeys, where the goal is to deliver fulvestrant to the experimental animal to evaluate its effects *in vivo*.

91. Dukes uses a long-acting arachis oil suspension formulation, a short acting propylene glycol formulation and a long-acting castor oil-based solution formulation of fulvestrant in the different studies described in the paper. Ex. 1025 at 1 (arachis oil), 3 (castor oil), 4 (propylene glycol). Dukes 1992 explains that the propylene glycol and castor oil based formulations were experimental formulations, meant to "facilitate other investigations of [fulvestrant]." Ex. 1025 at 6. No other components of the formulations were disclosed. With respect to the arachis oil suspension, Dukes 1992 notes that "[t]his formulation has been demonstrated previously to provide a sustained antioestrogenic effect on the

perineum (Wakeling *et al*. 1991)." Ex. 1025 at 3. Here, the arachis oil suspension formulation was shown to "completely block[] the uterotrophic action of oestradiol for 3-4 weeks." Ex. 1025 at 3.

92. Dukes 1992 notes that "these studies revealed a differential response to oestradiol between the myometrium and endometrium, where the endometrium appeared more sensitive, as reflected by a more rapid recovery from antioestrogen blockade." Ex. 1025 at 9. Based on the variability of fulvestrant's effects on two different tissues in the same *organ*, in the same species, a skilled formulator would be reluctant to predict the effects of fulvestrant in *other* tissues, which might also be different from the tissues studied in unpredictable ways.

93. Dukes 1992 discusses the effects of various fulvestrant formulations, but the formulations described are experimental formulations for research in animals, and there is nothing to suggest that any one is a final formulation for human use.

I) Dukes 1993 (Ex. 1026)

94. While Dukes 1992 studied the effect of fulvestrant on ovariectomised monkeys, Dukes 1993 studied the effect of fulvestrant on intact monkeys with normal menstrual cycles. Ex. 1026 at 1. Just as in Dukes 1992, this is a study using an MRI imaging protocol in monkeys, where the goal is to deliver fulvestrant

to the experimental animal to evaluate its effects *in vivo*, and not to formulate it for safety, tolerability, or effectiveness in humans.

95. Dukes 1993 describes two fulvestrant formulations for intramuscular administration: a short-acting propylene glycol solution formulation, administered intramuscularly once daily for 25 days; and a long-acting castor oil-based solution given as a single intramuscular injection. Ex. 1026 at 2. No excipients or other components of either formulation are identified.

96. Dukes 1993 found that "[i]n animals rendered anovulatory, growth of the endometrium was blocked completely by [fulvestrant]," while "[a]ntiuterotrophic efficacy was significantly less in monkeys which ovulated during treatment with [fulvestrant]." Ex. 1026 at 1. Dukes 1993 notes that "[w]hen the occurrence of ovulation was accounted for, no significant differences emerged between the effects of the different formulations and doses of [fulvestrant], with the exception that the 2.5 mg dose (F2) appeared slightly less effective ($P<0.05$) than the 4.0 mg dose in the second half of the cycle." Ex. 1026 at 5. Dukes 1993 concluded that "[t]he clinical usefulness of [fulvestrant] remains to be determined." Ex. 1026 at 7.

97. Like Dukes 1992, Dukes 1993 discusses the effects of various fulvestrant formulations, but the formulations described are experimental

formulations for research in animals, and there is nothing to suggest that any one is a final formulation for human use.

J) DeFriend (Ex. 1027)

98. DeFriend is a first-in-humans study to evaluate the biological activity of fulvestrant as an estrogen antagonist in primary breast tumors *in vivo*. DeFriend provides only "preliminary evidence to suggest" biological activity in primary tumors, i.e., inhibition of tumor cell proliferation. Ex. 1027 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. 1027 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. 1027 at 5. In other words, additional early stage work would need to be done to test biological activity in humans.

99. 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. 1027 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. 1027 at 1.

100. 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. 1027 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 4 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.

101. 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. 1027 at 5.

No further information regarding the components of this long-acting castor oil based fulvestrant formulation are provided. It is clear from DeFriend that this next planned study is another early stage research study on basic safety and biological action.

K) Riffkin (Ex. 1022)

102. 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.

103. Sesame oil was "chosen as the 'standard' vegetable oil to be compared with castor oil," because it was "universally accepted as a parenteral oil vehicle." Ex. 1022 at 3. The lesions and irritation caused by the castor oil formulations disclosed in Table IV teach the continued use of the sesame oil vehicle. Ex. 1022 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.

104. 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. 1022 at Table VI. Thus, the importance of the physicochemical characteristics of the active ingredient becomes apparent.

105. In fact, 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. Ex. 1022 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. 1022 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. 1022 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. 1022 at 3 (*Compare* 47-2 and 4704 with 47-3 and 47-5).

L) Lehmann 1976 (Ex. 1019)

106. Lehmann discloses 17 β-monoesters and 3-enol-17β-diesters of 17α-ethinyl-18-methyl-19-nortestosterone esters. Ex. 1019 at 1:10-12. Lehmann describes the disclosed compounds as "readily soluble" in "vegetable oils such as sesame oil, castor oil, cotton seed oil, sunflower oil, olive oil, and the like, as well as in synthetic solvents, for instance glycols, lactic acid esters, benzyl benzoate and the like." Ex. 1019 at 1:21-27.

107. Because of the "considerable solubility" of the compounds, "it is possible to employ solutions of the esters of the invention as injectibles and thereby also to utilize them as hormone depots." Ex. 1019 at 1:27-30. In particular, "[t]he compounds of the invention are administered in the conventional dosage forms, such as capsules, granulates, solutions, dragees, and tablets." Ex. 1019 at 1:58-60. Lehmann describes tablets that "are generally compounded with binding agents, lubricants and other substances which are commonly used in tablet manufacture such as magnesium stearate, stearic acid, talc, corn starch, lacto[s]e or the like." Ex. 1019 at 1:67-2:3. Lehmann provides many options but does not indicate a preference for any of the carriers or solvents. Lehmann does not mention fulvestrant, does not suggest any formulation for fulvestrant, and does not

provide any basis for predicting the results of any formulation as applied to fulvestrant (which as the '680 Patent specifically explains has an entirely different solubility profile from the Lehmann compounds).

M)Lu 1998 (Ex. 1014)

108. Lu 1998 describes inoculating mice with "estrogen dependent MCF-7 human breast cancer cells stably transfected with the aromatase gene." Ex. 1014 at 1. Lu 1998 investigated the effect on tumour size of antiestrogens (fulvestrant and tamoxifen) and of aromatase inhibitors, letrozole and anastrozole on tumour size. The fulvestrant was "injected in oil once per week." Ex. 1014 at 5. Lu 1998 concluded that "[t]amoxifen appears to be more effective than [fulvestrant]," and that "both aromatase inhibitors [letrozole and anastrozole] were more effective than the antiestrogens." Ex. 1014 at 1. Lu 1998 speculated that "[o]ne explanation for our results might be that [fulvestrant] has less favorable pharmacokinetics when injected once a week into the mouse, compared to daily injections of the other compounds." Ex. 1014 at 7.

N) Lu 1999 (Ex. 1030)

109. Lu 1999 describes "a model for postmenopausal, hormone-dependent breast cancer in nude mice which is responsive to both antiestrogens and aromatase inhibitors. Ex. 1030 at 1. Lu 1999 administered to this animal model combinations of letrozole, anastrozole, tamoxifen, and fulvestrant. Ex. 1030 at 1.

Fulvestrant was "injected once per week in oil." Ex. 1030 at 3. Lu 1999 discloses that fulvestrant was "formulated in castor oil and used as previously reported by Osborne et al. to be effective in the mouse model." Ex. 1030 at 7. Lu 1999 concluded that "treatment with the combinations of aromatase inhibitors with either tamoxifen or [fulvestrant] are not more effective in blocking estrogen stimulation of tumor growth than the aromatase inhibitors alone." Ex. 1030 at 1.

O) Dukes 1989 (Ex. 1007)

110. 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. 1007 at 2:3-6.

111. 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. 1007 at 4:32-37. Dukes 1989 also teaches

various excipients for each of the methods of administration. Ex. 1007 at 4:48-5:29. In this way, Dukes 1989 teaches the breadth of options available to a formulator.

112. 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. 1007 at 7:46-48. 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. 1007 at 8:35-39. 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. 1007 at 9:21-23. 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. 1007 at 9:20-25. Dukes 1989 does not indicate any preference among the example formulations.

P) GB '286 (Ex. 1020)

113. GB '286 relates to oily unsaturated depot solutions of gestagens for intramuscular injection. Ex. 1020 at 1:5-6. In particular, the inventors found that "a lengthening of the depot effect occurs when the volume of the injection solution

is increased, while retaining the quantity of gestagen to be administered." Ex. 1020 at 1:23-25. None of the "gestagens" described are fulvestrant, and one of skill in the art would know that fulvestrant does not belong to this category of drugs.

114. GB '286 states that solvents, such as benzyl benzoate or benzyl alcohol, can be added to the formulation. Ex. 1020 at 3:21-23. GB'286 provides options for vegetable oils, including linseed oil, cottonseed oil, sunflower oil, ground nut oil, olive oil and wheat oil, in addition to synthetic oils, such as polyethylene glycol, triglycerides of higher saturated fatty acids and monoesters of higher fatty acids. Ex. 1020 at 3:24-27. GB '286 lists a preferred solvent as 6:4 mixture by volume of castor oil and benzyl benzoate. Ex. 1020 at 3:27-28. GB '286 describes administering norethisterone oenanthate in 1.8 ml and in 0.6 ml of castor oil/benzyl benzoate (6:4). Ex. 1020 at 1:26-29.

115. From a formulator's perspective, GB '286 provides options for oily solvents. GB '286 does not disclose fulvestrant. Additionally, GB '286 does not teach the claimed combination of formulation excipients in their respective amounts or minimum plasma levels.

Q) Neumann (Ex. 1041)

116. Neumann discloses a pharmaceutical composition comprising an antiestrogen, such as tamoxifen, and an antigonadotropically effective

antiandrogen for treatment of prostate hyperplasia. Neumann states that "[f]or oral application, which is preferred, suitable particularly are tablets, dragees, capsules, pills, suspensions or solutions." Ex. 1041 at 9:13-15. Neumann provides two examples of tablet formulations. Ex. 1041 at 9:40-10:25. Neumann further states that "[s]uitable for parenteral, especially intramuscular administration are oily solutions, e.g., sesame oil solutions or castor oil solutions," and benzyl benzoate or benzyl alcohol can also be added as solubilizers. Ex. 1041 at 9:22-29. Neumann describes administering the drug substance "in 0.1 ml of castor oil containing a small amount of benzyl benzoate." Ex. 1041 at 5:26-27. Neumann further states that the drug compound can be "dissolved in a medium consisting of benzyl benzoate/castor oil (1:10)." Ex. 1041 at 7:9-11. Neumann provides one example of an oily solution with tamoxifen, castor oil, benzyl benzoate, and cyproterone acetate. Ex. 1041 at 10:30-39.

117. From a formulator's perspective, Neumann encourages oral administration. Neumann does not disclose fulvestrant. Additionally, Neumann does not teach the claimed combination of formulation excipients in their respective amounts or minimum plasma levels.

R) O'Regan (Exhibit 1013)

118. 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. 1013 at 1.

119. 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 N2) to mice by subcutaneous injection. Ex. 1013 at 2. O'Regan does not address formulations generally or discuss them in detail; despite this, Dr. Forrest points to O'Regan for a disclosure that "[c]linically, [fulvestrant] must be given by depot intramuscular injection because of low oral potency." Ex. 1003 at ¶ 60. The article does not cite any support for that conclusion.

120. O'Regan discloses only early stage formulations of fulvestrant in arachis oil for weekly subcutaneous administration to mice. 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.

XII) THE SKILLED FORMULATOR'S APPROACH TO FORMULATING FULVESTRANT

121. 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. 1008 (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 at ¶ 127-132.

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

122. Two clinical studies of fulvestrant, DeFriend (Ex. 1027) and Thomas (Ex. 2039) administered a daily formulation of fulvestrant by intramuscular injection. Ex. 1027 (DeFriend) at 1; Ex. 2039 (Thomas) at 1. DeFriend described the formulation used therein as propylene glycol-based. Ex. 1027 at 2. Thomas did not describe the formulation at all. Ex. 2039 at 1-2. On the other hand, Howell 1996 administered fulvestrant intramuscularly in a monthly long-acting formulation of castor oil. Ex. 1006 at 2. Neither DeFriend, Thomas, nor Howell provided any other information about the excipients used in the respective formulations. Thus, DeFriend, Thomas and Howell are not primarily studies of a particular formulation. But, rather, they are studies to determine the efficacy and tolerability of the fulvestrant molecule.

123. DeFriend uses language referring to the fulvestrant molecule, not the formulation: "treatment with ICI 182,780" (Ex. 1027 at 1, 3-6); "patients randomized to receive ICI 182780" (Ex. 1027 at 2); "ICI 182,780 caused no serious drug-related adverse events" (Ex. 1027 at 3); "ICI 182,780 was well tolerated after short term administration" (Ex. 1027 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. 1027 at 5); "provide preliminary evidence" (Ex. 1027 at 5); "produced preliminary evidence" (Ex. 1027 at 6).

124. Howell uses similar language to DeFriend and is similarly focused on the molecule, not the formulation: "the aims of the study here were to assess the long-term efficacy and toxicity of the specific anti-oestrogen ICI 182780" (Ex. 1006 at 1); "we have assessed the pharmacokinetics, pharmacological and anti-tumour effects of the specific steroidal anti-oestrogen ICI 182780" (Ex. 1006 at 1); "administration of ICI 182780 was associated with a lower than expected incidence of side effects" (Ex. 1006 at 1).

125. DeFriend found that daily administration of fulvestrant "produced demonstrable antiestrogenic effects in human breast tumors." Ex. 1027 at 1. Thomas found "a potent anti-oestrogenic activity *in vivo*." Ex. 2039 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. 1006 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. 1026 at 5. In fact, Dr. Forrest agrees that "Dukes 1993 demonstrated that the long-acting fulvestrant formulation provided antiestrogenic effects similar to that of the short-acting fulvestrant formulation." Ex. 1003 at ¶ 92. Thus, the formulator would understand that once daily administration was an option for fulvestrant.

126. 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. 1006 at 6; Ex. 1006 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 potency issue cited by Dr. Forrest (Ex. 1003 at ¶ 98) would be less of a concern, since less fulvestrant would need to be administered to reach the receptor.

B) The Formulator Would Prefer Oral Fulvestrant Formulations

127. The formulation art, viewed as a whole, teaches that oral administration would have been the preferred option for fulvestrant in 2000. 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."). In fact, Dr. Forrest does not cite any marketed endocrine therapy for breast cancer administered by intramuscular administration.

128. 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).

129. A skilled formulator would have known that oral formulations resulted in the best patient compliance. *See* Ex. 2083 (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.

130. 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.

131. Many drugs with low solubility 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 entry 4629. Hydrocortisone, with a solubility in water of 0.28 $mgml^{-1}$, is marketed in an oral dosage form. Ex. 2101 (Merck Index) at entry 4828. 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 entry 3780 (ethinyl estradiol); entry 4998 (indomethacin); entry 4571 (griseofulvine); entry 5262 (itraconazole); entry 1826 (carbamazepine). Despite being "almost insol[uble] in water," digoxin, and diethylstilbestrol are marketed in oral dosage forms. Ex. 2101 (Merck Index) at entry 3210 (digoxin); entry 3177 (diethylstilbestrol). Despite being "insol[uble] in water," norethandrolone and progesterone are marketed in oral dosage forms. Ex. 2101 (Merck Index) at entry 6789 (norethandrolone); entry 7956 (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 entry 3132 (diclofenac); Ex. 2101 (Merck Index) at entry 5262 (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.

132. 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).

133. Dr. Forrest cites the statement in O'Regan (Ex. 1013) that "in the clinical setting, fulvestrant must be administered intramuscularly." Ex. 1003 at ¶ 98. In other words, Dr. Forrest suggests that because it was known 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. 1013 at 2.

134. Dr. Forrest also argues that fulvestrant was known to have low oral bioavailability, based in part on Wakeling 1991 (Ex. 1008) and Wakeling 1992 (Ex. 1009). Ex. 1003 (Forrest Declaration) at ¶ 56. In fact, Wakeling 1991 (Ex.

1008) 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. 1008 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. 1008 at 3. Wakeling 1991 characterizes the difference in potency between fulvestrant administered subcutaneously and orally as an "order of magnitude." Ex. 1008 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.

135. Dr. Forrest cites Howell 1996 as having "demonstrated efficacy when fulvestrant was administered intramuscularly in castor oil depot injections." Ex. 1003 at ¶ 57. 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.

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

136. 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.

137. Riffkin, cited by Dr. Forrest, 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. 1022 (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.").

138. The formulator would have appreciated that intramuscular injections may also have issues with drug release. Ex. 2108 (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.").

D) The Prior Art Disclosed Numerous Fulvestrant Formulations

139. Dr. Forrest admits that "[t]he prior art disclosed a number of fulvestrant formulations," citing Ex. 1005 (McLeskey), Ex. 1006 (Howell 1996), Ex. 1007 (Dukes 1989), Ex. 1008 (Wakeling 1991), Ex. 1009 (Wakeling 1992), Ex. 1012 (Howell 1995), Ex. 1013 (O'Regan 1998), Ex. 1014 (Lu 1998), Ex. 1018 (Osborne 1995), Ex. 1025 (Dukes 1992), Ex. 1026 (Dukes 1993), Ex. 1027 (DeFriend 1994), Ex. 1028 (Wakeling 1993), and Ex. 1030 (Lu 1999). Ex. 1003 at ¶ 45. In addition, a PubMed search for publications that mention fulvestrant prior to 2000 reveals over 250 hits. However, Dr. Forrest 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.

140. To the contrary, Dr. Forrest claims that every one of these formulations "used conventional excipients . . . for their known purposes to achieve a formulated product." Ex. 1003 at ¶ 45. Furthermore, he says that "[t]he excipients used in prior art fulvestrant formulations are conventional excipients often used in injectable depots." Ex. 1003 at ¶ 46. Yet, when describing the scope of the art, Dr. Forrest picks out only the four excipients used in the claimed inventions. Ex. 1003 at ¶¶ 45-55. Dr. Forrest ignores all the other excipients 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.

141. Solvent options listed in references cited by Dr. Forrest include "linseed oil, cottonseed oil, sunflower oil, ground nut oil, olive oil and wheat oil, in addition to synthetic oils, such as polyethylene glycol, triglycerides of higher saturated fatty acids and monoesters of higher fatty acids." Ex. 1020 (GB '286) at 3:24-27. Aside from castor oil, fulvestrant had been formulated in arachis (peanut) oil (Ex. 1008 (Wakeling 1991) at 2), in sesame oil (Ex. 2109 (Wade 1993) at 2), in propylene glycol (Ex. 1027 (DeFriend) at 2), and in corn oil (Ex. 2110 (Lundeen

1997) at 2. A reference cited repeatedly by Dr. Forrest, Powell, ***does not even list castor oil*** as used in a single marketed parenteral product. *See* Ex. 1043 at 11 (listing consecutive alphabetical entries of "carboxymethylcullose" to "chloride"). In fact, Dr. Forrest cited formulations of fulvestrant in arachis oil to show efficacy in breast cancer but then failed to explain why a skilled artisan would have preferred castor oil-based formulations. Ex. 1003 at ¶ 97 (citing Ex. 1008 (Wakeling 1991)).

142. 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. 2111 (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.

143. Dr. Forrest characterizes each individual excipient in the castor oil-based formulation of McLeskey as "conventional." Ex. 1003 at ¶ 45. However, Dr. Forrest 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. Forrest has cited none. Other references cited by Dr. Forrest formulated fulvestrant in castor oil and benzyl alcohol but did not include ethanol or benzyl benzoate. Ex. 1007 (Dukes 1989) at 9. Yet, Dr. Forrest provides no motivation for preferring the claimed combination of excipients over the other options in the prior art. Consistent with this, the specification of the '680 Patent disclosed commercial products that used some but not all of the claimed excipients. Ex. 1001 at Table 1.

XIII) NON-OBVIOUSNESS OVER MCLESKEY (GROUND ONE)

A) No Reason To Select McLeskey

144. The skilled formulator would not have consulted McLeskey when seeking to deliver fulvestrant to humans for hormonal dependent breast cancer. McLeskey administered experimental formulations to mice, not humans. McLeskey provides no pharmacokinetic information. In terms of efficacy, McLeskey concluded that administration of fulvestrant was a "treatment failure." Ex. 1005 at 10. In fact, McLeskey suggested using agents that modify FGF signaling as an alternative to fulvestrant. Ex. 1005 at 12-13.

145. Other than noting with hindsight that the castor oil-based formulation in McLeskey is similar to the claimed inventions, Dr. Forrest's sole basis for selecting McLeskey is the unsupported assertion that "McLeskey would have been

of relevance to the POSA at least because it disclosed a castor oil-based formulation of fulvestrant suitable for parenteral administration in animals." Ex. 1003 at ¶ 96. Dr. Forrest does not explain why the skilled artisan would focus on castor oil-based formulations: McLeskey also used a peanut oil formulation as interchangeable with the castor oil-based formulation. Ex. 1005 at 2; Ex. 1005 at Figure 1. Nor does Dr. Forrest explain why McLeskey would appear more promising than other castor oil-based formulations, such as Example 3 of Dukes 1989. Ex. 1007 at 9 (using castor oil and benzyl alcohol).

146. Dr. Forrest cites Ex. 1006 (Howell 1996), Ex. 1008 (Wakeling 1991), Ex. 1009 (Wakeling 1992), Ex. 1028 (Wakeling 1993), Ex. 1018 (Osborne 1995), and Ex. 1027 (DeFriend 1994) to argue that a skilled formulator would have known that fulvestrant was "useful in treating hormonal dependent malignant breast cancer in women." Ex. 1003 at ¶ 97. Adopting Dr. Forrest's own argument, the Wakeling publications disclosed the success of fulvestrant and the exact composition of the fulvestrant formulations used (arachis oil and ethanol). Ex. 1008 (Wakeling 1991) at 2-3; Ex. 1009 (Wakeling 1992) at 2. But, Dr. Forrest provides no reason why a formulator would have rejected these formulations in favor of the McLeskey formulation, which McLeskey itself described as a "treatment failure." Ex. 1005 at 10. Indeed, for the additional reasons listed

below, the formulator would not have turned to the McLeskey reference for formulation information.

B) McLeskey Teaches Away From Using Fulvestrant

147. 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-resistan[t] *in vivo* to the antiestrogen ICI 182,780." Ex. 1005 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. 1005 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. 1005 at 5. McLeskey concluded that ICI 182,780 was a "treatment failure." Ex. 1005 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. 1005 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. 1005 at 12-13.

148. 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. 1005 at 12.

149. Instead of suggesting further use of the compounds used as research tools, McLeskey recommends the hormone-independent FGF pathway as potentially clinically relevant. Ex. 1005 at 12-13. Thus, the skilled artisan would have no reasonable expectation that starting with McLeskey would lead to a successful method of treating hormonal dependent benign and malignant diseases of the breast or reproductive tract given that McLeskey repeatedly described the use of fulvestrant as a treatment failure (see below). Hence, McLeskey teaches away from the claimed inventions.

C) The Skilled Formulator Would Not Have Modified McLeskey To Obtain The Claimed Inventions

150. McLeskey does not disclose the claimed inventions. 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. 1005 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 the claimed methods. Ex. 1005 at 2-3. McLeskey administered the formulation subcutaneously, not by the claimed intramuscular route. Ex. 1005 at 2 ("ICI 182,780 . . . was administered s.c."). McLeskey administered the formulation weekly, not monthly. Ex. 1005 at 2 ("ICI, 182,780 . . . was administered . . . every week."). McLeskey administered a dose of 5 mg per mouse, which is equivalent to 12,000 mg per woman (5 mg / 0.025 kg (weight of mouse) * 60 kg (weight of woman)). Ex. 1005 at 2. McLeskey administered 0.1 ml per mouse, which is equivalent to 240 ml per woman (0.1 ml / 0.025 kg (weight of mouse) * 60 kg (weight of woman)). Ex. 1005 at 2. Additionally, as described further below, McLeskey does not provide any instructions to the formulator for how to make the preformulated formulation. Infra at ¶ 188-189.

151. During prosecution of the application that was issued as the '680 patent, the examiner noted these differences between McLeskey and the claimed

inventions. Ex. 1002 at 313 ("Mc[L]eskey et al. does not expressly teach the use of fulvestrant in treating hormonal dependent diseases of breast. It does not expressly teach the dosing regimen to be once a month, intramuscular administration, or the volume administered. Mc[L]eskey et al. does not expressly teach the herein claimed serum concentration of fulvestrant.").

152. To reach the claimed inventions from the McLeskey disclosure, one would have to make the following changes: change the method from experimental investigation of hormonal-independent pathways to the treatment of hormone-dependent breast cancer; change the method from administration to experimental research animals to treatment of humans; change the route of administration from subcutaneous to intramuscular; change the dosing regimen from weekly to monthly; change the volume administered; and reach a defined serum concentration, for a certain period of time. But McLeskey, itself, provides absolutely no motivation or reason to modify its disclosures to achieve the claimed inventions and there is no reason to expect that these changes would be successful.

D) The Formulator Would Not Have Found McLeskey

153. 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).

E) No Motivation To Modify McLeskey Nor Reasonable Expectation Of Success In Doing So

154. There is no information in McLeskey (or the art) that would have motivated the many modifications, described above, needed to reach the claimed inventions, or would have led to an expectation that making those modifications would provide the results of the claimed inventions.

155. First, McLeskey teaches that the fulvestrant treatments used therein were ineffective at preventing tumor growth. In fact, the title of McLeskey proclaims that the tumors studied therein were "cross-resistan[t] *in vivo* to the antiestrogen [fulvestrant]." Ex. 1005 at 1. The McLeskey abstract teaches 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. 1005 at 1. McLeskey concluded that fulvestrant, as administered therein, was a "treatment failure." Ex. 1005 at 10.

156. Dr. Forrest cites Howell 1996, among other references, to argue that "fulvestrant was commonly known in the art to be useful in treating hormonal dependent malignant breast cancer in women." Ex. 1003 at ¶ 97. But, the McLeskey reference disparaged those very results in Howell 1996 as showing "***only about*** 30-40% of such patients have a positive response to subsequent [fulvestrant]." Ex. 1005 at 2 (emphasis added). And, instead of recommending antiestrogens like fulvestrant, McLeskey suggested that agents "directed against the autocrine or paracrine effects of FGFs" should be tried. Ex. 1005 at 12. Hence, the skilled artisan reading McLeskey would have been discouraged from using the castor oil-based formulation described therein for hormonal dependent breast cancer.

157. Nothing in McLeskey suggests that the formulations used therein are appropriate for human use. McLeskey administers animal formulations of the other antiestrogens, using subcutaneous pellets for tamoxifen and administration by oral gavage for letrozole. Ex. 1005 at 2. The skilled artisan would have recognized that these formulations are designed specifically for animal research, and would have had the same expectation for the fulvestrant formulations. The skilled artisan would not have expected any McLeskey formulation to be ready for human use.

158. Second, McLeskey provides no indication of how the formulation would behave when administered intramuscularly, as in the claimed inventions, instead of subcutaneously, and there is no way to predict those results. However, the skilled artisan would have known that administering the same formulation by a different route would have resulted in unpredictable effects. *See* infra at ¶¶ 191-197. Mylan asserts that "McLeskey's mice were administered fulvestrant s.c. due to their small muscle volume." Petition at 40; Ex. 1003 at 59 n. 3. McLeskey does not explain why subcutaneous administration was used, and nothing in McLeskey supports Mylan's theory. 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.

159. Third, the castor oil-based formulation in McLeskey was administered on a weekly basis. Ex. 1005 at 2. Nothing in McLeskey suggests that the castor oil-based formulation used therein would provide sustained release for four weeks, as in the claimed inventions. McLeskey provides no pharmacokinetic data for any formulation, so the skilled artisan could not have predicted whether the formulations used in McLeskey would provide sustained release over four weeks. To the contrary, the skilled artisan would have believed that the formulations in McLeskey would have to be administered on a weekly basis, because those formulations provided only one week of fulvestrant release.

160. Dr. Forrest states only that the individual excipients present in the McLeskey formulation had been used before in intramuscular injections. Ex. 1003 at ¶¶ 45-46. But, he cites nothing to demonstrate that this combination of excipients in these ratios could have the duration of action, blood plasma fulvestrant concentration or lack of side effects (including lack of precipitation and local irritation) of the claimed inventions.

161. 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. 2085 (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.

162. 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. 2085 (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 increased viscosity, which retards the transport of the drug from injection site to the systemic circulation.").

163. In addition to affecting release profile, excipients may also affect the tolerability of an injection. For example, Table IV of Riffkin, cited by Dr. Forrest, shows differences in "local irritation produced in rabbit muscle by injection of

various oil vehicles." Ex. 1022 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. 1022 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. 1022 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.

164. In Riffkin, Table V and Table VI provide data on injection site reactions for various formulations of 17-hydroxyprogesterone caproate and estradiol valerate, respectively. Ex. 1022 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. 1022 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.

165. 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, the inventors attributed differences in the 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 8:42-44.

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

166. 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 ¶¶ 45-51, 161-165. A skilled formulator could not have predicted the effect of changing any one parameter on blood plasma levels.

167. 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 plasma proteins, preventing absorption. Ex. 2108 (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 1980) at 4. These factors all depend, to some extent, on the species tested.

168. 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.

169. 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 fulvestrant formulation solubility 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 9:42-44; *see also* Ex. 1001 at Table 4 (data demonstrating that fulvestrant is most soluble in the Miglyol vehicle but that this formulation leads to the most precipitation of fulvestrant in the injection site for all the oils tested).

170. Most importantly, McLeskey provided no blood plasma fulvestrant levels for any formulation tested. Thus, the skilled formulator would have no information with which to predict the effect of changing the McLeskey formulation or administration method, let alone for all of the changes required to reach the claimed inventions. Dr. Forrest does not explain how the skilled formulator would have a reasonable expectation of success in modifying McLeskey.

XIV) NON-OBVIOUSNESS OVER MCLESKEY AND HOWELL (GROUND TWO)

171. Dr. Forrest's alternative argument is that the claimed inventions are obvious over Howell 1996 and McLeskey combined. However, Dr. Forrest does not identify a motivation in the references or in the art to combine Howell 1996 with McLeskey. Instead, Dr. Forrest improperly compares Howell 1996 to the claimed inventions: "The claims of the '680 patent claim treating hormonal dependent benign and malignant diseases of the breast or reproductive tract with fulvestrant. That is exactly the subject matter of Howell 1996. Howell 1996 is

therefore extremely pertinent to the POSA." Ex. 1003 at ¶ 130. Similarly, Dr. Forrest compares McLeskey to the claimed inventions, but does not link McLeskey to Howell 1996: "The element of claim 1 reciting the excipients in a castor oil-based fulvestrant formulation is found in McLeskey." Ex. 1003 at ¶ 134. By starting with the claimed inventions, Dr. Forrest performs a classic hindsight analysis, completely ignoring whether a reason or motivation existed for a skilled formulator to combine the teachings of Howell 1996 with McLeskey.

172. At most, Dr. Forrest appears to argue that Howell 1996 points to McLeskey, because McLeskey supposedly used a solution formulation of fulvestrant in castor oil. Ex. 1003 at ¶ 131 ("After reading Howell 1996, the POSA would have had to find a castor oil-based formulation that would solubilize fulvestrant."). However, this supposed link is not found in the references -- neither says that the formulation used is a solution or gives any solubility parameters of fulvestrant in the formulation or in the various formulation components. To the contrary, the very language of both references teaches away from combining McLeskey with Howell. McLeskey explicitly describes fulvestrant administration in both the peanut oil formulation and the castor oil formulation as a "treatment failure." Ex. 1005 at 10 ("In this report, we have shown that the estrogen-independent *in vivo* growth of FGF-transfected MCF-7 cells is not affected by [fulvestrant] or by either of two aromatase inhibitors. This **treatment failure**

cannot be attributed to an estrogen-, tamoxifen-, or FGF-induced decrease in the immunocompetence remaining in nude mice.") (emphasis added).

173. And, in fact, the title of the McLeskey paper notes this result by highlighting the cross-resistance of the studied tumors to fulvestrant: "Tamoxifen-resistant Fibroblast Growth Factor-transfected MCF-7 Cells Are ***Cross-Resistant*** **in Vivo** ***to the Antiestrogen ICI 182,780*** [fulvestrant] and Two Aromatase Inhibitors." Ex. 1005 at 1 (emphasis added). McLeskey concludes the opposite of Howell -- that, instead of using antiestrogen therapy, like fulvestrant, "[t]herapy of such tumors with ***agents directed against the autocrine or paracrine effects of FGFs*** might result in beneficial effects." Ex. 1005 at 12-13 (emphasis added).

A) McLeskey Disparaged The Results of Howell 1996

174. There was no reason to combine McLeskey and Howell 1996. In fact, McLeskey disparages the very results in Howell 1996 that Dr. Forrest cites. *See* Ex. 1003 at ¶ 79 (Dr. Forrest stating that "[t]hese [Howell 1996] data indicated that the formulation was long-acting, safe, and was effective in treating breast cancer."). But, McLeskey actually cites Howell 1996 to state that "early 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. 1005 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. 1005 at 12-13. Hence, the skilled formulator would not combine McLeskey with Howell 1996.

175. Additionally, before the inventions of the '680 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 used in Howell 1996.

B) The Skilled Formulator Would Not View The Castor Oil-Based Formulation Of McLeskey As A "Match" To The Formulation Of Howell

176. As noted above, the skilled formulator would recognize that the fulvestrant formulation used in Howell 1996 was simply an experimental formulation: "the aims of the study here were to assess the long-term efficacy and toxicity of the specific anti-oestrogen ICI 182780" (Ex. 1006 at 1); "we have assessed the pharmacokinetics, pharmacological and anti-tumour effects of the specific steroidal anti-oestrogen ICI 182780" (Ex. 1006 at 1); "administration of ICI 182780 was associated with a lower than expected incidence of side effects" (Ex. 1006 at 1). Thus, there is no basis for Dr. Forrest's apparent argument that, after reading Howell 1996, the skilled formulator would look for castor oil-based

formulations "that would solubilize fulvestrant". Ex. 1003 at ¶ 131. In any event, Dr. Forrest provides no reasoning to choose the castor oil-based formulation described in McLeskey over other formulations of fulvestrant in castor oil, particularly given that 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.

177. McLeskey describes basic exploratory biological studies in rodents while Howell discloses early studies in a small group of breast cancer patients. Howell reports intramuscular administration, while McLeskey uses subcutaneous injections. The castor oil formulation in McLeskey was not described as suitable for use in humans, and an ordinary formulator would expect it to be intended for animal use only.

178. 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 9 ("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. 2047 (Santen) at 8.

179. Dr. Forrest 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 dose and volumes used in McLeskey are exponentially higher when normalized to permit comparison between the two references. 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 ¶¶ 182-198.

Parameter	**Howell (1996)**	**McLeskey (1998)**
Frequency	**Monthly**	**Weekly**
Injection	**Intramuscular**	**Subcutaneous**
Dose	**250 mg/month/woman (65 kg)**	**5 mg/week/mouse (0.025 kg)** (5 mg/0.025 kg * 60 kg = **12,000 mg/week/woman)**
Volume	**5 ml**	0.01 ml (0.01 ml/0.025 kg * 60 kg = **24 ml/week/woman)**
Excipients	**Castor oil and ?**	**Ethanol, benzyl benzoate, benzyl alcohol,** castor oil

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

180. 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. Ex. 1007 at 9. Like Howell, Example 3 of Dukes 1989 used a

castor oil-based 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. 1007 at 9. On the other hand, McLeskey called fulvestrant administration a "treatment failure." Ex. 1005 at 10. Dr. Forrest has not explained why a skilled formulator would have preferred the formulation of McLeskey over Dukes 1989.

181. In fact, Example 3 of Dukes 1989 would have taught away from the addition of benzyl benzoate as used in the castor oil-based formulation in McLeskey. The Example 3 formulation of Dukes 1989 contained benzyl alcohol and castor oil and was administered every two weeks -- twice the duration of McLeskey. Ex. 1007 at 9. However, in addition to benzyl alcohol, McLeskey contained ethanol and benzyl benzoate, but was administered more frequently, once per week. Ex. 1005 at 2. Using the reasons of Dr. Forrest and ignoring the route of administration, the comparison of Dukes 1989 to McLeskey shows 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.

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

182. Dr. Forrest concludes, without explanation or support, that because "fulvestrant was commonly known in the art to be useful in treating hormonal dependent malignant breast cancer . . . the POSA would have understood the fulvestrant formulations disclosed in McLeskey to be useful in treating breast cancer." Ex. 1003 at ¶ 97. In other words, Dr. Forrest simply assumes that any fulvestrant formulation will work if administered as in Howell 1996, including McLeskey.

183. Dr. Forrest cites nothing to suggest that the formulation in McLeskey is the same as used in Howell 1996. In fact, as discussed above, 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

184. McLeskey disclosed experimental formulations for use in animals -- not clinical formulations for human use. Dr. Forrest acknowledges that the castor oil-based formulation in McLeskey was "suitable for parenteral administration in animals." Ex. 1003 at ¶ 96. But, Dr. Forrest provides no basis for supposing that the animal formulations in McLeskey would work in humans. 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.

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

185. 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.

186. Dr. Forrest has not cited any previously marketed product that contains the claimed combination of excipients, and I am not aware of any. In fact, Dr. Forrest 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. 1043 (Powell 1998) at 7-9; Ex. 2088 (Nema) at 3; Ex. 2111 (Avis Ch. 5) at 29.

187. Dr. Forrest 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. 1005 at 10.

3) Making The McLeskey Formulation Would Introduce Additional Unpredictability

188. 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 '680 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 11:65-12:3. 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.

189. 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. 1005 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 ¶¶ 62-65.

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

190. 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. 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

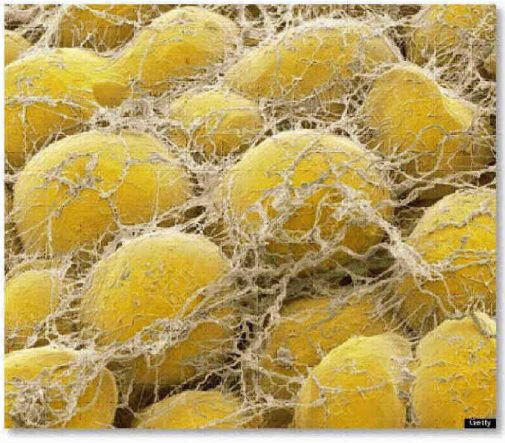
191. Dr. Forrest argues that a formulator would have known that "the formulation disclosed in McLeskey should be administered intramuscularly to perform fulvestrant's known function of treating breast cancer." Ex. 1003 at ¶ 98. But, McLeskey administered both formulations subcutaneously, not intramuscularly. Dr. Forrest provides no basis for supposing that the McLeskey formulations would work when administered intramuscularly instead of subcutaneously.

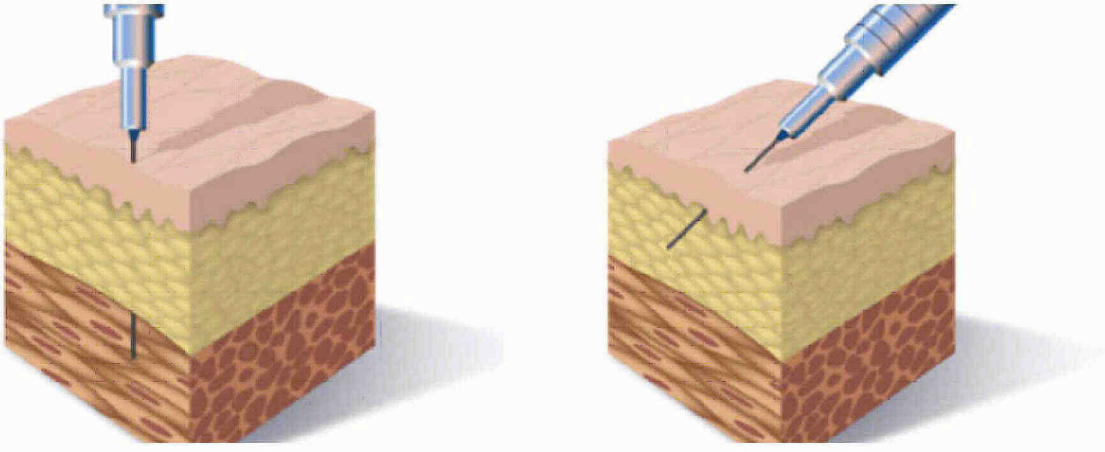
192. In fact, the skilled formulator would not expect a formulation administered subcutaneously to work as intended when administered intramuscularly. Specifically, the local environment a drug would encounter following an *intramuscular* injection is very different from the environment the same drug 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. 2108 (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. 2083 (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





193. "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. 2083 (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. 2119 (Tse II) at 1-5.

194. 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[.]").

195. 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. 2119 (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 ("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 not have adopted Dr. Forest's opinion that there would be no difference in release profile between subcutaneous and intramuscular injections. *See* Ex. 1003 at ¶ 76 (Dr. Forrest says that "[e]ven if the McLeskey formulation was an oil suspension, the POSA would have known that the two types of formulations would have behaved similarly in a human patient.").

196. 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. 2083 (Ansel Ch. 4) at 30.

197. 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 ¶¶ 166-168. 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 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.

198. In order to arrive at the formulation of the claimed method of treatment and to explain how a formulator could produce the formulation of the inventions based on available art, Dr. Forrest looks to a narrow selection of formulations disclosed in the scientific literature and proposes that a formulator would simply transpose a formulation used in one context to another context. He gives no reason why a formulator would look for existing formulations in the art in the first instance, nor why one would use a given formulation in a totally different

manner than its original application; he also gives no indication of how to predict that in doing so, one would arrive at the properties of the claimed inventions.

199. In sum, for all of the reasons discussed above, I disagree with Dr. Forrest's 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.

XV) UNEXPECTED RESULTS

A) The Unexpected Results Of The Claimed Inventions

200. 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 physical 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 5:55-59. 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 6:9-12. 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 6:13-18. 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.

201. 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 1:18-21. 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 8:58-60. This was surprising because aqueous suspension formulations caused "extensive local tissue irritation" as well as "a poor release profile." Ex. 1001 at 8:64-65. 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 9:7-8. 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 9:14-16. 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 9:17-23.

202. 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 9:42-44 (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 10:49-51. 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 10:35-37.

203. Dr. Forrest claims that the "supposed 'challenges' set forth in the '680 Patent do not find support in any publication specific to drug formulation and they are therefore immaterial." Ex. 1003 at ¶ 163. In fact, the literature at the time

highlighted the importance of drug solubility. Ex. 2094 (Aulton Ch. 13) at 32-33 ("The need for adequate drug solubility cannot be overemphasized."); Ex. 2081 (Remington's Ch. 75) at 13 ("When a drug substance has an aqueous solubility less than 1 mg/mL in the physiologic pH range (1-7), a potential bioavailability problem may exist and preformulation studies should be initiated to alleviate the problem.").

B) The Unexpectedly Superior Solubility Of Fulvestrant In The Claimed Formulation Was Not Taught In The Prior Art

204. 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.

205. Attempting to diminish the unexpected increase of fulvestrant solubility from benzyl benzoate, Dr. Forrest states that "the literature well known to the POSA established that a solute can have increased solubility in a mixture of solvents, despite the fact that the solute may not have high solubility in one or more of the individual solvents in the solvent mixture." Ex. 1003 at ¶ 163. In support, Dr. Forrest lists three examples in the literature (Ex. 1003 at ¶¶ 166-168) related to other active ingredients and solvent systems. However, Dr. Forrest does

not explain why a skilled formulator would associate his examples with fulvestrant, a molecule with very unique properties. Further, each of Dr. Forrest's examples contain a solvent with only a single co-solvent, unlike the solvent and three co-solvents of the claimed inventions.

206. Dr. Forrest states that the solubility of a drug depends on many factors, including the drug's solubility in each individual solvent. Ex. 1003 at ¶¶ 164-165, 170-171. I agree. Dr. Forrest cites to various handbooks and treatises to which, he argues, a formulator could refer in order to learn about the molecular rules that govern solubility, such as hydrogen bonding, polarity, and polar dipoles. Ex. 1003 at ¶¶ 170-171. However, Dr. Forrest does not suggest any specific conclusions that a formulator could draw from these treatises; instead, he asserts generally that a skilled formulator would "take[] into account intermolecular forces such as hydrogen bonding nature . . . and the number of polar groups." *Id.* at ¶ 171.

207. Dr. Forrest asserts that a skilled formulator would have expected benzyl benzoate to improve the solubility of fulvestrant in the solvent mixture, based on the fact that fulvestrant is a highly lipophilic molecule, with a sulfinyl group that might impart "some polarity and hydrogen bonding nature" to the molecule. Ex. 1003 at ¶¶ 172-173. But, this theory ignores the poor solubility of fulvestrant in benzyl benzoate compared to other solvents. Specifically, Dr.

Forrest has not shown how a skilled formulator could have predicted that any "additional hydrogen bonding and polarity" from benzyl benzoate would have compensated for fulvestrant's much lower solubility in benzyl benzoate than in castor oil and the alcohols. Dr. Forrest appears to start with the inventors' surprising discovery and then to speculate in broad terms how this result might be consistent with general solubility principles. But, Dr. Forrest has cited nothing in the art from before or after 2000 to support or confirm his speculations as applied to fulvestrant formulations.

208. Similarly, 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. Forrest does not explain why a skilled artisan would have selected benzyl benzoate over any other solvent. Dr. Forrest instead takes the selection of benzyl benzoate for granted and simply suggests why it might have worked.

209. I note that Dr. Forrest relies on the disclosures in the specification of the patents-in-suit for the assertion that fulvestrant was "already known in the art to be highly soluble in benzyl alcohol, ethanol, and castor oil." Ex. 1003 at ¶ 173. This is a misleading statement. These solubilities were not known in the prior art, but instead were disclosed by the inventors in the specification as part of the

inventions. Thus, contrary to Dr. Forrest's assertions, fulvestrant's solubilities were not "known in the prior art" at all, at the time of claimed inventions.

210. Dr. Forrest's assertions regarding the ability of a formulator to predict an increase in solubility based on the molecular character of an active ingredient contradict typical formulation practice and completely ignore the necessary step of a *pre-formulation screen*. A skilled formulator would not choose a commercially available formulation and expect to simply replace the active ingredient with fulvestrant. 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).

211. "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 14-15. 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.

212. 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 ('520 Patent) 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.

213. Dr. Forrest claims that the solubility of fulvestrant in various solvent mixtures could have been established by routine experimentation by using solubility parameters and solubility theory calculations. Ex. 1003 at ¶¶ 174-175. To the contrary, as discussed above, the solubility of an active pharmaceutical ingredient in each solvent of a multi-solvent system must first be established by

preformulation work. The solubility of each active ingredient would have to be established in each proposed multi-solvent system. Dr. Forrest's cited references do not even purport to enable the formulator to predict effects on the solubility of a solid, like fulvestrant, in a complex solvent and co-solvent system. Instead, Dr. Forrest's references are limited to predicting whether certain materials are miscible in each other. *See* supra at ¶¶ 69-70.

C) Additional Unexpected Properties Of The Inventions Were Not Taught In The Prior Art

214. Of the clinical publications cited by Dr. Forrest as disclosing experimental formulations of fulvestrant used in humans, none of them disclose all of the excipients of the fulvestrant formulations. For example, Howell 1996 (Ex. 1006) does not disclose the composition of any individual formulation. Additionally, Howell 1996 poses more questions than it answers. For instance, Howell 1996 stated that "a direct pharmacokinetic - pharmacodynamic link is not proven with the few patients to date." Ex. 1006 at 6. Howell 1996 suggested 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. 1006 at 6. Howell 1996 suggested that tamoxifen withdrawal may account for some of the responses seen in the patients. Ex. 1006 at 307. Howell 1996 concluded that "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. 1006 at 7.

215. As another example, McLeskey fails to disclose the castor oil formulation of the inventions of the patents-in-suit. The formulation of the inventions is an intramuscular formulation while the McLeskey formulations are administered subcutaneously. The formulation of the inventions is intended for administration once a month while the formulation in McLeskey apparently requires administration once a week. Ex. 1005 at 5. McLeskey does not provide the exact percentages of the formulation components. Ex. 1005 at 2. Additionally, 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 would be of little help to the skilled formulator in developing an appropriate formulation of fulvestrant for administration to humans.

216. The skilled formulator would not be able to predict the effect of changes in a formulation or administration method on the *in vivo* performance, i.e. the fulvestrant plasma levels and the fulvestrant release profile. 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. These possibilities could all cause serious problems for effective treatment of patients.

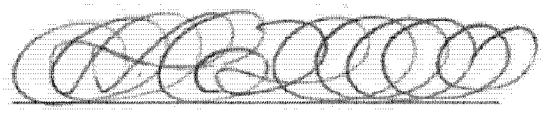
217. The patent specification describes the "satisfactory release of fulvestrant over an extended period of time" as an advantage of the inventions of the patents-in-suit: "We have surprising found that the above formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time." Ex. 1001 at 8:58-60. The inventors described this as surprising, because aqueous suspensions caused "extensive local tissue irritation at the injection site as well as a poor release profile." Ex. 1001 at 8:64-65. Moreover, 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 9:6-10. Based on the metabolism of benzyl benzoate, the inventors stated 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 9:14-16. However, 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 9:17-23.

XVI) CONCLUSION

218. For the foregoing reasons, it is my opinion that Mylan has not shown a reasonable likelihood that claims 1-20 of the '680 Patent are unpatentable.

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



Dated: October 6, 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, California, 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

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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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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)

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")
2039	E.J. Thomas, *The effects of ICI 182,780, a pure anti-oestrogen, on the hypothalamic-pituitary-gonadal axis and on endometrial proliferation in pre-menopausal women*, 9 Hum. Reprod. 1991 (1994) ("Thomas")
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2044	Innovative Research of America, Time Release Pellets for Biomedical Research, 2014 Product Catalog ("Innovative Research")
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2047	R.J. Santen, *Use of aromatase inhibitors in breast carcinoma*, 6 Endocrine-Related Cancer 75 (1999) ("Santen")
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2054	Suzanne C. Beyea et al., *Administering IM Injections The Right Way*, 96 A. J. Nursing 34 (1996) ("Beyea")
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 G. 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")

EXHIBIT C

Exhibit	Description
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2084	Kenneth E. Avis, *Parental Preparations*, *in* Remington's Pharmaceutical Sciences, Ch. 84 (Alphonso R. Gennaro ed., 18th ed. 1990) ("Remington's Ch. 84")
2085	J.L. Ford, *Parenteral Products, in* PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN, Ch. 21 (M.E. Aulton ed., 1988) ("Aulton Ch. 21")
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 & Gayle A. Brazeau eds., 1999) ("Gupta Ch. 1")
2088	Sandeep Nema et al., *Excipients and Their Use in Injectable Products*, 51 PDA J. Pharm Sci. Tech. 166 (1997) ("Nema")
2089	Vidal® 1999 Le Dictionnaire (75th ed. 1999) ("Vidal 1999")
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2092	Steven Abbott & Charles M. Hansen, HANSEN SOLUBILITY PARAMETERS IN PRACTICE, Introduction (2013), *available at* http://www.pirika.com/ENG/HSP/E-Book/Introduction.html ("Abbott & Hansen")
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")

EXHIBIT C

Exhibit	Description
2096	Howard C. Ansel et al., *Solutions, in* PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS, Ch. 12 (7th ed. 1999) ("Ansel Ch. 12")
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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 193-199 (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")

EXHIBIT C

Exhibit	Description
2108	Francis L.S. Tse et al., *Bioavailability of Parenteral Drugs I. Intravenous and Intramuscular Doses*, 34 J. Parenteral Drug Ass'n 409 (1980) ("Tse I")
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")
2111	Patrick P. DeLuca et al., *Formulation of Small Volume Parenterals*, *in* 1 PHARMACEUTICAL DOSAGE FORMS: PARENTERAL MEDICATIONS, Ch. 5 (Kenneth E. Avis et al. eds., 2d ed. 1992) ("Avis Ch. 5")
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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2114	J. Zuidema et al., *Release and absorption rates of intramuscularly and subcutaneously injected pharmaceuticals (II)*, 105 Int'l J. of Pharmaceutics 189, 189 (1994) ("Zuidema 1994")
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EXHIBIT C

Exhibit	Description
2119	Francis L.S. Tse et al., *Bioavailability of Parenteral Drugs II: Parenteral Doses Other Than Intravenous and Intramuscular Routes*, 34 J. Parenteral Drug Ass'n 484 (1980) ("Tse II")
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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*, 11 Anatomical Record 11 (1960) ("Chu 1960")
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