

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:) Confirmation No. 2093
EVANS et al.)
Application No.: 10/872,784) Group Art Unit: 1617
Filed: June 22, 2004) Examiner: Hui, San-Ming R
FOR: FORMULATION)
)

DECLARATION UNDER 35 U.S.C. § 1.132
OF PAUL RICHARD GELLERT

PAUL RICHARD GELLERT of AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK
declares:

1. I graduated from the University of Oxford in Chemistry in 1984. I undertook postgraduate research with Professor Brian Howard in the Physical Chemistry Laboratory at the University of Oxford leading to the award of a D.Phil in 1988. From February 1988 until the present I have been employed by AstraZeneca, (formerly Zeneca and ICI) initially as a Senior Research Scientist and subsequently as a Team Leader/Manager, Principal Scientist and, since 2004, a Senior Principal Scientist.
2. I have worked in the formulation and drug delivery area throughout my career with AstraZeneca, where my research and development work has covered a range of formulation types including sustained released injections, including fulvestrant.
3. During the course of my study of the subject application (hereinafter "the Evans Application") and the underlying data, I have become aware of several transcription or other errors between certain disclosures of the subject application and the underlying laboratory notebook data. One purpose of this Declaration is to point out the existence

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and nature of these errors and to report further testing that has been carried out under my guidance to obtain additional data (paragraphs 4-10 below and Attachments A-D). A further purpose of this Declaration is to set out and document the manner in which an experienced formulator would likely have approached the task of developing a sustained release injectable formulation suitable for human use for a steroidal compound such as fulvestrant in about early 2000, which I understand is when the priority applications supporting the Evans Application were filed (paragraphs 11 - 25 below and Attachment E). Citations to literature and patent references in this Declaration will be in the format Lead Author (Date), and the full citations are given in the Table of References at the end of this Declaration. A copy of each cited reference (or cited portions of the longer references) is included in Attachment F under the Tab number noted in the Table of References.

4. In Table 2 of the Evans Application, the solubility of fulvestrant in castor oil appears to have been transcribed incorrectly from the original source, the laboratory notebook. The value in the latter is 24.5 mg/ml and not 20 mg/ml. In other experiments to determine the solubility of fulvestrant in castor oil and also in benzyl benzoate, some variability was observed.
5. In Table 3 of the Evans Application, the given solubility values were generated at 4°C and not at 25°C as is stated in the title of Table 3. For fulvestrant formulations, it is preferable that the fulvestrant remains completely in solution at both 4°C and 25°C. The 4°C temperature corresponds to the storage temperature (2°C to 8°C in the FDA approved label for Faslodex), and the 25°C temperature corresponds to the administration temperature (ambient temperature). In addition, the specified solubility values on this Table 3 are mean values calculated from analysis of replicate samples from one or more trials. The individual values are shown in handwriting in the amended version of Table 3 in Attachment A. In addition, it appears that the mean values for the last three compositions have been incorrectly calculated. The corrected mean values, together with the correction of the temperature from "25°C" to read "4°C", are also shown in handwriting in the amended version of Table 3 in Attachment A.

6. I have evaluated the transcription and other errors against the original application disclosures and conclude that these do not change the ultimate conclusions made from the data as originally reported. The addition of 15% w/v benzyl benzoate to compositions having total alcohol concentrations in castor oil of 10%, 15%, 20% and 30% w/v unexpectedly provides a positive effect on fulvestrant solubility, significantly increasing the solubility of fulvestrant in the compositions despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.
7. An additional set of experiments has been conducted at 25°C under my guidance to obtain consistent data with reduced variability from a single set of rigorously controlled solubility experiments and to demonstrate that the unexpected increase of solubility of fulvestrant by adding benzyl benzoate into compositions containing ethanol, benzyl alcohol and castor oil, is present across the broader range of composition encompassed by the claims being presented with this Declaration. The solubility of fulvestrant in benzyl benzoate and in castor oil was also measured in the same set of experiments using the same batch of benzyl benzoate and the same batch of castor oil as were used to make up the compositions. The Experimental Test Procedure is described in Attachment B.
8. The results from these solubility experiments are shown in the table in Attachment C. These results show that the solubility of fulvestrant in castor oil alone (21.4 mg/ml) is significantly greater than the solubility of fulvestrant in benzyl benzoate alone (3.8 mg/ml) and demonstrate the unexpected increase in fulvestrant solubility on the addition of 10, 15 and 25% w/v benzyl benzoate, in place of an equivalent amount of castor oil, to compositions having total alcohol concentrations in castor oil of 10%, 15%, 20%, 25% and 30% w/v.
9. Thus, the results that were obtained from experiments conducted under rigorously controlled conditions and with an expanded range of compositions, as shown in Attachment C, confirm the ultimate conclusions drawn from the results shown in Table 3 of the original application disclosure, namely that the addition of 10% to 25% w/v benzyl

benzoate to compositions having total alcohol concentrations in castor oil of between 10% to 30% w/v unexpectedly provides a positive effect on fulvestrant solubility, significantly increasing the solubility of fulvestrant in the compositions despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

10. During the course of my study of the Evans Application and the underlying source materials it was drawn to my attention that some of the composition data given for Delestrogen and Delalutin somehow had been shifted one column to the right. Thus, for Delestrogen, the 78% and 58% figures shown under the BzBz column should have been under the OIL column; the 20% and 40% figures shown under the BzOH column should have been under the BzBz column; and the 2% figures shown under EtOH should have been under the BzOH column. Similarly for Delalutin, the "up to 2%" shown under the EtOH column should have been under the BzOH column. This table reports that the source of this data was J.Pharm.Sci (1964) 53(8) 891, which is Riffkin (1964) elsewhere referred to in this Declaration, and I have also verified the corrected data from the entries for Delalutin and Delestrogen in PDR (1973). A copy of Table 1 from the Evans Application is reproduced as Attachment D, on which these corrections have been made in handwriting, and I have additionally more correctly noted that Delalutin is 17-hydroxy progesterone *caproate*, and that the "COMP" designation for Delalutin should be "BMS" (Bristol-Myers Squibb). Attachment D also includes a one page explanation of the corrections to this Table 1.
11. In about early 2000, a person responsible for developing a sustained release injectable formulation suitable for administration to humans for a new steroidal compound such as fulvestrant, would have had specialized training and experience in developing pharmaceutical formulations and methods for their administration. In developing such a formulation for fulvestrant, the objective would have been to formulate an intramuscular (IM) injection that would provide for the satisfactory sustained release of fulvestrant over a period of at least two weeks and preferably over a period of at least four weeks to reduce the frequency of administration, and would have a target fulvestrant content of at

least 45 mg/mL so as to provide a fulvestrant dose of at least 250 mg in a single 5-6 mL injection. From my personal experience and knowledge of the literature at about that time, I believe that such an experienced formulator would likely have approached the task of developing a formulation for fulvestrant in about the following manner.

12. Given the foregoing objective, the experienced formulator would have appreciated that the traditional administration options to explore were intramuscular (IM) injection of a sustained release aqueous or oil suspension or an oil-based solution (depot) containing at least 250 mg of fulvestrant in a volume of vehicle that is tolerable for injection, *i.e.*, no more than 5 or 6 mL.
13. Because of the extremely low solubility of fulvestrant in water, a reasonable starting point would have been to investigate intramuscular injection of an aqueous or oil suspension of fulvestrant. However, the formulator would have found that injection of an aqueous suspension of fulvestrant resulted in extensive local tissue irritation at the injection site as well as a poor release profile, such as reported in paragraph [0042] of the Evans Application. Since suspensions thus were not an acceptable option for fulvestrant, the experienced formulator would have moved on to further explore whether 250 mg of fulvestrant could be solubilised in no more than 5-6 mL of an oil-based vehicle, *i.e.*, to achieve the target fulvestrant concentration of at least 45 mg/mL.
14. In the preformulation phase, the experienced formulator would have conducted a literature review or otherwise would have become familiar with commercially marketed injectable formulations, particularly injectable sustained release formulations of steroids or other relatively insoluble compounds such as those listed in Table 1 of the Evans Application, with the objective of identifying potential oil vehicles, co-solvents and other excipients that already had been found to be tolerated and/or to have passed through regulatory review, and which might be candidates for further consideration and testing for the fulvestrant formulation. This review also would have provided guidance with respect to concentration levels of such co-solvents and other excipients that generally had been found acceptable in sustained release oil-based intramuscular injections administered to

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