DECLARATION OF SANDRA MCLESKEY, Ph.D.

I, Sandra McLeskey, declare as follows:

I. Background

1. I earned a BS in chemistry from Duke University in 1963, a BSN in nursing from George Mason University in 1982, and a Ph.D. in pharmacology from Georgetown University in 1989.

2. After obtaining my Ph.D., I worked as a post-doctoral fellow in the laboratory of Francis G. Kern in the Department of Biochemistry at the Lombardi Cancer Center, Georgetown University. During that time, I conducted research on the mechanisms of cancer growth in tamoxifen-resistant breast cancer cells, including research that led to the publication of the article *Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant in vivo to the antiestrogen ICI 182,780 and two aromatase inhibitors*, Clin Cancer Res 4:697-711 (1998) ("McLeskey Publication").

3. I was the primary individual responsible for conducting the research discussed in this article, as well as the first author of the publication.

II. The McLeskey Publication

4. The McLeskey Publication discusses an academic research project aimed at elucidating the mechanism of cancer cell growth in tamoxifen-resistant breast cancer cells that do not depend on estrogen for growth stimulation. This property is called estrogen independence. These cells became estrogen independent and tamoxifen resistant when they were engineered to express a fibroblast growth factor (FGF). In particular, the paper explores the question of whether tamoxifen resistance is related to FGF signaling pathways.

5. The study was not designed to look at the treatment of any disease with fulvestrant. Rather, we used fulvestrant as a tool to help us in examining a possible pathway of tamoxifen resistance. In fact, we used three different drugs (fulvestrant and two aromatase inhibitors) as tools to make sure that the estrogen receptor (ER) was not activated by small amounts of estrogen synthesized by the mouse's liver and adrenal glands --with the goal being to determine if the activity of FGF (rather than estrogen) could drive tumor growth in tamoxifen-resistant breast cancer cells. We hypothesized that, "[i]f FGF-mediated growth pathways bypass the ER pathway to affect growth directly, we would expect that growth would be unaffected by hormonal treatments devoid of agonist activity." (See page 698).

6. The paper is clear that the formulations of these drugs were for research purposes for subcutaneous administration to mice--not treatment of humans. For example, we administered tamoxifen as sustained-release pellets implanted subcutaneously. Those pellets were available commercially for experimentation in mice and used for only that purpose--there is no corresponding formulation for humans. Similarly, the formulations of the other drugs were for use in mice subcutaneously for research, including the two different fulvestrant formulations: a peanut oil and a castor oil formulation. As is clear from the paper, and in particular Figure 1, we treated the peanut oil and castor oil formulations as interchangeable for the purpose of our research, and we did not draw any comparisons between the two formulations.

7. Our paper also does not include plasma or blood levels of any of the drugs used, including fulvestrant, nor any information regarding the rate or extent of absorption of the drugs following subcutaneous administration. This is not surprising, given that the study was designed to look at issues relating to basic science and not drug formulation.

8. For the same reason, our paper also does not specify whether the percentages in the castor oil formulation are in weight/volume (w/v) units or in volume/volume (v/v) units (in fact, I assumed that the percentages were in v/v units, because the components of the formulation were liquids).

9. In my opinion, the McLeskey Publication clearly reflects that the purpose of our research was not to evaluate methods of treating any disease using fulvestrant. In fact, to the extent that we discuss the effect of fulvestrant, the point is that it did not inhibit estrogen-independent tumor growth of FGF-expressing breast cancer cells, as we hypothesized. Specifically, the abstract states that the formulations "did not slow estrogen-independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice." Additionally, 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 ICI 182,780 [fulvestrant]." (See page 701).

10. The McLeskey Publication was published in *Clinical Cancer Research,* which is a journal of the American Association for Cancer Research (AACR). The AACR is a professional organization of cancer researchers. The manuscript was submitted to *Clinical Cancer Research* because that journal has an expressed interest in publishing research on mechanisms of drug sensitivity and resistance.

11. In short, in my opinion, a scientist interested in developing a treatment for humans using fulvestrant would not have looked to the McLeskey Publication for guidance given that it is directed to exploring a pathway of cancer growth different and independent of fulvestrant's mechanism of action, and it provides no information about how to formulate an intramuscular preparation providing sustained release for humans. Moreover, the McLeskey

Publication appeared in a journal whose target readership is cancer researchers, and the formulations used were research formulations for use in mice.

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

10/1/14

Date:

Sandra W. McLeskey

Sandra McLeskey, Ph.D.