Robert M. Califf, MD

Commissioner of Food & Drugs

U.S. Food & Drug Administration

10903 New Hampshire Avenue

Silver Spring, MD 20993

Dear Dr. Califf

In May 2019, the Contraceptive Study Group (CSG) submitted a Citizen’s Petition to the FDA requesting updating the prescribing information and patient information of hormonally active contraceptives. In the petition, the CSG pointed out that hormonally active contraceptives have been on the market for over sixty years and, while their formulations and routes of delivery have changed, their basic mechanism of action has remained the same. In the intervening years since hormonally active contraceptives were first introduced, numerous studies have documented their myriad side effects. Some of these side effects appear over time, some within weeks, and others may take months or years to materialize, but all can have a serious impact on a woman’s health and quality of life.

The CSG performed a series of comprehensive literature surveys to better understand the immediate and long-term side effects of hormonally active contraceptives. The results of this literature review uncovered a significant number of side effects that range from likely to definitively related to hormonally active contraceptive use, some of which are lethal. Some of these risks and side effects are acknowledged by current prescribing information and package inserts, yet many more are not mentioned at all.

Among the unacknowledged side effects for depot medroxyprogesterone acetate (DMPA) is a significantly increased risk of contracting HIV infection. For combination hormonally active contraceptives, the unacknowledged side effects include: breast cancer, cervical cancer, Crohn’s disease, ulcerative colitis, systemic lupus erythematosus, depression, mood disorders and suicides (especially among women twenty-five years of age and younger, in the first six months of use), multiple sclerosis, interstitial cystitis, female sexual dysfunction, osteoporotic bone fractures (especially for progesterone-only contraceptives), and weight gain. Misleading prescribing information regarding cardiovascular and thrombotic risks is also noted.

In one case—that of DMPA—the increased risk of contracting HIV has been conclusively demonstrated to be both real and unique to this drug. Considering the availability of numerous alternatives, there is no justification for the continued marketing of DMPA to the public.

Through research and review, the CSG was able to assess that up to 1.2 million American women are currently affected by one or more of these serious medical conditions, as a result of their past or current use of hormonally active contraceptives. The CSG also deduced that between 300-400 women die per year from VTE directly related to their use of hormonal contraceptives.

It has now been over 4 years since we submitted the Citizen’s Petition to the FDA reporting these serious issues. In that time, the information in the petition has been published, and is available on PubMed in 4 separate peer-reviewed journal articles. These are referenced below.

These articles confirm the unacknowledged risks and misleading information in the prescribing information and package inserts for hormonally active contraceptives. As you are undoubtedly aware, online providers like NURX directly market these potent medications to women without a face-to-face interaction with a physician, and without presenting sufficient information regarding their risks. As online retailers of birth control continue to proliferate, more young women will experience side-effects, some with tragic consequences, as a result of this lack of information. Also, the FDA has announced the decision to make one class of progesterone-only contraceptives (POCs) available over the counter. The numerous unacknowledged risks associated with POC use raises additional serious concerns to making these potent steroidal agents widely available without physician supervision.

Since the initial submission of the Citizen’s Petition, additional studies have been published and the petition has been updated accordingly. This includes updated information on several risks previously noted as well as new information on the development of autism in the children of individuals taking hormonally active contraceptives at the time of conception.

The CSG would like to acknowledge the response of the FDA regarding to the increased risk of breast cancer with hormonally active contraceptives. The CSG applauds the thoughtful and thorough review of the FDA regarding breast cancer risk. However, the CSG does not concur with the FDAs mandated changes to hormonally active contraceptive labeling as detailed in the attached updated petition.

Only the FDA can correct this dire situation and require more transparency from pharmaceutical manufacturers and prescribers.

We appreciate your consideration of this urgent matter. We are counting on your understanding of the need of women to receive comprehensive, accurate information on these risks --and on your commitment to serve them.

Our concern is solely for women’s health. We urge you to take action on their behalf.

Sincerely,

William V. Williams, M.D.

On behalf of the Contraceptive Study Group

620 South Eagle Road

Havertown, PA 19083

Cc: Patrizia Cavazzoni, MD

Director

Center for Drug Evaluation and Research

U.S. Food & Drug Administration

10903 New Hampshire Avenue

Silver Spring, MD 20993

References:

Williams WV. Hormonal contraception and the development of autoimmunity: A review of the literature. Linacre Q. 2017 Aug;84(3):275-295.

Williams WV, Mitchell LA, Carlson SK, Raviele KM. Association of Combined Estrogen-Progestogen and Progestogen-Only Contraceptives with the Development of Cancer. Linacre Q. 2018 Nov;85(4):412-452

Williams WV, Brind J, Haynes L, Manhart MD, Klaus H, Lanfranchi A, Migeon G, Gaskins M, Seman, EI, Ruppersberger L, Raviele KM. Hormonally Active Contraceptives Part I: Risks Acknowledged and Unacknowledged. *The Linacre Quarterly*. 2021;88(2):126-148.

Williams WV, Brind J, Haynes L, Manhart MD, Klaus H, Lanfranchi A, Migeon G, Gaskins M, Seman, EI, Ruppersberger L, Raviele KM. Hormonally Active Contraceptives Part II: Sociological, Environmental, and Economic Impact. *The Linacre Quarterly*. 2021;88(3):291-316.