October 28, 2019

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: FDA-2019-D-2966, Male Breast Cancer: Developing Drugs for Treatment Draft Guidance

To Whom It May Concern:

Thank you for the opportunity to submit comments on behalf of our organizations and the millions of Americans we represent.

We applaud the FDA's efforts to provide direction on the inclusion of men in breast cancer drug clinical trials. This population has long been overlooked. Our communities have a strong interest in the inclusion of men in breast cancer drug clinical trials. As the guidance document states, "[b]reast cancer is rare in males, with less than one percent of all breast cancer cases occurring in male patients." While the majority of breast cancers in men are thought to be sporadic, risk is increased to 7-8% in men who carry a BRCA2 mutation and to 1% in men with a BRCA1 mutation. Up to 14% of men diagnosed with breast cancer harbor a BRCA2 mutation. Some studies have reported worse prognosis in male breast cancer patients with a deleterious BRCA1 or BRCA2 mutation compared to those without a mutation. Other studies suggest that mutations in the CHEK2, PTEN and PALB2 genes might also increase the risk of male breast cancer.

The FDA advises that eligibility criteria for clinical trials of breast cancer drugs should allow for inclusion of both males and females. We fully support this recommendation, as large independent randomized controlled trials of male breast cancer patients are difficult to achieve and less likely to have as much statistical power as trials including both men and women. This would also allow transgender individuals to be eligible for clinical trials. We approve of efforts to increase clinical trial inclusivity and urge the FDA and trial sponsors to consider the unique needs of this population.

PARP inhibitors are a promising class of drugs initially developed for people with germline BRCA mutations and now have indications for those with somatic mutations as well. Lynparza and Talzenna are labeled as treatment for "adult patients"—with no mention of gender. However, many people with metastatic breast cancer are treated with other agents, such as CDK4/6 inhibitors. Of these, only palbociclib explicitly includes men in the package label. Ribociclib and abemaciclib are labeled specifically for women with metastatic breast cancer. We believe this guidance will be beneficial in facilitating the inclusion and

enrollment of men, and is likely to increase access to an expanded number of therapies for male breast cancer patients by providing clarity about which treatments are appropriate for them.

Further, our organizations support the FDA's suggestion that sponsors submit clinical development recommendations discussing the degree to which trial results can be extrapolated to males. Industry is encouraged to provide information on anticipated gender differences in drug efficacy and safety, based on factors such as drug mechanism of action and earlier preclinical or clinical data. The draft guidance goes on to state, "further data may be necessary to support extrapolation of findings and an FDA-approved indication for male patients with breast cancer," and "a variety of trial designs using different data sources, including small-single arm trials and studies using real-world evidence sources" can facilitate the generation of this information. We agree that information on how male breast cancer patients might respond to certain therapies would be useful, but the ideal scenario is inclusion of this population in clinical trials.

Under the 21st Century Cures Act, the FDA was directed to launch a Real-World Evidence (RWE) Program to evaluate the potential use of real-world data (RWD) to generate RWE of product effectiveness to support approval of new indications for drugs. The 2018 Framework for FDA's Real World Evidence (RWE) Program described the "potential use of RWE to support changes to labeling about drug product effectiveness, including adding or modifying an indication, such as a change in dose, dose regimen, or route of administration; adding a new population; or adding comparative effectiveness or safety information." This draft guidance provides some clarity on where studies using RWD may provide information on a new population for inclusion in drug labeling. Further FDA direction on use of RWD to support label changes would be useful.

While this is only a guidance document—not a mandate—we believe it serves as a positive step toward addressing the historic disparity in breast cancer trials and drug development for men with breast cancer. We encourage industry sponsors to improve their inclusion of men in breast cancer clinical trials and collaborate with FORCE and other organizations that serve the male breast cancer community to increase enrollment and improve knowledge regarding their responses to therapies.

Sincerely,

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