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September 8, 2020

VIA ELECTRONIC SUBMISSION

Stephan Hahn, M.D.
Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Office of Women’s Health Strategic Priorities; Establishment of a Public Docket; Request for Comments (Docket No. FDA–2020–N–1391)

Dear Commissioner Hahn:

I am writing to you on behalf of Susan G. Komen (Komen) in response to the Food and Drug Administration (FDA)’s request for information, “Office of Women’s Health Strategic Priorities.” Komen is the world’s leading nonprofit breast cancer organization representing the millions of women and men who have been diagnosed with breast cancer. Komen has an unmatched, comprehensive 360-degree approach to fighting this disease across all fronts—we advocate for patients, drive research breakthroughs, improve access to high quality care, offer direct patient support and empower people with trustworthy information. Komen is committed to supporting those affected by breast cancer today, while tirelessly searching for tomorrow’s cures. We advocate on behalf of the estimated 279,100 women and men in the United States who will be diagnosed with breast cancer and the more than 42,690 who will die from the disease in 2020 alone.

Comments on Draft Guidance

Komen appreciates the opportunity to provide suggestions and information for consideration as the FDA’s Office of Women’s Health (OWH) develops research priorities driven by data gaps and areas of unmet need; topics for education among consumers, health professionals, and other stakeholders; and outreach to women, especially underserved and diverse populations.

Efforts to Encourage Analysis and Detection of Potential Sex and Gender Differences in Safety, Efficacy and Use of FDA-regulated Products

While many disease site research projects lack appropriate representation of women, in breast cancer the opposite is true. While an estimated 2,670 men in the United States will be diagnosed with primary invasive breast cancer, men are often excluded from breast cancer clinical trials. Thus, Komen applauds the FDA for recently finalizing the Guidance to Industry on Developing Drugs for Men with Breast Cancer. **Komen recommends FDA consider similar guidance for health research where women are under-represented – such as in cardiovascular disease, hepatitis, HIV, kidney disease, and digestive disease -- to ensure that the proportion of female participants reflects the gender distribution of real-world patients.**

Similarly, FDA also finalized Guidance for Industry on Cancer Clinical Trial Eligibility Criteria for Patients with Organ Dysfunction or Prior or Concurrent Malignancies. As the guidance acknowledges, as the lifespan of the general population increases, a greater number of patients are anticipated to have prior or concurrent malignancies. By excluding individuals from cancer clinical trials who have major organ dysfunction or previous or concurrent cancers, trial recruitment may favor younger patients, which may not be fully representative of the population for whom the drug will be indicated. Finally, FDA's draft guidance on Inclusion of Older Adults in Cancer Clinical Trials will be important for breast cancer patients as age is a well-established risk factor for breast cancer. The median age of diagnosis of breast cancer in the U.S. for men is 67 and 62 for women, with approximately a quarter of all cases in women occurring in those from age 75-84.¹ **Komen appreciates and supports this and future similar guidance that seeks to ensure inclusion and allow robust analysis of efficacy.**

Efforts to Anticipate, Meet, and Respond to Existing and Emerging Issues Related to Women's Health and FDA-regulated Products

With more than 40,000 deaths from breast cancer each year in the United States, Komen knows investment in biomedical research to support the development of innovative drugs and devices remains imperative. However, today's novel therapies and technologies require novel approaches to safety, drug development and clinical practice.

Reliable access to safe, high-quality and affordable drugs is a critical part of treating cancer. Patients with breast cancer are treated with some combination of surgery, radiation therapy, and/or drug therapy, with treatment tailored to the biology or type of breast cancer, stage of breast cancer and the patient's overall health and preferences. Patients must have access to all treatment options to ensure the best outcomes.

Precision medicine depends on a full understanding of the benefits and risks associated with a treatment option. Patients expect that drugs will be effective in treating their cancers; maintaining high quality of life is also an important priority in care, necessitating as many treatment options as possible, including drugs in different classes and with different mechanisms of action, different risk profiles, and different toxicities. **Komen suggests that the FDA consider minimally effective dose versus the maximum tolerated dose in drug development.**

Precision medicine also depends on high-quality information, data sharing and reporting of results. Clinical trials can only improve patient care with timely, accurate reporting of results – both positive and negative. Further, because clinical trials increasingly use surrogate endpoints and/or don't follow patients beyond 5 years, post-approval clinical trials and real-world evidence are critical to understanding the efficacy and long-term consequences of therapy

As of January, 2020, the FDA had never imposed a fine on a clinical trial sponsor for failing to report results despite high-profile allegations that failure to submit data may be hampering investigations into safety and effectiveness.^{2,3} **We encourage FDA to utilize enforcement authorities and consider collaboration with other agencies, such as the Department of Health and Human Services (HHS),**

¹ Howlader N, Noone AM, Krapcho M, et al. (editors). SEER Cancer Statistics Review, 1975-2016. Tables 1.10 and 1.11. Median age of cancer patients at diagnosis, 2012-2016. National Cancer Institute. Bethesda, MD. Accessed on April 23, 2020.

² <https://science.sciencemag.org/content/367/6475/240>

³ <https://www.statnews.com/2020/08/04/nih-warns-missing-clinical-trial-data/>

Office of the Inspector General (OIG), as appropriate. Also, FDA must ensure completion of post-approval clinical trials to ensure understanding the efficacy (or lack thereof) and long-term consequences of therapies.

Komen supports including diverse patient voices in all stages of drug development to ensure a patient's needs, values and perspectives are integrated into these discussions. **We applaud the FDA's development of patient-focused drug development (PFDD) guidance documents to address how stakeholders can collect and submit patient experience data and other relevant information from patients and caregivers for medical product development and regulatory decision making.** As patients are the ultimate consumers and beneficiaries of new drugs, their feedback is vital to improving clinical pathways and outcomes. We look forward to future phases of PFDD.

Finally, young women being treated for breast cancer are concerned about loss of fertility. Chemotherapy attacks fast-growing cells, and this includes not only cancer cells but also healthy cells in other parts of the body, like the ovaries. Additionally, cancer treatment can bring on natural menopause earlier than normal which limits time for pregnancy and childbirth, especially for women who are older than 40 during treatment.⁴ **More research is needed on preserving fertility during cancer treatment, including examination of how a treatment could protect ovaries from damage during chemotherapy and lower the chances of early menopause and help preserve fertility.**^{5,6,7}

Direct Outreach to Diverse Groups of Women to Promote Access to Relevant Information About FDA-regulated Products, Encourage Participation in Clinical Trials, and Maintain Dialogue about Critical Women's Health Topics

Knowledge is only powerful if patients understand what they are learning. On average, U.S. adults read at an eighth-grade level. As such, the Centers for Disease Control and Prevention (CDC), the American Medical Association (AMA) and the National Institutes of Health (NIH) all recommend that medical information for the public be written at no higher than an eighth-grade reading level. However, research estimates that 75 percent of patient education materials are written at a high school or college reading level.⁸ In fact, a recent examination of 68 pages on COVID-19 on the CDC's own website registered at an eleventh-grade reading level.⁹ **As such, we suggest that the FDA consider in-depth investigation into improving patient communication, and such tactics may include whether governmental entities, researchers and providers need augmented training and/or standards for patient communication.**

⁴ Partridge A, Gelber S, Gelber RD, Castiglione-Gertsch M, Goldhirsch A, Winer E. Age of menopause among women who remain premenopausal following treatment for early breast cancer: long-term results from International Breast Cancer Study Group Trials V and VI. *Eur J Cancer.* 43(11):1646-53, 2007.

⁵ Moore HC, Unger JM, Phillips KA, et al. for the POEMS/S0230 Investigators. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med.* 372(10):923-32, 2015.

⁶ Lambertini M, Boni L, Michelotti A, et al. for the GIM Study Group. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovarian function, pregnancies, and disease-free survival: a randomized clinical trial. *JAMA.* 314(24):2632-40, 2015.

⁷ Munhoz RR, Pereira AA, Sasse AD, et al. Gonadotropin-releasing hormone agonists for ovarian function preservation in premenopausal women undergoing chemotherapy for early-stage breast cancer: a systematic review and meta-analysis. *JAMA Oncol.* 2(1):65-73, 2016.

⁸ Wallace LS, Lennon ES. American Academy of Family Physicians patient education materials: can patients read them? *Fam Med.* 2004;36(8):571-574.

⁹ Mishra V, Dexter JP. Comparison of Readability of Official Public Health Information About COVID-19 on Websites of International Agencies and the Governments of 15 Countries. *JAMA Netw Open.* 2020;3(8):e2018033.

With specific regard to breast cancer, Komen is a long-time supporter of the Breast Density and Mammography Reporting Act, which was critical legislation to provide information to women and doctors on breast density and the potential impact it has on the detection of breast cancer. We applaud last year's release of Mammography Quality Standards Act (MQSA) Proposed Rule and implementation of that law's requirements to add information about breast density to the mammography law summary letter provided to patients. However, **we encourage you to release a final rule that revises the required text to make it as clear as possible that a person's breast density is high or low, so that they can discuss the findings and potential impact with their physician. Accordingly, we join with other breast cancer organizations to respectfully request that the Agency revise 21 C.F.R. § 900.12(c) as described further in Komen's public comments.**¹⁰

With regard to breast cancer clinical trials, Komen continues to educate patients about clinical trials and advocate to increase access to clinical trials for all breast cancer patients, including underserved populations currently underrepresented. Unfortunately, many patients are unaware of opportunities for participation in clinical trials since their health care providers do not discuss the options with them; are unable to travel long distances since trials are not available where they live; or they do not meet eligibility requirements and are consequently unable to join and receive the many associated potential benefits.

Even though African-Americans make up 12 percent of the U.S. population, less than five percent participate in clinical trials and even fewer Black women participate. Similarly, Hispanics account for 18 percent of the total population but just one percent in trials. There are several barriers, which hinder the inclusion of minority populations in clinical trials, including community perception and distrust of both the government and medical providers, lack of diversity in the healthcare workforce, and geographic and financial access to services.

Komen encourages the FDA to go beyond encouraging diversity of trials to making diverse trial populations the default. **We encourage FDA to consider requiring that study populations reflect the entire patient population who will ultimately use the drug.** For example, just as the Taskforce on Research Specific to Pregnant Women and Lactating Women, mandated by the 21st Century Cures Act, recommended that studies justify the exclusion of pregnant women and lactating women in their study designs¹¹, the FDA could require sponsors to either ensure that the trial participants reflect the patient population who may use the drug (whether that be men with breast cancer, the elderly, people with metastatic breast cancer, Black women, etc.) or provide a rationale for why the trial does not. There should be consequences and accountability for trials that do not meet this standard. For example, FDA could require additional studies in specific populations, with some sort of conditional approval that expires if not completed. FDA could also require that documentation and reporting of diversity be publicly available on clinicaltrials.gov in plain language.

Komen also suggests that the FDA examine clinical trial inclusion criteria through the lens of health equity. Seemingly reasonable eligibility criteria may contain implicit bias. For example, if people with high blood pressure are excluded from trials, then fewer Black men may be eligible as they experience the highest rates of hypertension in the U.S. **Further efforts by FDA to improve diversity could include promotion of innovative research networks and dissemination of knowledge of safe and effective use of medicines in underrepresented patient sub-populations.**

¹⁰ <https://www.regulations.gov/document?D=FDA-2013-N-0134-0132>

¹¹ https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf

Komen believes that where you live should not determine whether you live - and that all people should have equal access to needed high-quality breast health care. As a result, **we encourage the FDA to identify solutions to remove geographical barriers to participation in clinical trials.** Often, breast cancer patients who live far from academic medical centers--where many trials are conducted--are not made aware of opportunities to participate in trials and if they are, the burden and expense of traveling hours at a time is prohibitive to participation. Therefore, we encourage you to consider policies to diversify the institutions that participate in clinical trials. Community-based hospitals and clinics may be better located to recruit diverse trial participants, but this would require reducing the administrative burden on these sites.

Coordination and Collaboration with other Federal Agencies and External Stakeholders to Support Research and Programming on Women's Health Topics

Komen understands that coordination and partnership is crucial to improving the lives of people with breast cancer. Komen would appreciate any opportunity to work with the FDA on research and programming related to breast cancer, including diversity in clinical trials and achieving health equity.

For example, through our African American Health Equity Initiative (AAHEI), Komen is working to implement evidence-based interventions through quality improvement of cancer treatment in partnership with the American Society of Clinical Oncology (ASCO), culturally responsive patient navigation, capacity building for community-based service providers, public policy and advocacy, and cross-sectoral community engagement in 10 cities. However, we know that systemic discrimination is not limited by geography, and Komen believes that broader applications of similar initiatives could advance health equity for breast cancer patients.

We further suggest that FDA examine work of the National Cancer Institute (NCI) and other governmental bodies to improve diversity in clinical trials.¹² Researchers have found that the NCI trials have higher rates of participation of Black patients at nine percent, when compared with industry-led trials at three percent. Such evidence suggests NCI may be a useful partner for improving clinical trial diversity.

More collaboration and research are needed to address barriers in treatment adherence. We know that cancer treatments can be very expensive and require long-term monitoring and follow-up care. Many breast cancer patients face significant financial hardship at a time when the entire country is experiencing economic downturn resulting from the pandemic. More and more stakeholders in the cancer community are recognizing the financial toxicity associated with adhering to treatment as prescribed, which can not only expose patients to financial ruin but also can negatively affect their health if they are forced to delay or stop treatment or make suboptimal treatment decisions due to cost. **We encourage FDA to investigate financial toxicity and how it impacts patients' treatments and overall health.**

Komen also suggests examination of other barriers to care, including transportation and childcare. As the provision of assistance to patients may implicate fraud and abuse restrictions, we recommend that FDA work closely with the OIG to enable such efforts.

¹² <https://www.swog.org/news-events/news/2020/06/22/nci-trials-enroll-more-black-cancer-patients>

Komen encourages FDA to work with the Centers for Medicare & Medicaid Services (CMS) to improve participation in clinical trials for beneficiaries of government sponsored insurance. Patients face unexpected costs when participating in clinical trials, especially those who are the most vulnerable which often includes Medicaid beneficiaries. Komen supports Medicaid coverage of the routine care costs of clinical trial participation for enrollees with life-threatening conditions. The financial pain caused by the COVID-19 pandemic has made enacting this policy even more urgent.

The FDA has a unique role to play in coordinating research priorities across industry and companies. Breast cancer patients and providers need more research to understand combination therapies, including the appropriate sequencing of therapies. Different companies bring different therapies to market, making research across and into the interactions among various products difficult. However, the FDA is in a unique position to incentivize this type of research collaboration and address this gap. FDA also can encourage companies to consider sharing data with the government and other stakeholders to improve our understanding of treatment options and disease and inform future drug development.

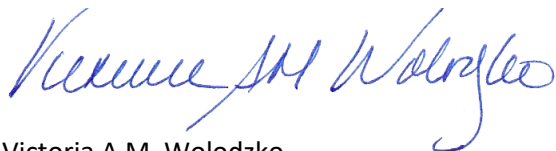
Identification of Regulatory Decisions that Can Benefit from Participation of Women across the Lifespan (e.g., reproductive-age women, pregnant women, post-menopausal women, and elderly women) and Women with Certain Health Conditions.

While these topics were addressed in previous section, we reiterate the urgent need for clinical trials to represent all individuals, across all life stages and life courses.

Conclusion

Again, Komen thanks the FDA for the opportunity to provide suggestions and information. We share the goal to ensure the best possible outcomes for breast cancer patients and survivors today and in the future. If you have any questions, or we may be of further assistance, please do not hesitate to reach out to Molly Guthrie, Director of Public Policy and Advocacy, at mguthrie@komen.org.

Sincerely,



Victoria A.M. Wolodzko
Senior Vice President, Mission
Susan G. Komen