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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

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Citizen Petition Requesting the FDA to Modify its Approach for Addressing Metastatic Cancer

Dear Commissioner Margaret Hamburg, M.D.:

Cancer causes over 550,000 deaths in the United States each year, and 90% of those deaths derive from metastatic cancer. Additionally, a disproportionately high share of the $200+ billion in annual cancer care spending is attributable to metastatic cancer.

As explained herein, the FDA's drug approval process was designed for other circumstances and it is effectively blocking the advancement of compounds for treating metastatic cancer. The result is that metastatic cancer patients are receiving second-class care and society is suffering from the ever increasing cost burden of treating metastatic cancer.

Accordingly, this Petition requests the FDA to undertake an internal examination of its practices, regulations and organizational structure for addressing metastatic cancer, and to modify those items as recommended herein.

Summary of Findings

As documented herein, the FDA lacks sufficient organizational focus on metastatic cancer which has contributed to inappropriate trial procedures and the absence of viable methods to treat metastatic cancer.

This Petition requests that the FDA put a more pronounced focus on this burdensome disease by establishing a Center for the Treatment of Metastatic Cancer.

This new Center would advance new procedures for conducting trials for metastatic cancer, reflecting the differences between metastatic and primary cancer.

In particular, the FDA should collapse its current trial design structure from three phases to two phases for testing the compounds that address metastatic cancer. The regulatory process for these two phases should be tailored to fit the situation as it relates to metastatic cancer.

Finally, after modifying its trial procedures, the FDA and its new Center for the Treatment of Metastatic Cancer should champion an increase in the government's research budget for metastatic cancer from roughly 8% to 15% of the total federal government spending on cancer research. The additional funds

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should be earmarked for grants to research institutions that conduct human trials on compounds that have proven to be effective in retarding metastasis in animal models.

Environmental Impact

The Petitioner claims a categorical exclusion under Part 25.30 of the FDA's Administrative Practices and Procedures regarding the requirement to file an environment impact statement.

Documentation

Over 550,000 people in the U.S. die each year from cancer. See, e.g., the National Cancer Institute website at: http://seer.cancer.gov/statfacts/html/all.html. Tumor metastases are responsible for approximately 90% of all cancer-related deaths. See, e.g., "Molecular networks that regulate cancer metastasis", Spano D, Heck C, De Antonellis P, Christofori G, Zollo M., Semin Cancer Biol. (2012).

In turn, the 5-year survival rate of all patients with metastatic cancer is approximately 20%. See, e.g., "Cancer: Principles & Practice of Oncology, Volume Two", Devita, Hellman and Rosenberg, p. 1729 (2008). This compares to a 5-year survival rate of 67% for all cancers. See: "Cancer Facts and Figures 2012" http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf .

The cost to treat cancer in the United States has been estimated to be over $200 billion per year. See, e.g., http://www.cancer.org/cancer/cancerbasics/economic-impact-of-cancer .

While accurate estimates for the total cost to treat metastatic cancer on an annual basis are not readily available, the cost to treat metastatic cancer is known to be disproportionately high. See, e.g., "Estimates of Lifetime Direct Costs of Treatment for Metastatic Breast Cancer", Berkowitz, Gupta, Silberman, Value In Health (2000). See also: "Metastatic Prostate Cancer: Common, Deadly, Costly", http://www.ucdmc.ucdavis.edu/ucdavismedicine/issues/summer2003/news/news7.html?aID=7 (2003). For estimates of the cost of care by the designated phases of cancer, see: "Economic Impact of Cancer", http://www.cancer.org/cancer/cancerbasics/economic-impact-of-cancer .

On the other hand, while the process of tumor dissemination has been known since 1829, the efforts to address cancer have been focused – for practical reasons – mostly on the primary cancers of specific organs, not metastasis.

For example, in the article entitled: "10 Cancer Treatment Breakthroughs That May Help You", all ten treatments are focused on the primary cancer of a specific organ. See: http://www.carepages.com/cancer/cancer-breakthroughs-of-2009.html .

The spending on research also reflects the historical dichotomy between the focus on primary versus metastatic cancer. For example, the National Cancer Institute reports an annual budget for cancer research of about $5 billion. See: http://www.cancer.gov/cancertopics/factsheet/NCI/research-

funding/print. The category labeled "metastasis" receives about $400M per year, or about 8% of the total. See: http://fundedresearch.cancer.gov/nciportfolio/.

Not surprisingly, metastasis is largely incurable today.

Of course, the approach of focusing on primary cancer by organ has made sense over time based on the relative complexity and understanding of primary versus metastatic cancer.

However, that balance is now changing. See, e.g., "Unlocking the Mysteries of Metastasis" at: http://www.cancer.org/cancer/news/expertvoices/post/2013/01/23/unlocking-the-mysteries-of-metastasis.aspx.

In addition to a better understanding of the process of metastasis, scientists are now uncovering new potential avenues of treatment. For example, Dr. Erik Sahai of the London Research Institute discovered two important molecules that work together to control the spread of cancer. See: http://www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2009-02-10-gene-controllers-crucial-for-cancer-spread.

And positive results are beginning to take hold. For example, a new study from the USC Norris Comprehensive Cancer Center showed that targeting both hormone receptors and the human epidermal growth factor receptor 2 (HER2) in the first-line treatment of metastatic breast cancer patients significantly increased overall survival times. See: http://news.usc.edu/#!/article/50584/study-shows-dual-targeting-of-metastatic-breast-cancer-improves-survival-rates/

Historically, oncologists have believed that the chemotherapy used to eradicate the primary cancer was also the best way to suppress metastasis. However, that view is changing as well. For example, researchers have developed and validated compounds that can inhibit a wide range of metastasis-related pathways in animals. See, e.g., Morton, J. et al. Gastroenterology 139, 292-303 (2010); Criscuoli, M.L., et al. Blood 105, 1508-1514 (2005); Yang, Y. et al. J. Clin. Invest. 109, 1607-1615 (2002); and Muraoka, R. et al. J. Clin. Invest. 109, 1551-1559 (2002).

However, follow-on research in humans for these compounds has not occurred. The principle reason for this vacuum is that the existing clinical trial design ensures that these compounds will fail. In particular, the compounds are not designed to meet the current Phase 2 trial requirement of shrinking existing tumors.

Additionally, the time and cost required for the compounds to meet the current trial design is prohibitive, particularly given that the goal of metastatic cancer trials is delay. This renders the trials to be a non-starter given the projected economics.

Rather, a new approach to trial design is required recognizing the unique aspects of metastatic cancer. More specifically, the current trial design should be collapsed into two phases.

Phase 1 would address both safety and efficacy at various dosages and would consist of a larger sample size than traditional Phase 1 trials. Given the poor prognosis of metastatic cancer patients, the FDA's

role should be limited to oversight to ensure that participants are not subject to an unreasonable risk of accelerated death. Additionally, there should be no requirement that the compounds in the trials have an impact on the existing tumor. Rather, the end point should be length of delay until a metastasis occurs.

If the Phase 1 trial demonstrates promise of metastatic delay, the Phase 2 trial should be afforded a presumption of approval to proceed, enabling proof of safety and effectiveness for drug approval when used in combination with other drugs for treating the primary cancer.

For a discussion of a similar proposed trial design for metastatic cancer by a world-renowned scholar, see Dr. Patricia S. Steeg, Nature 485, S58-59 (May 2012).

Finally, as a steward of public health, the FDA should take a more active role in promoting improved treatments for metastatic cancer. In addition to the dramatic disparity between the research spending and the cost to society of treating metastatic cancer, the care of metastatic patients currently leaves a lot to be desired.

For example, on the one hand, patients place a high value on metastatic cancer therapy—on average, twenty-three times higher than its cost. See: "Patients Value Metastatic Cancer Therapy More Highly Than Is Typically Shown Through Traditional Estimates", Seth A. Seabury, Dana P. Goldman, J. Ross Maclean, John R. Penrod and Darius N. Lakdawalla (May 2013).

But as Drs. Thomas J. Smith and Dan L. Longo observe: "Self-deception is a valuable personal coping tool", New England Journal of Medicine, October 25, 2012.

The fallout from the personal impact of a diagnosis of metastatic cancer may be that the resulting treatment is often far from optimal. For example, a report from the Dartmouth Atlas Project demonstrates that many hospitals and physicians aggressively treat patients with curative attempts that are not appropriate. In essence, many patients are acquiescing to more aggressive care without fully understanding its impact on the length and quality of life. "Quality of End-of-Life Cancer Care for Medicare Beneficiaries": Regional and Hospital Specific Analyses", Goodman et al., November 16, 2010.

In short, the deck is currently stacked against advances in the treatment of metastatic cancer. Without an increased focus, revised clinical trial procedures and additional research funds, there will continue to be limited treatment options for metastatic cancer and the cost to society and patients from metastatic cancer will continue to grow.

Legal Basis for Requested Relief

The statutory purpose of the Food and Drug Administration (FDA) is to protect public health by ensuring that the products under its domain are safe and effective for human use.

The FDA has the discretion to develop different safety guidelines for different categories of products under its jurisdiction. For example, safety guidelines vary between products such as cosmetics, medical devices, dietary supplements, etc.

Under the current drug approval process, the FDA currently seeks to identify and assess the significance of the adverse events reported in studies/clinical trials.

Heretofore, the FDA has grouped trials addressing primary cancer and metastatic cancers together for purposes of determining efficacy and safety. However, as previously noted, the parameters of primary versus metastatic cancer differ. For example, a much higher percentage of metastatic cancer victims are expected to die in a relatively short period of time. Also, the end goal of delay in the trials for metastatic patients lengthens the phases of the trials (and increases the resulting costs). And the requirement for these compounds to show tumor suppression is inappropriate in the case of trials for metastatic cancer.

When faced with different parameters, the FDA has the discretion to tailor its safety guidelines to fit the needs of the participants in particular trials such as those for metastatic cancer. In fact, with the growing evidence that different compounds are better for treating metastasis than those used for the primary cancer, the FDA is obliged to update its trial procedures to reflect the new reality.

On a related point, the establishment of the Center for the Treatment of Metastatic Cancer would improve the overall efficiency of the FDA and industry participants in the treatment of cancer. As a second-level organization change at the FDA, it could be undertaken without further action or approval required by Congress.

Taken as a whole, the FDA has the authority to modify its approach for addressing metastatic cancer as recommended herein.

Certification

The undersigned certifies, that, to his best knowledge and belief, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

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