DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

JUL 28 2014

Steven A. Zecola
1 Thorton Court
Sterling, VA 20165

Re: Docket No. FDA-2013-P-0695

Dear Mr. Zecola:

This letter responds to your citizen petition (Petition), which the Food and Drug Administration (FDA or the Agency) received on June 6, 2013. The Petition requests that FDA establish a new Center for the Treatment of Metastatic Cancer to focus the Agency's efforts on approving products to treat metastatic disease. The Petition also requests that FDA modify the current clinical trial design structure for products treating metastatic cancer from three phases to two phases. Finally, the Petition requests that the Agency "champion an increase" in the federal research budget for metastatic cancer from approximately 8 percent of the total federal government spending on cancer research to 15 percent.

FDA has carefully considered the information submitted in your petition and other relevant information available to the Agency. Although we agree that it is critical, from a public health perspective, to continue to encourage research on the treatment and prevention of metastatic cancer, and to facilitate approval of products to both treat and inhibit the development of metastatic disease, we do not agree that the steps you have proposed are appropriate means to accomplish that goal. Accordingly, for the reasons described below, your petition is denied.

I. BACKGROUND

A. Localized Versus Metastatic Disease

In oncology, a distinction is made between localized disease and metastases. Localized cancer is confined to one organ or body system (e.g., localized breast cancer). In contrast, in a patient with metastatic disease, the primary tumor has spread from the originating organ to one or more other parts of the body, often through lymph nodes or blood vessels.[1] In general, localized disease is easier to treat, and the prognosis for a patient with localized cancer is better than for a patient with metastatic cancer. For example, recent estimates indicate that metastases are responsible for 90 percent of all cancer-related deaths.[2]

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[1] See e.g., Saxe C, Unlocking the mysteries of metastases, January 23, 2013, American Cancer Society, available at http://www.cancer.org/cancer/news/expertvoices/post/2013/01/23/unlocking-the-mysteries-of-metastasis.aspx.

[2] Id. See also, Spano D. et al., Molecular networks that regulate cancer metastasis, *Seminars in Cancer Biology*, 2012 Jun; 22(3):234-249.

In general, localized disease is treated with surgery or radiation. For certain tumors, even in the absence of known metastases, adjuvant therapy is utilized to delay or, hopefully, prevent growth of metastases. This is most common for breast and prostate cancer.

B. Design of Clinical Trials

As part of a new drug application (NDA), a sponsor must include "reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use."[3] The NDA will not be approved unless the application adequately demonstrates that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling, and provides "substantial evidence" that the drug will have the effect it purports or is represented to have under those conditions. Substantial evidence means evidence consisting of adequate and well-controlled investigations.[4]

Traditionally, sponsors divide premarket clinical trials into three phases. Phase 1 studies test the drug in a small number of people to determine the safety and tolerability of various doses of the product, identify the drug's common side effects, and evaluate the pharmacokinetics and pharmacological action of the compound.[5] Phase 2 studies, sometimes referred to as "proof of concept" trials, are intended to evaluate the effectiveness of the product for a specific indication in a targeted population.[6] Phase 3 studies are usually performed to further support FDA approval of the product. In a phase 3 trial, the drug is given to large groups of people to confirm its effectiveness, monitor side effects, and collect additional safety and other information.[7]

Although many clinical development programs follow the three-phase framework, the phases describe sponsors' usual drug development process and nothing in the Federal Food, Drug, and Cosmetic Act (FD&C Act) or FDA's regulations **requires** that drugs undergo testing in distinct phases. Moreover, the FDA regulations on adequate and well-controlled studies describe various types of controlled studies, but do not prescribe any particular type of trial design.[8] Rather, the

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[3] 21 U.S.C. § 355(b)(1)(A).

[4] 21 U.S.C. § 355(d); 21 CFR 314.126.

[5] 21 CFR 312.21(a). Pharmacokinetic data provide information on what the body does to the drug once it is administered, for example, information on how the drug is metabolized. Pharmacological action refers to what the drug does to the body, for example, the drug's mechanism of action in humans.

[6] 21 CFR 312.21(b).

[7] 21 CFR 312.21(c).

[8] See 21 CFR 314.126, see also, Guidance for industry- International Conference on Harmonization (ICH) - *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001) , available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm: (under ICH–Efficacy) (providing recommendations to applications on choosing a control group for clinical trials intended to demonstrate the efficacy of a treatment).

Agency provides general advice on clinical trial design and often meets with sponsors early in the drug development process to discuss proposed studies.[9]

FDA also has programs intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of serious or life-threatening conditions. For example, FDA's regulations at 21 CFR part 312, subpart E (subpart E) are intended to speed the development of new safe and effective therapies to patients with serious and life-threatening conditions, especially when there are no satisfactory alternative therapies.[10] This approach may include early consultation between FDA and the sponsors of such products, including agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support approval of the product.[11]

Certain products may also be eligible for accelerated approval. Accelerated approval allows for expedited approval of drugs for serious conditions that fill an unmet medical need. Accelerated approval can be based on a drug's effect on a surrogate or intermediate clinical endpoint that is "reasonably likely…to predict [a drug's] clinical benefit" for approval.[12] For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.[13] In oncology, for example, a traditional clinical

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[9] In addition to the Agency's investigational new drug (IND) regulations (21 CFR part 312), many guidance documents provide information relevant to clinical trials, including the following guidances available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm:

- Draft guidance for industry on *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* (December 2012) (under Clinical/Medical) (proposing suggestions on how to enrich the patient population in a clinical trial to make detection of a treatment effect (if there is any) more likely)
- Guidance for industry on *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (May 2007) (under Clinical/Medical) (providing recommendations to applicants on choosing endpoints for cancer clinical trials and discussing clinical trial design considerations, including single-arm studies and noninferiority trials)
- Guidance for industry on *FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products* (December 1998) (under Clinical/Medical) (discussing the evidence needed to support supplemental applications for new indications for already approved oncology products)
- Guidance for industry on Adaptive Design Clinical Trials for Drugs and Biologics (February 2010) (under Clinical/Medical) (provides information regarding adaptive design clinical trials when used in drug development programs)
- Guidance for industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998) (under Clinical/Medical) (provides guidance on the evidence to be provided to demonstrate effectiveness when submitting a new drug application, biologics license application or application for supplemental indications).

[10] 21 CFR 312.80, 21 CFR 312.81.

[11] 21 CFR 312.82. The subpart E regulations specifically recognize that patients and physicians are generally willing to accept greater risk (and uncertainty about benefit) for a treatment for a serious condition where there is an unmet medical need. *See* 21 CFR 312.80 (purpose) and 312.84 (risk-benefit analysis).

[12] 21 U.S.C. § 356(c); 21 CFR 314.510; 21 CFR 601.41.

[13] FDA's Guidance for Industry on Expedited Programs for Serious Conditions –Drugs and Biolgoics (Expedited Programs Guidance) at 17, available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

endpoint indicative of direct clinical benefit is overall survival, but the surrogate endpoint of tumor response rate or time to radiographic progression have been the basis for many approvals.

Finally, in addition to flexibility in designing clinical trials, FDA has various other programs to facilitate and expedite development and review of new drugs, including those intended to either treat or inhibit the development of metastatic cancer, such as:

- Fast track designation[14]
- Breakthrough therapy designation[15]
- Priority review designation[16]

FDA's Expedited Programs Guidance explains these programs (and accelerated approval) in greater detail. Fast track, breakthrough therapy, and priority review are all designations intended to expedite the development and review of qualifying products. For example, fast track and breakthrough therapy designated products may be eligible for rolling review of the application (i.e., the Agency may consider reviewing portions of a marketing application before the sponsor submits the complete application). Sponsors of breakthrough therapies are afforded intensive guidance on drug development during the IND process, and priority review products are subject to shorter review clocks.[17] Generally, products intended to treat serious conditions and that meet an unmet medical need may qualify for fast track designation, and products intended to treat serious conditions and for which clinical evidence indicates the drug demonstrates improvement over available therapies may qualify for breakthrough therapy designation. In addition, products that treat serious conditions and offer a significant improvement over existing products may qualify for priority review designation.[18]

II. DISCUSSION

A. A New Center for The Treatment of Metastatic Cancer Is Not Necessary

The Petition requests that FDA establish a new Center for the Treatment of Metastatic Cancer to focus the Agency's efforts on approving products to treat metastatic cancer and to encourage FDA to take a more active role in promoting improved treatments for metastatic cancer (Petition at 1, 4). Specifically, the Petition states that FDA currently lacks "sufficient organizational focus" on metastatic cancer (Petition at 1) and that the creation of a new Center devoted to metastases will "put a more pronounced" emphasis on the disease (Petition at 1) and "improve the overall efficiency" of both FDA and industry in the treatment of cancer (Petition at 5).

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[14] Section 506(b) of the FD&C Act (21 U.S.C. 356(b)).

[15] Section 506(a) of the FD&C Act.

[16] Prescription Drug User Fee Act of 1992.

[17] Expedited Programs Guidance at 10.

[18] Id. at 7 for a discussion of the qualifying criteria specific to each designation.

According to the Petition, the new Center would advance new procedures for conducting clinical trials for products to treat metastatic cancer and champion an increase in the federal research budget for metastatic cancer (Petition at 1).

FDA does not agree that it should create a new Center for the Treatment of Metastatic Cancer. The Agency reorganized its oncology review office in 2011 (now called the Office of Hematology and Oncology Products (OHOP)) in the Center for Drug Evaluation and Research[19] and does not believe that its current structure lacks "sufficient organizational focus" on metastatic disease, is inefficient, or otherwise impedes the conduct of clinical trials for products intended to either treat or retard the development of metastatic cancer. On the contrary, OHOP has been effective in supporting innovation and helping to advance the development of new cancer therapies, the majority of which are directed at metastatic malignancies.[20]

FDA approved 14 new molecular entities (NMEs) for oncologic indications in calendar year 2012, 8 in 2013, and 7 so far in 2014.[21] Moreover, in 2012, six of the NMEs were for metastatic disease; in 2013, five were for metastatic disease; and so far, in 2014, five were for metastatic disease.[22]

Finally, there is no evidence that OHOP is an impediment in designing or conducting clinical trials. As discussed in the Background section and again in Section B below, FDA encourages alternative clinical trial designs when appropriate and has various programs available to facilitate and expedite development, review, and approval of new drugs, including treatments for metastatic cancer.

FDA believes that OHOP's current organizational structure is well suited to the review and approval of oncology products and that further reorganization is unnecessary. Accordingly, the Agency declines to establish a new Center for the Treatment of Metastatic Cancer.

B. Collapsing the Current Clinical Trial Structure is Not Necessary

In addition to establishing a new Center, the Petition requests that FDA "collapse" the current typical clinical trial design structure for products treating metastatic cancer from three phases to two phases. According to the Petition, the new clinical trial structure would reflect the differences between metastatic and primary cancer (Petition at 1) and recognize the unique aspects of metastatic disease (Petition at 3). More specifically, under your approach, a phase 1 trial would address both the safety and efficacy of the new compound at various dosages. It would enroll a larger number of patients than traditional phase 1 trials, and the endpoint would

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[19] Press Release, FDA announces changes in drug center's oncology office, September 12, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm271501.htm.

[20] Id.

[21] See FDA's Drug Innovation Web page at http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/default.htm.

[22] Id.

be length of delay until a metastasis occurs, rather than impact on the existing tumor. If the phase 1 trial shows a promise of metastatic delay, the Petition argues that the phase 2 trial should be afforded a presumption to proceed. The phase 2 trial would further test the safety and efficacy of the drug, when used in combination with other drugs for treating the primary cancer (Petition at 3-4).

You suggest a new clinical development program paradigm in the Petition, because you argue that novel compounds to treat metastases are destined to fail under the current trial structure because they cannot meet the "current phase 2 requirement of shrinking existing tumors" (Petition at 3). The Petition also states that the cost required to conduct a clinical trial demonstrating delay in metastasis is prohibitive under the current structure because of the extended length of time and large number of enrollees that would be required to meet the endpoint (Petition at 3). As an example, you cite research on compounds that could potentially inhibit a wide range of metastasis-related pathways in animals, but that have not advanced to testing in human subjects because of the challenges the Petition identifies with current clinical study requirements.[23]

The "collapsing" you propose is unnecessary, because, as explained in the Background section, the FD&C Act and FDA's implementing regulations allow sponsors to propose alternative series of clinical trials along the lines of the framework proposed in the Petition. In addition, the statute and regulations are flexible enough to allow for approval of a product to treat or retard the development of metastatic cancer based on a non-traditional clinical trial program. Although most drugs are developed in three clinical trial phases, as described above, these phases are often compressed, particularly in oncology. OHOP has approved products in which the clinical trial development was greatly compressed from the "3 phase" paradigm. For example, Xalkori (crizotinib) Capsules received accelerated approval for the treatment of metastatic lung cancer based on the surrogate endpoint of overall response rates in two single-arm trials that would have been typically categorized as "phase 2" trials.[24] Subpart E regulations specifically refer to a two-phase clinical trial program where the phase 2 (first controlled) study is well designed and capable of supporting approval.[25] Because subpart E is directed at expediting development of products that meet an unmet medical need (i.e., no satisfactory alternative therapy exists), this pathway may be particularly appropriate for a novel compound that is intended to delay and/or prevent metastasis by blocking metastasis-related pathways. FDA's current regulations are thus flexible enough to allow a sponsor to propose a variety of non-traditional clinical trial programs for a product to treat or retard the development of metastatic cancer. FDA does not **require** any one particular clinical trial design, but is open to considering many different pathways.

You seem most concerned about the current clinical trial paradigm because you believe most novel metastatic cancer drugs (particularly those intended to retard rather than treat metastasis) will fail given the "requirement of shrinking existing tumors" (Petition at 3). In fact, there is no

[23] Petition at 3, citing Morton J et al., Dasatinib inhibits the development of metastases in a mouse model of pancreatic ductal adenocarcinoma, *Gastroenterology*, 2010; 139:292-303.

[24] See http://www.cancer.gov/cancertopics/druginfo/fda-crizotinib.

[25] 21 CFR 312.82(b).

requirement that a compound intended to inhibit or treat metastasis would need to demonstrate an ability to shrink the primary tumor.

FDA's guidance document to help applicants choose appropriate endpoints — the guidance for industry on *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics — specifically* discusses disease-free survival (or "delay in metastasis" as phrased in the Petition) as an acceptable endpoint for approval of oncology products. Other potential endpoints that demonstrate direct clinical benefit include progression-free survival, improvement in survival, and improvement in quality of life.[26]

In sum, FDA does not believe it is necessary to "collapse" the current clinical trial framework into two phases. The Agency is willing to work with sponsors to design appropriate clinical trials to support approval of new products to treat or inhibit the development of metastatic cancer.

C. It Is Not Appropriate for FDA to Advocate for Cancer Research Funding

The majority of federal funding for cancer research is managed by the National Cancer Institute (NCI), part of the National Institutes of Health, FDA's sister agency in the Department of Health and Human Services.[27] It is not appropriate for FDA to advocate for additional funding for another agency or to dictate how another agency should allocate its budget. We note, however, that you provided a copy of your petition to NCI, and we have likewise shared this response with them. Although we appreciate your concerns, we defer to NCI regarding federal funding of cancer research and, specifically, funding dedicated to metastatic cancer research.

III. CONCLUSION

For the reasons discussed above, the Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

cc: Harold Varmus, MD
National Cancer Institute

[26] Guidance for industry on *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* at 5-6.

[27] See e.g., Fact Sheet on Cancer Research Funding (National Cancer Institute), http://www.cancer.gov/cancertopics/factsheet/NCI/research-funding.