

CANCER LEADERSHIP COUNCIL

A PATIENT-CENTERED FORUM OF NATIONAL ADVOCACY ORGANIZATIONS
ADDRESSING PUBLIC POLICY ISSUES IN CANCER

March 1, 2013

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: Creating an Alternative Approval Pathway for Certain Drugs Intended to Address
Unmet Medical Need, FDA-2012-N-1248-0001

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Dear Dr. Hamburg:

The undersigned cancer patient, physician, and research organizations appreciate the opportunity to comment on the possible alternative approval pathway for certain drugs intended to address unmet medical need. We are pleased that the Food and Drug Administration (FDA) is seeking advice about the potential new pathway for regulatory review that was recommended by the President's Council of Advisors on Science and Technology (PCAST) in the September 2012 *Report to the President on Propelling Innovation in Drug Discovery, Development and Evaluation*.

In the last several months, FDA has taken important steps to define regulatory standards and pathways for developers of cancer drugs. In May 2012, the agency published an important guidance, *Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval*. In a Perspective piece in the *New England Journal of Medicine*, Drs. Tatiana M. Prowell and Richard Pazdur describe the approach of the guidance document and the need to balance limited safety data, uncertainty about the predictive value of pathological complete response, and the desire to incorporate promising investigational agents in standard treatment for early-stage breast cancer.^[1] We applaud the publication of the

^[1] Prowell TM and Pazdur R. Pathological complete response and accelerated drug approval in early breast cancer. *N Engl J. Med* 2012; 377:2438-2441.

guidance document, which expresses a flexible agency approach to breast cancer drug development and review.

FDA also collaborated with the National Institutes of Health (NIH) in November 2012 to convene a two-day workshop, “The Science of Small Clinical Trials.” This meeting provided a forum for discussion of “strategies and trial designs that are conducive to overcoming the problem of executing clinical trials using small study populations.” Even before the workshop, sponsors had proceeded with and FDA had approved trials that employ adaptive trial design.

In December 2012, the agency published a draft guidance for industry, *Enrichment Strategies for Clinical Trials to Support Approval for Human Drugs and Biological Products*, providing advice on three enrichment strategies: strategies to decrease heterogeneity, prognostic enrichment strategies, and predictive enrichment strategies. This document expresses in large part strategies that are already employed in the development of targeted cancer therapies, but the development and publication of the thinking of the agency on this topic is useful for drug developers and the patients and physicians who benefit from the new products.

In its September 2012 report, PCAST recommended a new pathway for drugs shown to be safe and effective in a specific subgroup of patients. The report stated, “This would be an optional pathway under which sponsors could propose early in the development process to study a drug for a narrow population.” PCAST also suggested, “For many innovative drugs, it may be possible to demonstrate a favorable benefit-risk balance in certain groups of patients with serious manifestations of a disease or especially high risk of developing a disease long before it is possible to establish the benefit-risk balance for larger patient populations.”

The draft guidance on enrichment strategies for clinical trials and the use of accelerated approval for cancer drugs combine to provide sponsors of cancer drugs a pathway to study and obtain approval for a drug in a narrow population, a cancer subtype, or a group of patients with a specific molecular diagnosis. In light of these existing regulatory pathways and guidance from the agency on development and review of cancer drugs, we are uncertain of the role of the alternative approval pathway that has been recommended by PCAST and on which FDA seeks comment.

We urge FDA, before making a decision regarding the PCAST recommendation, to provide additional guidance regarding existing regulatory mechanisms and their relationship to each other. We believe that this agency effort would answer questions about the need for the alternative pathway. Specifically, we recommend that FDA develop and publish a guidance regarding the breakthrough therapy designation that was authorized by the Food and Drug Administration Safety and Innovation Act (P.L. 112-144). The agency has granted a few breakthrough therapy designations, but the benefits of such designation are not clear to drug developers. We also suggest that FDA develop a document that describes and differentiates: 1) fast track designation, 2) accelerated approval pathway, 3) priority review, and 4) breakthrough therapy designation. A

guidance of this sort would educate sponsors about the pathways that may be available to them and might also serve to answer patient and provider questions about the need for the alternative approval pathway.

PCAST recommended in September 2012, “It would be possible for the FDA to approve drugs for narrow indications based on limited development programs without broader studies, provided that the risk of widespread off-label use could be adequately mitigated. For such a pathway to be effective in constraining the use of certain drugs to certain patients, it would require a special designation that would strongly discourage prescribers from using these drugs off-label and discourage payors from reimbursing off-label use.” In the notice of public hearing and request for comments on the alternative approval pathway, FDA asks, “Would the use of a formal designation and logo to reflect approval under this pathway, with clear labeling of clinical information that only supports use in the indicated subpopulation, but without other constraints from FDA be effective in limiting use to the indicated subpopulation?”

We are concerned that the PCAST recommendation and the FDA question suggest a less rigorous standard of review for drugs approved under the alternative pathway, compared to current FDA review standards. As patients and providers who want FDA approval to provide assurance of a determination of safety and efficacy, we are concerned about an unexplained and arguably unjustified change in the standard for review.

Even if there is no intention to suggest a different standard for review, we remain concerned about the use of a special logo or labeling that might be interpreted as representing a different review standard under the alternative pathway. Third-party payers use aggressive tools, including formulary restrictions and utilization limits, to control prescription drug expenditures. We are concerned that third-party payers would embrace the suggestion of a different standard of review (or labeling that hints at a different standard) to limit access to drugs that have been reviewed according to the alternative pathway.

We do not support the recommendation that drugs approved according to the alternative pathway could not be prescribed for off-label use. We assume that research on supplemental uses of drugs approved under the alternative pathway would continue after approval and that off-label uses would be appropriate according to compendia listings or on the basis of the scientific literature. Such use is authorized under the Medicare statute, and the labeling of a drug to restrict off-label use would be conflict with Medicare standards.

In order to assess the impact on patients, providers, and the approval process of an alternative approval pathway, a number of questions must be addressed: 1) the relationship of this pathway to existing pathways and review mechanisms, 2) the standard of review that would be utilized according to this pathway, 3) the possible response of payers to drugs approved according to the alternative pathway, and 4) possible restrictions on off-label use as part of the alternative pathway. It is critical that the

alternative pathway be shown as an adequate regulatory pathway to fully assess safety and efficacy and protect patient access to new therapies.

We applaud a number of important initiatives of FDA, including recent publication of draft guidance documents that will assist developers of cancer drugs. The alternative approval pathway, as proposed by PCAST and advanced by FDA, represents uncertainty rather than clarity and may not provide any benefit to drug developers or the patients who rely on their innovations.

Sincerely,

Cancer Leadership Council

American Society for Radiation Oncology
American Society of Clinical Oncology
Bladder Cancer Advocacy Network
The Children's Cause for Cancer Advocacy
Fight Colorectal Cancer
International Myeloma Foundation
Kidney Cancer Association
LIVESTRONG
Lymphoma Research Foundation
National Coalition for Cancer Survivorship
National Lung Cancer Partnership
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