



March 1, 2013

Rachel Sherman, M.D., PhD  
Director of Medical Policy  
Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

**RE:: Docket No. FDA-2012-N-1248, Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Needs**

Dear Dr. Sherman:

The Leukemia & Lymphoma Society (LLS) is the world's largest voluntary health agency dedicated to blood cancer. Each year, over 140,000 Americans are newly diagnosed with blood cancers, accounting for nearly 10 percent of all newly diagnosed cancers in the United States. LLS funds lifesaving blood cancer research around the world and provides free information and support services. The mission of LLS is to cure leukemia, lymphoma, Hodgkin's disease and myeloma and improve the quality of life of patients and their families.

LLS appreciates the recent opportunity to participate in the public hearing and to provide comments on questions posed by the FDA regarding this proposed alternative approval pathway.

**Q1:** Would this type of pathway increase therapeutic options for serious conditions where an unmet medical need exists?

LLS applauds the FDA's initiative to create a potential new pathway to expedite the development of new drugs for serious or life-threatening conditions that would address unmet medical needs. The concept of a limited-use pathway could accelerate the development of new therapies and present opportunities for blood cancer patients to have more timely access to precision medicines. That said, we urge the FDA to provide additional guidance regarding existing regulatory pathways and their relationship to each other so that stakeholders can best evaluate the need for an additional pathway. Specifically, we recommend that FDA provide additional guidance regarding the breakthrough therapy designation. While several products have recently been granted breakthrough therapy designations, the pathway forward is still unclear for those products and for future products with that designation.

We also understand that FDA intends to develop a document that describes and differentiates: 1) fast track designation, 2) accelerated approval pathway, 3) priority review, and 4) breakthrough therapy designation. This type of document could be particularly helpful in understanding the

parameters of each pathway as well as understanding the applicability of each to different therapies, and assessing the need for an alternative approval pathway.

**Q2:** The FDA has requested that we identify specific serious or life-threatening conditions for which an unmet medical need exists and for which this approval pathway may benefit subpopulations of patients.

Since our founding in 1949, LLS has invested almost 1 billion dollars on research for cures of life-threatening hematological malignancies. That research has touched or directly supported nearly all of the therapies that have been approved by FDA for blood cancer in the last 40 years. Because of the ready accessibility of blood cells, our understanding of the molecular drivers of blood cancer is at the cutting edge. Building upon breakthroughs in genomics, epigenomics, and proteomics, we have identified the critical pathways amenable to therapeutic intervention. Despite these insights, there are many obstacles that still remain, such as the high cost and extended timelines of developing drugs for small patient populations.

The novel precision medicines being developed to treat the hematological malignancies will inherently benefit small subpopulations of patients. Just within the field of immunotherapy, there are a wide variety of treatments that work in different ways. One such example is the pioneering immunotherapy research being done at the University of Pennsylvania (led by Carl June and funded by LLS), using genetically engineered autologous T-cells for patients with leukemia who have relapsed after standard treatments. The New York Times recently featured a front page article about Dr. June's breakthrough immunotherapy. Of twelve cancer patients treated to date, four have experienced sustained, complete remissions. The article chronicled the experience of one of those patients, Emma Whitehead, a six year old who was near death from relapsed acute lymphoblastic leukemia. Emma is now cancer free and in remission for six months.<sup>[1]</sup>

It is clear that large, randomized trials are simply not feasible for many of these immunotherapeutic approaches; therefore an expedited pathway for approval could greatly accelerate the availability of these treatments to all patients who meet the diagnostic criteria of the particular subpopulation.

It will be critical for FDA to define terms such as "limited-use," "serious conditions," and "well-defined subpopulations" in order to understand how inclusive this pathway will be. As stated above, every blood cancer is a serious or life-threatening condition; many of the therapies in development will be used in small, well-defined patient populations, many of whom share a risk tolerance that is much higher than in the overall population.

**Q3:** What approaches could be undertaken to monitor use of drugs approved under this pathway to determine whether they are being used consistent with the terms of approval?

While LLS understands the desire to manage or limit use in a broader population where safety and efficacy have not yet been demonstrated, we are concerned that efforts to discourage off-label use could impair legitimate access to drugs that are approved for limited uses.

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<sup>[1]</sup> Grady, Denise, "In Girls Last Hope, Altered Cells Beat Leukemia," *New York Times*, December 10, 2012 (p.A10), <http://www.nytimes.com/2012/12/10/health/a-breakthrough-against-leukemia-using-altered-t-cells.html?pagewanted=all&r=0>; Velleca, Mark, "New Cancer Treatments," *New York Times*, December 16, 2012 (Opinion Pages), <http://www.nytimes.com/2012/12/17/opinion/new-cancer-treatments.html>

The Federal Register notice specifically mentions antibacterial drugs where there is a public health interest that extends beyond the protection of each individual patient. However, in the treatment of blood cancers, no such "additional" public health interest exists. Oncologists make difficult decisions with their patients every day about how to balance the risk of life threatening side effects against the possible benefits. The FDA should not have a singular approach to these differing situations.

LLS believes that efforts to ban evidence-based off-label use for drugs approved through a limited-use pathway or to impose penalties for using a drug outside the approved population imposes undue rigidity to an oncologist's decision-making process. There are numerous examples of oncology drugs that were used "off-label" but, guided by compendia guidance and scientific evidence, those drugs demonstrated efficacy in additional indications. Perhaps the best known case is the use of Gleevec in patients with gastrointestinal stromal tumor (GIST). It is appropriate to preserve a physician's ability to prescribe drugs off-label under these types of situations.

CDER Director Janet Woodcock recently stated that because drugs approved under a limited-use pathway would have less data than is normally required, FDA would want to alert physicians and the healthcare system that caution should be exercised when considering use outside the population indicated on the label. LLS agrees that providers using these products should understand the associated risks but would want to ensure that any such alert does not constitute a restriction on off-label prescribing or an implicit reimbursement communication to insurers.

**Q6:** We were also asked whether the use of a formal designation and logo to reflect approval under this pathway, with clear labeling of clinical information supporting use only in the indicated subpopulation, but without other constraints from FDA, would be effective in limiting use to the indicated subpopulation. We believe that a formal designation to reflect approval under this pathway should suffice to limit use to the indicated subpopulation. The use of a companion diagnostic could also be a powerful tool to guide usage to the appropriate patients.

LLS recognizes the importance of alternative and expedited approval pathways and the impact these pathways have on the blood cancer community. Gleevec was granted accelerated approval for the treatment of CML in 2001 and has now saved thousands of lives. Collectively, we need to ensure that there is an appropriate pathway for the many new immunotherapies, precision medicines, and other potential life saving advances currently in development. Thousands of blood cancer patients are waiting for these therapies so that they can lead longer, better, healthier lives.

LLS looks forward to working with FDA on this important initiative and to providing FDA with informative and reliable research data. We look forward to continued dialogue on this issue.

Sincerely,

A handwritten signature in black ink, appearing to read "Mark Velleca". The signature is fluid and cursive, with the first name "Mark" being more prominent than the last name "Velleca".

Mark Velleca, M.D.,Ph.D.  
Chief Policy and Advocacy Officer