School of Public Health
UNIVERSITY OF CALIFORNIA, BERKELEY

Forum for Collaborative HIV Research

March 11, 2011

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

Re: New path needed for HIV drug development

Dear Dr. Birnkrant:

We are very concerned about the future of new HIV drug approvals in the era of HAART. While we are extremely heartened by the recent availability of a diversity of agents from new and existing classes of ARVs, we also recognize the requirement for new agents that offer highly treatment experienced patients treatment options. But, the path to approval for new agents has hit a road-block as drug developers struggle with the central question of this problem: how to evaluate the contribution of an investigational HIV agent in the presence of a fully suppressive background regimen in the era of combination ARV therapy. The inability to see a path forward in the current HIV therapeutic environment has prompted companies to stop developmental programs for promising compounds, thereby depriving highly treatment experienced patients new treatment options-- an area of great unmet need. This is of great concern and interest to all involved in HIV: patients, clinicians, advocates from academia and community and the pharmaceutical industry.

The FDA has traditionally required superiority trials to demonstrate an investigational agents' effectiveness, but such trials are becoming increasingly difficult to perform. This is especially true for second and later generation drugs in a class as well as for new drug classes because the optimized background regimen to which the new agent is added already provides maximal virological benefit as assessed by viral load. Hence, showing the incremental benefit of a third or fourth drug is becoming increasingly difficult. Recently Victor-E Phase 3 trials of the CCR5 antagonist vicriviroc, which had enrolled a high percentage of patients with three or more active drugs in their background regimen, failed to demonstrate efficacy. But, pre-specified subset analysis showed impressive differences in individuals who had 2 or fewer active drugs in their background regimen. In the meantime, clinical development of this drug has been abandoned.

1608 Rhode Island Avenue NW • Suite 212 • Washington DC 20036

202.833.4617 • Fax: 202.872.4316

www.hivforum.org

These issues were addressed on September 30th, 2010 at a meeting sponsored by the Forum. Expert contributions were made by representatives of the FDA, EMA, academia, clinicians, community advocacy and industry. Providing a neutral and independent platform, the meeting served to discuss a series of new proposals for advancing HIV drug development.

We were very encouraged by FDA's "two-part hybrid" proposal for treatment-experienced patients where early short-term (10 days to 2 weeks) superiority is assessed followed by longer term evaluation at 24 weeks to evaluate a potential dose response, safety, durability of initial response, and resistance. Since 1997 clinical trial data have shown that failure to achieve short term (2 weeks) virologic response reliably predicts failure to achieve long term effectiveness of investigational agents. In addition, full suppression of HIV RNA has been shown to be associated with clinical benefit. For a little over a decade, virological response has been the basis for accelerated approval (based on 24 week data) for nearly 20 drugs, all of which went on to receive traditional approval (based on 48 weeks data). Thus, with ample short and long term data from trials we are confident that drugs that yield viral load decreases in the first two weeks are better than placebo, and 24-week evaluation will permit assessment of whether the virological response is durable. These points form the basis for the proposed new paradigm. Even though the initial efficacy evaluation will be conducted in a superiority study format (comparing the investigational agent to placebo), followed by safety evaluation, this new approach will provide regulators with a sufficiently large database to assess safety and durability of efficacy of the investigational agent. The short duration of the trial minimizes the threat of drug resistance. In addition, if needed, flexibility in this new trial format allows for testing different doses, or, under properly specified rules, changing patient numbers as the trial progresses. The absence of a placebo arm in the second part of the trial should facilitate the recruitment of patients into studies. In our opinion this study design may help open up the HIV drug pipeline and offers a new and clear pathway for approval. This new paradigm also fulfills the FDA's 1992 Accelerated Approval regulation that allows earlier approval of drugs to treat serious diseases, and that fill an unmet medical need based on a surrogate endpoint.

We, the undersigned, urge you to approve and implement this new paradigm that provides a clear path forward for new antiretroviral development and would be responsive to the needs of HIV patients requiring new treatment options.

Sincerely,

Jeff Berry
Co Chair, Drug Development Committee, AIDS Treatment Activists Coalition
Editor, Positively Aware Magazine

Director of Publications, Test Positive Aware Network

Nikos Dedes
International Treatment Preparedness Coalition

Lynda Dee
AIDS Treatment Activists Coalition

Victor DeGruttola
Professor and Chair, Director of SDAC
Harvard School of Public Health

Jerome Ernst, MD
Medical Director, ACRIA

Roy Gulick, MD
Professor of Medicine, Weill Cornell Medical Center

Bob Huff
AIDS Treatment Activists Coalition

Dan Kuritzkes, MD
Director of AIDS Research, Brigham and Women's Hospital
Professor, Harvard Medical School

Nina Mani, PhD, MPH
Senior Research Scientist, Forum for Collaborative HIV Research

Veronica Miller
Executive Director, Forum for Collaborative HIV Research

Robert J. Munk, PhD
Assistant Professor, University of New Mexico School of Medicine

Michal Odermarsky, MD, PhD
European AIDS Treatment Group

Jeffrey Schouten, MD

HANC Director, Fred Hutchinson Cancer Research Center

Jur Strobos, MD
Deputy Director, Forum for Collaborative HIV Research

Nelson Vergel
Director, Program for Wellness Restoration