



**Prostate  
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**LESLIE D. MICHELSON**  
*Vice Chairman and Chief Executive Officer*

July 30, 2004

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

**Submitter:** Leslie D. Michelson  
**Organization:** Prostate Cancer Foundation

Re: Critical Path Initiative (Docket No. 2004N-0181, 69 Federal Register, 21839, April 22, 2004); Establishment of a Docket

Dear Madam/Sir:

**The Prostate Cancer Foundation** is the world's largest philanthropic source of support for prostate cancer research. In the decade since it was founded, The PCF has invested over \$150 million to support more than 1,100 research programs in more than 100 research centers around the world. In addition, we have been active leaders in encouraging the government to increase its annual support for prostate cancer research from \$25 million to \$500 million, have worked closely with the National Cancer Institute (NCI) to develop innovative ways to fund prostate cancer research, and the FDA to develop ways to simplify, make clearer and hasten the process for reviewing and approving drugs to treat prostate cancer.

Prostate cancer is the most common non-skin cancer in America striking 230,000 American men each year. In addition, prostate cancer is the cancer with the highest expected increase in incidence during the next decade. As baby boomer men reach the target zone for prostate cancer, which begins at age 50, the number of new cases will increase by almost 50% during the next decade. The unique epidemiology of prostate cancer makes the efforts of the FDA, as reflected in the Critical Path Initiative, especially important to us and the community we represent. Improvements in the Critical Path would benefit not only the two million men battling prostate cancer today but also the three million more men who will be compelled to join the battle over the next decade. Attached is a presentation of the epidemiology of prostate cancer.

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This effort is also vitally important to prostate cancer researchers and patients because certain aspects of the disease make prostate cancer research particularly challenging. First, prostate cancer typically grows very slowly. While this obviously is highly desirable for patients, it makes it difficult to conduct prostate cancer-related research. Second, we do not have a good understanding of the myriad prostate cancer variants. Third, we do not have a clear and detailed understanding of the natural history of prostate cancer. Although we know that about 15% of men who are diagnosed with prostate cancer succumb to the disease, our ability to predict with precision who has aggressive and who has indolent disease is relatively limited. Fourth, when prostate cancer metastasizes, it typically spreads to bone. Existing imaging and other detection modalities are not sufficiently robust to provide a precise means of tracking disease progression. We simply do not have a library of validated biomarkers that can be used as endpoints for clinical trials or guideposts for treatment decisions.

We have met with many biotechnology and pharmaceutical companies who are focused on discovering and developing cancer treatments. Most have told us that they only reluctantly select prostate cancer as a focus for research due to the above challenges. As a result, drugs with the potential to help the largest group of cancer patients, those with prostate cancer, are developed for other cancers and are used off label for prostate cancer. This places patients with prostate cancer at a terrible disadvantage, not only because of the widespread delays in getting the drugs to market, but because in addition, many important and difficult questions related to dosage, interaction with other drugs, and timing of usage are not answered in the thoughtful and controlled environment of an NDA. Thus, we heartily endorse the FDA for its leadership in launching the Critical Pathway Initiative. We sincerely hope that the effort continues to be a top priority for the FDA and that prostate cancer is one of the diseases on which the FDA will focus.

We have joined Faster Cures in the thoughtful comments they have prepared and submitted and wish to submit additional brief comments that focus on issues of particular importance to the prostate cancer community. We recognize that some of these comments may address issues beyond the purview of the Critical Pathway Initiative or the FDA but we nonetheless are providing these comments in the hope that they will enable the FDA to determine its course of action in the context of a broad understanding of the issues and relevant environment.

1. **Surrogate Endpoints.** The most important thing the FDA could do to help accelerate prostate cancer research would be to identify surrogate endpoints that would enable researchers to design trials with more proximate and measurable endpoints. We commend the FDA for its efforts already in this regard and would strongly encourage the agency to continue along this path.
2. **Clinical Trial Design:** The design of clinical trials to assess the efficacy and safety of drugs to treat prostate cancer is quite difficult, in part due to the endpoint issue addressed above. Determining what stage of the disease to include in the trial, determining the proper endpoints, and developing proper evaluation plans are all challenging for prostate cancer researchers. We believe that the FDA should stimulate more collaborative efforts to develop better clinical trial designs. We applaud the Oncology Division of the FDA for

its recent initiative to define proximate endpoints for prostate cancer clinical trials. Translating these initial dialogues into practical guidance for the design and conduct of trials is the next step and we encourage the Agency to pursue this step aggressively.

3. Institutional Review Boards: We all benefit from the oversight provided by IRBs to ensure that human subjects receive the protections to which all humans are entitled. Yet, we believe that it may be time to review this system to see if there are alternate ways to improve it, especially when it comes to trials being conducted in multiple academic centers. We have been advised that it can take months and even longer to get multiple independent IRBs to approve a trial even when the matter about which there may be disagreement may be relatively minor. To be sure, any exploration in this realm should not run the risk of limiting the protections for human subjects.
4. Legal and Contracting: Many trials being undertaken in academic centers are delayed due to the lengthy and uncertain process of negotiating contracts and conducting legal reviews. These reviews typically focus on issues related to liability and intellectual property. It may be that standardized clauses to address these issues could be developed that would simplify and accelerate these reviews.
5. Patient Recruitment: Many clinical trials are delayed due to the long and unpredictable process of recruiting patients. Some centers have demonstrated better performance than others. Perhaps there is a way to identify best practices that could be disseminated to other centers. In addition, as the major academic medical centers have increasingly concentrated on providing tertiary and quaternary care, a larger proportion of patients are being treated in community-based settings. Yet, it is often difficult to obtain the participation of community physicians in clinical research due to the steep learning curve to become a research investigator and the competing priorities of community physicians. We would suggest that the FDA consider ways to make it easier for community physicians to participate without compromising the rigor with which trials should be conducted and reviewed. In addition, most prostate cancer patients are diagnosed by urologists and may remain within the care of urologists for initial treatment. Yet, much of the research on treatments for advanced disease is conducted by oncologists. We believe that the FDA should consider exploring ways to help bridge this chasm in ways that reinforce both quality and continuity of care.
6. Inclusion and Exclusion Criteria: Many prostate cancer patients who participate in clinical trials have advanced disease and are elderly. Thus they have a relatively high incidence of co-morbidities. When clinical trials are designed with excessively restrictive inclusion and exclusion criteria, it becomes even more difficult to enroll patients and the results are even less reflective of the community for which the drug would be used. Thus, we believe the FDA should explore working with industry and academia to determine model sets of inclusion and exclusion criteria, perhaps based on disease stage and type of drug, to ensure meaningful results while minimizing unnecessary exclusions.

7. **Combination Therapies:** Most of the experts we have interviewed believe that the most effective treatments for prostate cancer will involve combination treatments, and that physicians will need to adjust those treatments over the course of the disease. Industry and academic researchers would benefit considerably from an effort to clarify the process for conducting clinical research on combination therapies and changing therapy based on results.
8. **Knowledge:** A striking aspect of the Critical Pathway Initiative White Paper document is the vast knowledge FDA collects in reviewing plans, protocols and data from hundreds of companies. While in many cases these observations result in formal Guidance Documents, we would like to see further dissemination of these observations. A “no strings attached” stance by the Agency would be fine. But sponsors need this information acutely to avoid potentially time consuming and expensive regulatory errors.

In conclusion, we commend the FDA for its leadership in launching the Critical Pathway Initiative. It demonstrates the agency’s commitment to improvement and to doing everything possible to expedite the development and marketing of safe and effective drugs, especially for diseases where the options are limited. We deeply appreciate the opportunity to present these comments and stand ready to support this effort in any and every way.

Best regards.

Very truly yours,

A handwritten signature in black ink, appearing to read "Leslie D. Michelson". The signature is fluid and cursive, with the first name being the most prominent.

Leslie D. Michelson