

# Critical Path to the Cure

Linking NIH and Private Foundation Research Efforts to  
FDA Policy on Outcomes evaluation for New Medical Products

## Preliminary Draft

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### Preface

This is a proposal for the FDA which that involves targeting NIH / Foundation research toward explicit policy on the clinically relevant endpoints or outcome measures that are supported by science. Clearer guidance by the FDA where the science supports the legal FDA standard that endpoints for FDA regulated clinical trials be 'reasonably likely' to measure a real benefit to patients will reduce the time and effort that Industry must spend on study design and will yield a truer picture of the efficacy of the therapy in development. Dr. Ken Marek (imaging and disease progression), Dr. Laura Marsh (Cognitive and emotional) and Dr. David Goldstein (autonomic system) have agreed to help flesh in some details from their educated view of the science in three key areas. Significant research is going on in these areas already. This proposal points it downstream in product development and therefore is perfectly compatible with the road map and Dr. Zerhouni's translational initiative. The concept has been discussed with many of the key people at FDA from the Commissioner's office and from the review divisions, principally with Dr. Katz in Neuro, who is expecting to receive the written document.

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## Introduction

On March 16, 2004 the outgoing FDA Commissioner issued a policy initiative that reinforces his earlier strong emphasis on speeding the benefits of science into better therapies to improve public health without compromising public safety. The rationale for this effort echoes and generalizes the data seen at last week's ASENT (American Society for Experimental Neuro-Therapeutics) meeting in Bethesda Maryland. In sum, medical research funding from both government and private industry (inputs) is trending up while new treatments for patients (outputs) are trending down.

Parkinson' disease is typical of this trend, and in many ways is excellent example for demonstration of management techniques available to address public policy issues. Federal science funding for Parkinson's disease (PD) has increased dramatically as much as five times or more in the past 8 to 10 years, but no new drugs any only one new therapy have reached the market in more than 6 years. The science has not failed; More is known about PD than any other brain disease, and with some three dozen compounds currently in the clinical phases of pipeline scientists' and clinicians anticipate that improved treatments will soon begin to emerge. a rich array of new products including neuro protection, nerve growth factors, and more effective delivery of medications are entering late stages of clinical trials. New science has opened many new targets for effective intervention, based on such factors as the increasing understanding of fundamental cell mechanisms.

Recently, the NIH Roadmap has begun to apply management theory to orient the science more toward applications. From a systems management perspective similar to the Roadmap, the FDA report articulates the concept of 'critical path' which is the shortest route to complete a complex project with many independent subtasks. Delays on the critical path delay the entire project and conversely improvements in the critical path speed the whole project. The commissioner's paper draws the same conclusions as the Parkinson Pipeline Project as drawn from observations of drug development process in our work with FDA, clinical research scientists and pharmaceutical companies over the past 3 years. That is the important role of scientific validation of the efficacy of surrogate markers of disease and other more precise clinical outcome measures. In collaboration with the Office of Special Health Initiatives, this paper introduces a PD policy initiative to link on-going scientific research at NIH and academic research centers to the critical path FDA policies that can either accelerate or hinder the introduction of new medical therapies.

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## **PD Policy Initiative**

The idea is to explicitly link the already on-going research efforts of NIH, and other Federal Agencies in collaboration with private research and service support from the Parkinson's Community (major PD Foundations and grass roots leaders) to FDA policy development and guidance on biomarkers and other clinical outcomes measurement.

Specifically, NIH (NINDS, Directors Roadmap, NIMH, NIA and others) with PD Community will build on existing activities to convene scientific workshops (including scientists from industry, academia, and government as well as informed patients) aimed at identification and evaluation of the validity and appropriateness of measures of disease detection and clinical outcomes or endpoints in 3 broad areas:

- 1) Progression of disease process and disability,
- 2) Cognitive and emotional effects of PD,
- 3) Effect of PD on autonomic system functions (e.g. swallowing, digestion).

The FDA will convene 'Advisory Panels' under their regulations to formally consider the status of the scientific data and based on sound scientific criteria will adopt and disseminate standards to determine efficacy of an experimental therapy, including qualitative caveats as well as quantitative milestones. All panels and workshops will suggest the future research priorities necessary to support maximum improvements in the critical path. This interagency focus on the innovation pipeline will update the process of developing new medical products with the advances in medical science on regular basis.

Leading scientists in each of these have agreed to sketch out briefly the background and a set of key questions to be addressed in each of these broad areas, as well as a preliminary specification of the key researchers and research programs that should be included in the series of workshops.

The remainder of this paper quotes sections of the FDA paper, "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" that are supportive of proposed PD initiative.

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## **Innovation or Stagnation?**

### **Challenge and Opportunity on the Critical Path to New Medical Products**

#### **Passages from FDA Publication**

##### **Executive Summary**

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This report provides the Food and Drug Administration's (FDA's) analysis of the *pipeline problem* — the recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients.

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What is the problem? In FDA's view, the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process. For medical technology, performance is measured in terms of product safety and effectiveness. Not enough applied scientific work has been done in creating new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs. As a result, the vast majority of investigational products that enter clinical trials fail. Often, product development programs must be abandoned after extensive investment of time and resources. This high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive failures. In addition, the path to market for successful candidates is long, costly, and inefficient, due in large part to the current reliance on cumbersome assessment methods. In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century's candidates.

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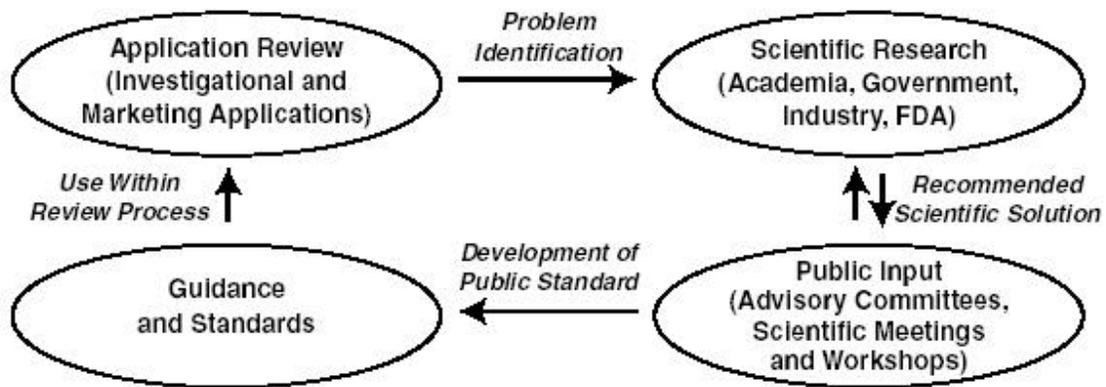
FDA is planning an initiative that will identify and prioritize (1) the most pressing development problems and (2) the areas that provide the greatest opportunities for rapid improvement and public health benefits. This will be done for all three dimensions along the critical path — safety assessment, evaluation of medical utility, and product industrialization as described in this report. It is critical that we enlist all relevant stakeholders in this effort. We will work together to identify the most important challenges by creating a ***Critical Path Opportunity List***. Concurrently, FDA will refocus its internal efforts

## Innovation or Stagnation?

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Figure 8 shows how FDA's review and oversight of clinical trials and marketing applications lead to a cycle of problem identification and attempted resolution. Recurring problems identified during review trigger efforts to develop scientific solutions to prevent such problems in future applications. Multiple cycles of research and public input may be required. "Public standards" include, for example, accepted laboratory test methods, animal efficacy models or safety test protocols, clinical trial designs or endpoints, and clinical monitoring methods. Once publicly accepted, these tools may be used by all developers. FDA often seeks international acceptance of such standard tools, thus reducing unnecessary animal or human testing worldwide.

**Figure 8: Problem Identification and Resolution  
During the FDA Product Review Process**



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There is currently an urgent need for additional public-private collaborative work on technologies such as genomics, proteomics, bioinformatics systems, and new imaging technologies to be better applied to the science of medical product development. Properly applied, these new technologies could provide tools to detect safety problems early, identify patients likely to respond to therapy, and lead to new clinical endpoints. New medical technologies, including bioengineered tissues, cellular and gene therapies, nanotechnology applications, novel biomaterials, and individualized drug therapies, will all need new product development tools and standards, as discussed below, to be able to move from the laboratory to the market quickly and safely.

There is also an urgent need for improvement in the efficiency and effectiveness of the clinical trial process, including improved trial design, endpoints, and analyses. The NIH is addressing very important clinical research infrastructure problems in its Roadmap initiative, and FDA is collaborating in the Roadmap efforts. In addition, much more attention and creativity need to be applied to disease specific trial design and endpoints intended to evaluate the effects of medical products.

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**Opportunity:** "The appearance of new quantitative measuring technologies absolutely galvanizes new drug research." 26 Additional biomarkers (quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness) and additional surrogate markers (quantitative measures that can predict effectiveness) are needed to guide product development. In some cases, data mining and analysis, with possibly a single additional clinical trial, may be all that is necessary to confirm the surrogacy of a particular marker. In other cases (e.g., the NIH's Osteoarthritis Initiative<sup>27</sup>), epidemiologic studies on disease natural history must be undertaken to provide data on markers of disease processes. For biomarkers that currently appear promising, specific projects need to be undertaken to:

- Assemble existing data on the association of the marker with clinical outcomes
- Assemble existing data on the performance of the marker during intervention trials compared to the performance of current outcome measures
- Identify any data gaps or remaining uncertainties
- Identify clinical trials under development in which the remaining questions could be addressed in a straightforward manner

As previously stated, strengthening and rebuilding the disciplines of physiology, pharmacology, and clinical pharmacology will be necessary to provide the capacity to develop and evaluate new biomarkers and bridge across animal and human studies.

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**Opportunity:** For many therapeutics, effectiveness criteria are best defined by the practitioners and patients who use the products. Much work needs to be done on clinical trial design and patient-driven outcome measures to ensure that endpoints in new therapeutic areas accurately reflect patient needs and values. Community (health professional and patient) consensus on appropriate outcome measures and therapeutic claims can lay a clear development path for new therapeutics, especially when there is international regulatory harmonization.

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## ***A Path Forward***

Greater success along the *critical path* demands greater activity in specific type of scientific research that is directed at modernizing the product development process. Such research — highly pragmatic and targeted in its focus on issues such as standards, methods, clinical trial designs and biomarkers — is complementary to, and draws extensively from, advances in the underlying basic sciences and new technologies. Without a concerted effort to improve the critical path, it is likely that many important opportunities will be missed and frustration with the slow pace and poor yield of traditional development pathways will continue to escalate.

Dealing with product development problems is the day-to-day work not only of clinical research and product developers, but also of FDA review scientists. The Agency frequently attempts to resolve problems when they are identified during the review process. Extensive experience in evaluating and working to solve hundreds of product development challenges and roadblocks has enabled FDA to intervene in a targeted manner, helping to reduce or remove specific obstacles in areas critical to public health. Agency scientists and other experts from academia, industry, and government have identified a host of additional opportunities where more progress is both necessary and possible. Due to the scope of the existing problems in product development and the expected surge in products resulting from investments in translational research, we believe that *critical path* research and standards programs should be high priority to help ensure that scientific innovations can be translated efficiently into public health benefits. These additional efforts should be targeted towards removing specific identified obstacles in development.

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Ensuring that the development pathway keeps pace with biomedicine is crucial to advancing the health of Americans. This must be a joint effort involving the academic research community, industry, and scientists at the FDA, and it must be launched soon to have a timely impact. In the months ahead:

- FDA intends to lead in the development of a national ***Critical Path Opportunities List*** intended to bring concrete focus to the tasks that lie ahead
- We will develop this list through extensive consultation with all public and private stakeholders.
- In addition, FDA will make internal changes to intensify its ability to surface crucial issues and to support high-priority critical path research efforts.