A Patient's Perspective on Key Policy Issues for User Fees and Drug Safety Legislation

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My remarks come from the patient perspective. My name is Perry Cohen. I am 60 years old and have been diagnosed with Parkinson's disease almost 11 years. In March of 2000 I became a patient representative for PD at the FDA, and over the past 7 years I have continued to work with the FDA, industry and clinical neuroscientists and other patients as a patient advocate within the context of FDA legal authority to balance the risk and benefit tradeoffs of scientific advancements intended to improve the public health.

Public Safety and Treatment of Chronic Disease

The FDA's public health mission is aimed at nearly a quarter of the US economy, including the food supply and cosmetics as well as medicine and medical products. In recent years the traditional mission of FDA to assure safety of these products has been modified for medical therapies to also demonstrate effectiveness of marketed products. My comments are directed to that portion of the FDA mission concerned with the approval of new therapies for "serious and life threatening illnesses" where the criteria for evaluation of safety and efficacy and the roles and requirements for regulators and industry take on a very different character than is expected for protection of public safety of consumer products or regulated medicine for less serious conditions. Distinction between these different missions is important to any policy changes for safety considerations.

User fee renewal (PDUFA IV) provides and opportunity to align FDA authority and mission toward truly patient centered goals and outcomes. In the context of this "must pass" user fee legislation, a number of proposals have been advanced to addresses such issues as on-going safety monitoring of medical therapies as they are used by wider groups of patients over longer periods of time and access to experimental therapies Patients with serious illness have requirements different from the general public and so that any change in policy should consider these unique needs.

Patient Participation and Patient Centered Health

My key message is that a patient-centered system for new therapy development is the necessary core for improvement of our system of regulation of new medical therapies in order to gain the public health benefits from of large investments and advances in science. Legal authority and practices of FDA need to be examined and steps must be taken to move further toward patient centered health.

Although it is axiomatic that the patient's interest is the bottom line in health care, it is remarkable how little input actual patients or their personal representatives (mainly family) have in the key decisions affecting their lives. I believe that the most simple and powerful action that can be taken to improve the system for regulating the development of medical

therapies is to recognize the value and importance of 'patients' at the table at all stages of the process and to incorporate the patient perspective into policies, design decisions and interpretation of results of the evaluation of new therapies. Pioneering efforts in development of treatments for HIV and cancer have demonstrated the many ways patients can participate directly in the process not only as research subjects, but also as consultants to regulators and sponsors on design criteria and as partners with scientists in the evaluation process.

I founded the Parkinson Pipeline Project to educate patient advocates to take these roles. Our motto is "the missing ingredient in the development of therapies is the voice of the patient." This was the bottom line suggestion of journalist Clifton Lief in his thoughtful analysis of FDA and advancement of medical science, in Fortune (2/20/2006), entitled "Deadly Caution." How can this be achieved?

- The Congress needs to fund the FDA to expand the pilot programs in cancer and now Parkinson's for patient consultants to bring this unique patient perspective to the table in negotiations with industry on the conduct of clinical trials.

- The laws and practice on conflicts of interest and necessary clearances of potential conflicts (which have interfered with Parkinson's patient consultants' participation in FDA processes) should distinguish between patients with serious illness whose primary concern for their health far outweighs the value of their stock portfolio.

Self Determination and Choice

A fundamental concept in a patient centered health care model for new therapy development, which differs significantly from the "public safety" approach, is the importance of empowerment of patients to actively take charge of their own health. Purchasers of consumer products seek peace of mind through guarantees of safety, but more active roles benefit patients with chronic diseases. Fundamental premises of this patient centered view are:

1) There are no perfectly safe medicines; all medical interventions involve risks.
2) All decisions about treatments involve risk and benefit tradeoffs.
3) Patients with serious or life threatening illnesses must have the discretion to make those tradeoffs based on their own values and life situation with the consultation of expert advisors, usually their physician.
4) Patients making these choices require full and unbiased information on all available research and experience with the treatment.

Urgency

Time is not neutral for a person with serious illness. Advancing patients feel a sense of urgency to get improved therapies on the market and into the clinic. While medical professionals often mistake this urgency for desperation, we patients view ourselves as informed and realistic. Where certainty of disease progression is the baseline in any risk-

benefit analysis, patients are more concerned about avoiding Type II errors ("false negatives" that keep effective treatments off the market) than Type I ("false positives" that might expose patients to high risks of side effects from treatments that offer no potential benefit) which is the ethical core of modern medicine ("Do no harm."). Well informed patients living with chronic, debilitating conditions are willing to take risks because the greatest risk is a lack of new and improved treatment options.

INNOVATION

The flip side of safety and caution to protect the public from dangers is innovation and risk to go where we have not gone before. A patient with a chronic disease, who is facing the certainty of disease progression toward death or disability, is likely to have an increased tolerance for risk and be more concerned with innovations in medical treatments than in absolute safety of the medicine. Likewise for industry, risk is the basis of our market economy and the freedom to take risks is the primary engine of entrepreneurial activity that is necessary to deliver the cures. Innovation is necessary in science to better understand disease processes and innovation by industry is necessary to actualize a medicine to treat or cure diseases. We also need innovation in the regulatory process and public health practice to develop, validate and adopt more efficient and accurate methods to evaluate new therapies and to monitor and assess medical care quality in the community over the life cycle of treatments.

To a PD patient with a slow, but relentless progression toward total disability, the goal of treatment is not necessarily an absolute cure. A desirable outcome would be sequence of incremental improvements in treatment to maintain our functioning and quality of life at an acceptable level while newer more effective treatments are evaluated. Continuous innovation provides "hope" which is an essential ingredient to maintain the spirit against the constant hammering of the disease on your body for the 24/7 roller coaster ride through a half dozen daily medication cycles characteristic of PD.

The FDA proposals for implementation of the Critical Path Initiative address many of these concerns, and FDA needs substantial, continuous funding from the Federal budget to carry out these important public health initiatives.

Applying the skills acquired from my doctoral studies organizational behavior and systems management and enriched over a career as a health care management and policy consultant, I have learned more about the process of new therapy development as a patient advocate for 10 years, and I must say this insight has increased my cynicism about the process. New legislation should recognize the reasons for such cynicism and try to counter this trend.

Breakdown in the Engine of Innovation

As documented in a recent (Nov. 2006) GAO report on drug development, the medical miracles of science and the pharmaceutical industry have begun to taper off sharply. We see an increasing crisis of confidence from the public about the extent that the institutions

of science, industry and government are looking out for the public interest. Inherent ethical conflicts in values underlying the needs of scientists for experiment control, the patients and their doctors for optimal care, and the needs of industry for large capitalization and return on investment are too often resolved in favor of narrow private interests, even while patient interests are advanced as the rational for choices. A paradigm change to a patient centered model is necessary to invigorate the process.

Transparency and Innovation in Medical Science

The increasing cynicism about the ability of science and industry to fulfill its medical promise has roots in the process of discovery and the conflicts of interests of the key players in the processes. While science flourishes in an information rich environment, business seeks competitive advantage and wants to restrict access to proprietary information. Demand is increasing for greater transparency of data and analyses from both successful and unsuccessful clinical trials. The editors of major scientific journals have called for registering all study data and results, both positive and negative, as a prerequisite for consideration for publication of the findings.

FDA law should recognize the public interest in the transparency of data and more open communications between industry and review staff. Currently all meetings between sponsors and FDA staff for guidance are proprietary. The system would be more trustworthy and responsive to patient needs if

- ◊ FDA has flexibility and discretion to release information of interest to the public
- ◊ FDA made widespread use of skills and unique perspective of patient consultants in the decision processes early enough to make maximum impact.

Innovation in Methods for Evaluation of new Therapies

We have a new therapy development process that is too unwieldy, too long, and too costly to make optimal use of the enormous and highly productive investments we have made as a nation in medical science. The scientific model for hypothesis testing based on statistical criteria and assumptions in double blind placebo controlled studies is rigorous and precise, but to a fault.

- Precision is different than accuracy.
- Statistical significance is different than clinical difference.
- Assumptions about experimental control where all other factors are static may break down in the 1-2 year time frame necessary to wash out ‘placebo’ effects in brain research.
- Linear statistical models may miss important implications of non-linear processes and interactions among variables <Animal models can never be fully predictive of human reactions to medicines. This is why we do clinical trials. This is particularly true if we are talking about brain diseases where if you study you change it.>

Innovation in methods would place high priority in testing alternatives to this science as usual ‘gold standard’ whose assumptions only approximate reality. For example, adaptive

trial designs using Bayesian statistical models (conditional probabilities) and based on knowledge about gene and protein markers or other patient characteristics may tell us more about safety and benefits of drugs, in potentially shorter time frames, exposing fewer people to experimental treatments, and resulting in clinical trials that may not only be more efficient, but also more attractive to potential participants and their physicians.

Funding from congress is needed to support FDA's efforts to advance the science of evaluation of treatments for initial evaluation and on-going monitoring of safety over the life cycle of a product. FDA should aggressively advance the scientific methods for evaluation of new therapies and safety such as:

- Alternative statistical methods
- Patient preferred outcome measures and endpoints.
- Continuous monitoring of medical quality with specialty enriched EMR's.

Innovation in Communication among Patients, Scientists, Industry, and FDA

Beyond our own participation and need for self-determination in patient care, patients play a unique role in the evaluation of new therapies, that of research participant. The regulatory approach to establish proof of safety and efficacy for new therapies requires that patients volunteer to act as research subjects in controlled clinical trials. This requirement gives patients a unique position of first hand experience with treatments, well beyond the ability of science to measure this experience. While this experience is not a total substitute for external observations of biological activity and behavior, it is part of the equation not fully appreciated or utilized in the evaluation of new therapies.

Particularly when it comes to central nervous system disorders such as PD, the human element complicates the experimental scientific model. Self awareness distinguishes humans from animals, and this knowing can change the outcome. Ethical standards for clinical trials regarding recruitment of volunteers to take unknown risks on new procedures call into question the deceptions established to control these human reactions (i.e. placebo effects) to the most fundamental aspects of good medical care (e.g., positive expectations, hope). As patients become more informed about the importance of participation in clinical trials, they will also become aware of their rights as research participants. Scientists and industry will be ethically constrained from making decisions about design of clinical trials and interpretation of results without input from patients. A collaborative model will be necessary and beneficial.

The advent of powerful information and communication technologies, not only provides access to information on the progress of science to inform patients about how they can be more proactive in their on health care planning, but also has afforded opportunities for advocate leaders to organize in "on-line" communities to provide tools and training of patients and advocates to carry out larger scale education and advocacy activities. A constructive collaboration between patients and developers of new therapies will greatly enhance the process.

The role of FDA in this context is to establish criteria for evaluation of new treatments with input from patients as well as providers of treatments so that outcomes more meaningful to patients are addressed, and assure that information is valid and available to patients and doctors in complete but understandable format and language.

The Next Frontier – Informatics and Integration of Systems

My remarks are based on 30+ years experience working in health care policy and medical research at national levels as well as management public health and medical applications at local levels, and more recently with industry and regulators at FDA as a patient representative for Parkinson's disease.

Chronic diseases are the major problems facing the aging population. They are the primary killers in our advanced industrial society, and present the most challenging medical problems as well as system development problems for a medical care treatment and payment system designed to provide acute care, mostly in institutions such as hospitals and derivative organizations. Indeed the medical miracles of the last half of the 20th century are mainly due to advances in advances in acute care treatments. Still high on the list of medical problems are chronic diseases such as cancer, diabetes, and heart disease as well as a broad range of neurological conditions, including Parkinson's that represent the most wide open frontiers of knowledge.

Large investments in basic science have totally transformed the most promising targets of research, where new knowledge in fields such as genetics and proteomics have begun to uncover the underlying mechanisms of cell death and other fundamental processes. Equivalent advances are needed in the science of measurement and evaluation of therapies and in educational methods to disseminate improved treatments in practice in order to translate that scientific knowledge into innovative treatments for patients and to manage the cost and access to care in order to bring the promised health gains from the scientific advances to the population. Leaders at the NIH and FDA have advanced management systems improvement methods as models for the major thrust for their management improvement emphases: the NIH "roadmap" and the FDA "Critical Path Initiative"

All the key issues in evaluation and implementation of innovation in health care and medical practice as well as cost and quality of care (including monitoring drug safety) come together in the regional specialty care referral networks. Building from the science base and highly specialized expertise in academic medical centers, clinical researchers are the lynch pin to disseminate knowledge about new treatments gained from evaluation of new treatments. Outreach to community providers of primary care and to non medical service providers by multi-disciplinary teams including patients experienced with clinical trials will enhance linkages among care providers and organized comprehensive care networks. Innovations in informatics and electronic medical records, including personal health records and specialty disease management systems for physicians are the next essential component in delivery of cures.

Managing chronic disease in an era of scientific discovery is a dynamic process that uses system's management concepts and techniques, and advanced information systems technology to coordinate care, educate providers about new science, populate clinical trials and provide comprehensive information on treatment activities that can be aggregated and analyzed for monitoring the safety of drugs and other elements of quality as well as manage the utilization and cost of care. In the long run these data will provide essential information not only for planning and management of diffusion of new treatment, but also they provide powerful research tools for a myriad of scientific questions.

Conclusion

I have described elements of a patient centered health care system which I believe will motivate the essential streamlining necessary for faster availability of life saving new medical treatments by recognition of the active roles for patients in a process that emphasizes innovation and full disclosure of information. Changes in FDA roles and authorities as well as new roles for patients are suggested to be incorporated into policy in the context of PDUFA renewal.

What patients want

- From Medical Care
  - Restore health
  - Minimize risk
  - Informed choice
  - Human dignity
  - Incremental improvements
  - Faster cures
  - Continued monitoring
  - Fair compensation for providers and manufacturers

- From Clinical Research
  - Informed Consent on risks and benefits
  - New science for evaluation to allow earlier access to experimental treatments
    - Adaptive designs
    - Interim outcomes, biomarkers
  - Planning and execution of studies
    - Study design that incorporates patient centered outcome, and methods to obtain data that minimize risks to patients.
    - Contingency plans for early termination of studies
    - Continual monitoring of participants to identify and adjust for longer term safety concerns
  - Full follow up of research contributions of volunteer participants
    - Feedback on data gathered from each patient
    - Full access of study results to the scientific community
    - Consideration of risks taken by patients on behalf of sponsors whether or not the study is successful.
    - Continued access to follow up treatment on request
  - 2 way Communication
    - Input
    - Timely feedback
    - Follow up
  - Collaboration
    - Among scientists
    - Between patients and scientists
    - Between patients and sponsors