



Statement

**Before the Subcommittee on Retirement and
Aging**

**Committee on Health, Education, Labor and
Pensions**

United States Senate

Alzheimer's Disease: FDA's Role In New Product Development

Statement of

ANDREW C. von ESCHENBACH, M.D.

Commissioner of Food and Drugs

Food and Drug Administration

U.S. Department of Health and Human Services



**For Release on Delivery
Expected at 2:30 p.m.
Tuesday, July 17, 2007**

INTRODUCTION

Madam Chairman and Members of the Subcommittee, I am Dr. Andrew C. von Eschenbach, Commissioner of Food and Drugs at the Food and Drug Administration (FDA or the Agency). I would like to applaud the Subcommittee for holding this roundtable discussion to discuss Federal initiatives to address the cruelly debilitating condition known as Alzheimer's disease. FDA shares your commitment to vigorously addressing Alzheimer's disease, and shares your hope that safe and effective treatments for this condition will be approved in coming years. It is a pleasure to be here today with my colleagues from the Department of Health and Human Services, Dr. Julie Gerberding, Dr. Elias Zerhouni, and Dr. Richard Hodes.

I very much appreciate the opportunity to join this discussion to explain FDA's role as it applies to new products being developed for treatment of Alzheimer's disease. Further, I will describe several initiatives FDA is undertaking to transform the Agency in an effort to meet the regulatory challenges arising from rapid advancements occurring in all areas of medical research including Alzheimer's disease, and several special initiatives underway at FDA that are directed toward Alzheimer's disease.

In the two recent hearings on Alzheimer's disease before this Subcommittee you heard current statistics recently released by the Alzheimer's Association including that this disease now afflicts one in eight Americans over the age of 65 and some 47 percent of Americans over the age of 85. At the present rate, the estimated 4.5 million cases of Alzheimer's disease today can be expected to rise to around 16 million by 2050. With

the aging of the baby boom generation over the next several decades, without safe and effective treatments and preventatives, a huge population of seniors stands to be robbed by this disease of the enjoyment of their later years. In addition to the burdens placed on patients and their families, insurance programs surely will face overwhelming demands on their services and resources.

There is cause for some cautious optimism. You also heard of exciting advancements in research on Alzheimer's disease such as identification of amyloid peptide as a possible molecular cause of Alzheimer's disease. Some researchers believe it is realistic to expect that the progress of Alzheimer's disease can be slowed or halted by products developed to affect the amyloid peptide. However, researchers also have emphasized that this is a very complex disease that will need to be approached from several different directions. A number of promising new treatments in many areas are in the works; a few were mentioned in your previous hearings as approaching the stage of clinical trials.

As you may know, FDA is legally restricted from discussing any individual products that already may be under review by the Agency. This precludes me from being able to discuss specific unapproved products in today's public forum. I can tell you, however, that Alzheimer's and other neurological diseases are very active areas of research and of work within the Agency. FDA reviewers interact constantly with manufacturers and sponsors of prospective new products (drugs, biologics, medical devices or combination products) to help develop, and then to review, suitable clinical trials to test whether their

products are safe and effective. This is a very intricate and time-consuming process. Our reviewers work with industry in all phases of the development of a new product, both before and during clinical trials, as requested by the sponsors. As always, FDA stands ready to expeditiously review applications for any breakthrough products that are presented to us.

FDA recognizes its dual role as evaluator of the safety and effectiveness of new therapies and as the encourager and facilitator of efforts to apply new scientific discoveries to patients who are in need. FDA serves as a bridge to the future of successful new medical product development. The Agency has a proud record over the past hundred years of being the world's gold standard in medical product regulation, but FDA cannot rest on its past and must come to grips with the new realities of our regulatory responsibilities. Therefore, we have embarked on a process of looking internally at transformations that must occur within the Agency, and to identify opportunities to collaborate with drug developers and other scientists on the discovery, development, assessment and delivery of new treatments. I would like to share some of these efforts with you.

THE CRITICAL PATH INITIATIVE

In today's world of health care and medicine, we are on the brink of unprecedented advances in our ability to predict, diagnose, and treat disease. Approximately one hundred years ago, our ability to understand disease moved from the macro level,

where we were limited to what was visible to the naked eye, to the micro level – when we gained a microscopic view of disease at the cellular level. In the last decade or two, we have been able to approach disease at the molecular level, where we now can observe and understand disease as a process. As our knowledge of genetic molecular mechanisms evolves and our understanding improves, we will be uniquely positioned to develop interventions against disease processes at the molecular level.

Yet a problem emerges. Despite an unprecedented increase in funding for biomedical research, both in the private sector and through Federal funding, this increased research has not translated into many new medical products being available in the medical marketplace. There are exceptions, of course, notably in the development of new treatments for cancer and AIDS, and some inflammatory diseases. Close to nine in 10 pharmaceutical products in phase 1 clinical testing are never approved for marketing, and half of all drugs that enter phase 3 clinical trials are never approved. In an effort to help expedite and simplify the medical product development process, in 2004, FDA advanced the notion of focusing on the critical path which medical products must travel from the earliest stages of development to their use in patients. The Critical Path Initiative is FDA's effort to stimulate and facilitate a ***national*** effort to modernize the sciences through which FDA-regulated products are developed, evaluated, and manufactured.

FDA is working with the academic community, the public, the pharmaceutical industry, and other Federal health agencies (e.g., the National Institutes of Health (NIH), the

Centers for Medicare & Medicaid Services, and the Department of Veterans Affairs) to modernize and transform the development and use of medicines. After intensive consultation with many stakeholders, last year the Agency published our *Critical Path Opportunities Report*, which details 76 specific scientific projects with great promise for smoothing the path from lab to bedside. Last December, we followed up by announcing more than 40 very promising scientific projects that we have helped launch. These projects support the development and approval of new treatments for conditions such as Alzheimer's, diabetes, cancer, and chronic pain. For example, improved predictive and evaluative tools that help identify candidate products that are likely to fail early in the development process will enable the investment of resources in those products most likely to succeed. Streamlining clinical trials – making them more efficient and safer – will help move new therapies to patients sooner while protecting clinical trial participants. Among many other activities, the Initiative also supports the implementation of information technologies that will enable us to tap into existing data repositories to expand research into disease areas and improve efficiencies. The Critical Path Initiative is a long-term, national effort that is helping to ensure that promising new therapies in the development pipeline today will reach the patients who need them sooner and at less cost. The projects under way today as part of the Critical Path Initiative will improve treatment, improve safety, and improve patient access.

Another example of the Critical Path Initiative is The Biomarkers Consortium launched in October 2006. This is a public-private biomedical partnership established by FDA and many colleagues in the scientific community that is supported by the Foundation for

the National Institutes of Health. The Biomarkers Consortium strives to accelerate the delivery of successful new diagnostic approaches and therapies to prevent, detect early, diagnose, and treat a wide variety of diseases. Among other efforts, the Consortium seeks to identify biomarkers and develop tests to determine whether a drug is appropriate for an individual patient. It also is working to find “markers” that will show whether a drug is having the right effect in the patient. For example, researchers have found that patients whose tumors have specific genetic mutations or surface properties respond to particular treatments. This mutation then serves as a “marker” to identify the patients who are best treated with these medications.

Over time, similar discoveries related to other tumors, other diseases and conditions, and other drugs will yield a major public health impact – and that is the point of the Critical Path Initiative. Working with all stakeholders, the Critical Path goal is to get the right medicine to the right patient, in the right dose, and at the right time. It will make innovative medical products available sooner, increase our ability to monitor their safe use once they have reached the medical market, provide for personalized diagnosis and treatment, and introduce great efficiencies while reducing risk.

TWO EXAMPLES OF ALZHEIMER’S RESEARCH WITHIN THE AGENCY

Now, I would like to talk about two Alzheimer’s-specific projects that FDA has undertaken. First, FDA scientists from our National Center for Toxicological Research (NCTR) collaborated recently with scientists at the University of Arkansas for Medical

Sciences, the University of Arkansas at Little Rock, and the Central Arkansas Veteran's Health Care System to conduct an automated cognitive assessment of persons with and without Alzheimer's disease. The study investigated performance on metrics for a variety of behavioral test tasks that measure timing perception ability, short-term memory, and learning ability using an automated system called the NCTR Operant Test Battery (OTB). The study outcome indicated that the persons with Alzheimer's disease were significantly less accurate in the time perception and short term memory tasks and were rarely responsive in the learning task. The OTB is a non-invasive, automated, non-threatening assessment technology that can differentiate between normal controls and persons with Alzheimer's disease. This automated assessment instrument has the potential to provide reliable, objective measures that can be used to monitor the progression and severity of the disease process and assess effectiveness of interventions over time. A report on this study is in preparation.

Currently, FDA/NCTR scientists are initiating a study to develop a histochemical test battery for assessing the efficacy and toxicity of putative anti-Alzheimer's disease drugs, the safety of which will need to be evaluated in the FDA regulatory review process.

There are two broad categories of anti-Alzheimer's drugs: those that provide symptomatic relief and those designed to prevent or slow the degenerative process.

So far, those in the first category have been developed and shown effective, and are approved for use by FDA. Those designed to cure or reverse the disease process are in early development or, in some cases, in clinical trials. The development of a therapeutic histochemical test battery has the potential to help identify earlier and more

reliably drugs that might slow the degenerative process. This study is scheduled to begin later this fiscal year.

THE PATIENT REPRESENTATIVE AND CONSULTANT PROGRAMS

FDA also has engaged with the Alzheimer's disease patient advocacy community regarding that community's involvement in FDA decision-making during development of new medical products. Through FDA's Patient Representative Program, they will be able to participate in FDA advisory committee meetings, advising the Agency on marketing approval decisions and in response to issues arising with marketed products, as well as help advise the Agency about the development of investigational drugs. Their involvement is important to FDA's capacity to make informed regulatory decisions that are sensitive to the needs and preferences of those affected by this disease.

This expansion of FDA's programs has involved considerable challenge, as FDA has negotiated with Alzheimer's disease advocacy organizations regarding the role of Alzheimer's disease patients themselves. FDA considers patient involvement important, since patients with a given disease are generally best able to speak for others with that disease. Involvement of patients with Alzheimer's disease is also an important priority to the Alzheimer's disease advocacy community. However, participation of patients with Alzheimer's disease is problematic because of diminished intellectual function that is a primary manifestation of this disease. This challenge is

exacerbated by Alzheimer's disease patients' deterioration in intellectual function over time.

After extensive negotiation, we have agreed to recruit advocates from the Alzheimer's community, including couples consisting of a patient with early-stage disease and his or her caregiver, both of whom have a background appropriate for involvement as FDA patient advocates. The caregiver will serve as the primary spokesperson for the couple, but both parties will have access to materials for review, will be able to review and discuss those materials prior to their engagement with FDA, and will have the opportunity to participate. When the patient is no longer able to participate, the caregiver will continue to serve with FDA. FDA and the Alzheimer's community agree that this approach involves challenges, but both parties are willing to work to maximize involvement of patients.

THE FDA INTRA-AGENCY NEUROLOGY WORKING GROUP

Next, I would like to mention FDA's Intra-Agency Neurology Working Group. Neurology products regulated by FDA, comprised of drugs, devices, biologics, and combination products, are a diverse group of products aimed at advancing patient care in a number of disease areas for which the unmet therapeutic need is great. Some diseases affect a large number of patients, such as Alzheimer's disease and Parkinson's disease, while others affect smaller numbers of patients. In either case, the consequences can be devastating for patients and their families.

FDA's goal is to improve communication about neurological disease across the Agency among the various groups charged with regulating these products. To accomplish this end, FDA has established a Working Group to serve as a forum for information exchange on leading-edge developments, enable sharing of technical and regulatory expertise, and provide for greater consistency of review standards and processes across the Agency. Further, we are expanding patient advocate involvement in FDA neurological disease-related review and decision-making to include Parkinson's disease, Alzheimer's disease, and other neurological diseases as Agency resources allow.

Meetings occur monthly and are chaired by Dr. Celia Witten, Director, Office of Cellular, Tissue, and Gene Therapy in our Center for Biologics Research and Evaluation (CBER), and Dr. Robert Temple, Director, Office of Drug Evaluation I and Director of the Office of Medical Policy in our Center for Drug Evaluation and Research (CDER). Other members include Dr. Russell Katz, Director of the Division of Neurology Products (CDER), and supervisors, reviewers, and project managers from CDER, CBER, and our Center for Devices and Radiological Health. Also included are staff from the Office of the Commissioner, including the Office of Critical Path Programs, the Office of Special Health Issues (OSHI) and the Office of Science Health Coordination. Standing agenda items include policy development (guidance, workshops, and advisory committee meetings), opportunities for Critical Path projects, significant review projects (major investigational/marketing applications under review, marketing approvals, studies of

interest, etc.) upcoming neurology-related meetings and patient advocate involvement, and OSHI updates.

ADDITIONAL FDA ALZHEIMER'S-RELATED ACTIVITIES

The Agency is engaged in a number of additional Alzheimer's-related activities. For instance, FDA is helping with a study called the Alzheimer's Disease Neuroimaging Initiative. This is a five-year public-private initiative involving industry, academia and the NIH. The goal of this study is to obtain standardized MRI, biochemical, and clinical data over several years in prospectively followed groups of normal elderly patients with mild cognitive impairment, considered the very early stages of Alzheimer's disease, and patients with diagnosed Alzheimer's disease. We anticipate that this study will help in the use of some of these measures in future clinical studies to expedite the development and approval of drugs to treat patients with Alzheimer's disease, especially in its very earliest stages. A particularly exciting and important aspect of this study is that the data are available to scientists all over the world in real time as the data are acquired and entered into the database.

Additionally, FDA has a productive and close working relationship with the Alzheimer's disease advocacy community. For example, FDA has worked closely for many years with the Alzheimer's Association on scientific, technical, and advocacy issues. Their counsel and direct assistance to FDA have been invaluable as we have worked to

improve our regulation of Alzheimer's disease treatments and to expand patient involvement in FDA decision making.

FDA recently met with, and remains in contact with, the Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) Coalition. They are concerned that the Agency retains a strong focus on drug development for Alzheimer's disease. The Agency works and keeps in contact with these organizations through OSHI. I certainly encourage this important exchange of ideas with advocacy groups.

Development of drugs with an effect on disease progression is the most critical need in Alzheimer's disease, as it is with other progressive neurological diseases. FDA is planning a future public meeting to discuss design of clinical trials and how to design studies to determine whether or not a drug for Parkinson's disease has an impact on the underlying cause of the disease and not just the symptoms of the disease. It is expected that the designs useful in Parkinson's disease should be equally applicable to drugs for Alzheimer's disease.

In addition, FDA is organizing an upcoming meeting with neurological disease organizations involved in advocacy and medical research. This meeting will involve discussion of scientific, technical, and advocacy issues related to their and FDA's roles in development of important new treatments for serious neurological diseases, including Alzheimer's disease.

CURRENTLY APPROVED DRUGS FOR ALZHEIMER'S TREATMENT

Finally, I want to make sure that I mention to the Committee that there currently are five drugs approved for the treatment of Alzheimer's disease: Cognex (tacrine); Exelon (rivastigmine); Razadyne (galantamine); Aricept (donepezil); and Namenda (memantine). All except Namenda are approved for the treatment of mild to moderate Alzheimer's disease. In addition, Aricept also was approved recently for severe Alzheimer's disease. Exelon was approved on July 6, 2007, in the form of a transdermal patch, which reduces gastrointestinal side effects compared to the oral form of the medication. All of these drugs except Namenda act by increasing brain levels of acetylcholine, a neurotransmitter that is abnormally low in patients with Alzheimer's disease. Nerve pathways in the brain that are thought to be involved in memory and cognition, that "use" acetylcholine as a neurotransmitter, degenerate in patients with Alzheimer's disease.

Namenda is approved for the treatment of moderate to severe Alzheimer's disease only. It works differently than the other approved drugs. It interacts with a receptor that is thought to be involved in preventing the death of certain cells in the brains of patients with Alzheimer's disease. However, the drug has never been shown to prevent or slow the underlying nerve degeneration in these patients, nor have any of the other approved drugs been shown to do anything other than treat the symptoms of Alzheimer's disease.

CONCLUSION

We await, together with the rest of the world, for new drugs that may some day be able to treat the underlying cause of this insidious disease as well as other neurological diseases, not just the symptoms. We are very encouraged by the progress being made in the scientific community and pharmaceutical industry on products you heard about in testimony in the previous two hearings. As indicated earlier, FDA stands ready to facilitate any breakthrough product applications that are submitted to the Agency for review.

This concludes my formal statement. I will be pleased to respond to any questions from the Subcommittee.