

Wyeth

Wyeth Pharmaceuticals

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

Re: Docket No. 2004N-0355: Critical Path Initiative; Developing Prevention Therapies; Planning of Workshop, August 3, 2005 (70 FR 44660-44662)

Dear Sir/Madam:

Reference is made to the above-mentioned Federal Register notice inviting comment on the proposed program for an upcoming public workshop on chemoprevention therapies. Wyeth Pharmaceuticals is submitting the following comments related to the scope of the planned 2-day workshop.

Wyeth is one of the largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer and marketer of prescription drugs, biopharmaceuticals, vaccines, and over the counter medications.

Wyeth appreciates the opportunity to comment on the proposed scope of the upcoming workshop. We support the broad objectives of the Agency's Critical Path Initiative to identify a new product development toolkit that would advance the use of new scientific and technical methods for assessing the safety and effectiveness of innovative medical therapies, and we commend the Agency for its ongoing efforts to involve interested stakeholders in this initiative. We have the following recommendations concerning the proposed agenda for the planned workshop.

Development of Novel Therapies for Alzheimer's Disease

We recommend that a breakout session be devoted to the clinical development of new therapies for Alzheimer's disease, and the identification of new biomarkers that have potential utility for early assessment of safety and effectiveness.

Alzheimer's disease (AD) is a progressive neurodegenerative disease and is the leading cause of dementia in the elderly. The global Alzheimer's dementia population is estimated at 15 million people, of which 4 million are in the US. The prevalence of dementia in the US alone is projected to reach 5.6 million by the year 2010 (one in ten people over age 65), and 9 million by 2030. The prevalence of dementia doubles every 5 years after the age of 65 and affects all races.

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AD places an enormous financial burden on the US healthcare system with annual treatment costs that range as high as \$80-100 billion/year. Presently AD is the 3rd most expensive disease to treat in the US, exceeded only by cancer and heart disease.

On a human level, AD has a tremendous impact on patients, their families, and their caregivers. Alzheimer's dementia is dehumanizing, debilitating, and leads to increased mortality. The psychosocial and financial burdens on the family can be profound.

Despite the remarkable advances in our understanding of the molecular underpinnings of AD, therapeutic advances have lagged behind. The approved treatments, which augment neurotransmitter systems, have a modest effect on symptoms but do not influence the underlying dementing process.

There is clearly an urgent need for additional, more effective treatment options for this devastating disease. Therefore, efforts should be encouraged towards developing new therapies that slow or halt disease progression and result in meaningful functional improvement. In addition, steps should be considered by the Agency in collaboration with stakeholders on ways to expedite development and accelerate the approval of new therapies for Alzheimer's, similar to those effected for oncologic therapies for treating cancer, and anti-viral therapies for treating AIDS.

There are, however, several obstacles to the development of such disease modifying agents for AD:

1. The lack of accepted biomarkers or surrogate endpoints: Since cognitive decline often lags behind pathological changes, biomarkers should be identified and accepted for assessing efficacy (e.g., cessation or slowing of disease progression) during the course of treatment. These surrogate endpoints may include imaging, plasma, or CSF biomarkers. Efforts focused at validation of such endpoints are already ongoing through the Alzheimer's disease Neuroimaging Initiative. This initiative should be encouraged and supported with ongoing input from FDA scientists.
2. Acceptance of biomarkers as co-primary endpoints in clinical studies: No formal guidance exists regarding the design of clinical studies to be relied upon for proof of efficacy for AD disease modifying treatments. However, study designs that assess the change in slopes of deterioration (of cognition and function) have frequently been suggested. Such designs require studies of long duration (possibly up to 1.5-2 years) that would markedly delay bringing these drugs to market. The use of validated biomarkers as endpoints in these studies could accelerate drug development and approval. Confirmatory chronic clinical studies might then be completed post-

approval. This approach has been used successfully in the development of oncology drugs, but has not been explored for CNS drug development.

3. The lack of adequate clinical endpoints: The cognitive endpoints used in previous development programs of symptomatic AD treatments, such as the ADAS-cog, may not be appropriate for disease modifying agents. The development and validation of more sensitive cognitive measures should be encouraged and supported.
4. The level of risk tolerance versus benefit: If a new treatment were to halt the relentless progression of AD and profoundly improve cognition and function, then a new paradigm of risk/benefit assessment may need to be discussed to allow successful development of these treatments.

Dedicating a breakout session to specifically discuss and address the above issues would therefore represent a much-needed step in the right direction.

Clinical Development of New Antithrombotics

In addition, we also recommend a breakout session on the development of novel antithrombotics for the treatment of vascular thrombotic disorders including acute coronary syndromes (ACS) which encompass myocardial infarction (MI) and unstable angina (UA), embolic stroke, venous thromboembolism including deep vein thrombosis (DVT) and pulmonary embolism (PE) and systemic atherosclerotic vascular occlusive diseases such as peripheral arterial disease (PAD) and associated intermittent claudication (IC). New antithrombotics with improved oral availability and no (or decreased) hemorrhagic side effects would significantly improve patient safety and decrease the need for in-patient hospitalizations, thus providing both a clinical and economic benefit.

Cardiovascular disease (CVD) accounts for over 38% of all cause deaths in the U.S. every year (2.4 million). A large proportion of the overall morbidity and mortality is due to thrombosis related diseases where a clot or thrombus disrupts blood flow to a vital organ.

The foundation of antithrombotic drug therapy is focused on anticoagulants, which block one or more pathways in the cascade of enzymatic events leading to clot formation, and antiplatelet agents which block the ability of these blood borne cellular fragments to participate in the formation of thrombi. Anticoagulants are primarily used in the prevention and treatment of venous thrombosis while antiplatelet strategies have been targeted to the arterial thrombotic events. The vast majority of agents in both cases carry significant liabilities, the foremost of which is an increase in both major and minor bleeding, which clearly limits their widespread use.

This is particularly true for the only approved oral anticoagulant, warfarin. In use for almost 60 years, significant drug-drug interactions and dietary restrictions

require that patients on warfarin therapy be closely monitored to make sure the proper anticoagulation state is maintained to prevent excessive bleeding or thrombotic episodes. These factors have led to warfarin being used primarily in high-risk patient populations, leaving at risk a large percentage of patients that could benefit from antithrombotic therapy. The lack of any alternative to warfarin has stimulated many academic and industrial research groups to search for improved strategies for oral antithrombotic therapy with agents that provide predictable and efficacious antithrombotic efficacy without the significant limitations of warfarin.

With this as background, we suggest that the following issues be considered for discussion at an anti-thrombotic breakout session:

1. Would ultrasonography be considered as a replacement for venography in the evaluation of lower extremity DVT in patients post-operatively? Is there a statistical model that could be utilized or developed to incorporate the sensitivity, specificity, and/or predictive value of alternate, and newly developed, diagnostic tests in clinical trials of efficacy (or safety) for these endpoint evaluations?
2. Would a warfarin comparator (started post-operatively) be considered adequate in a head to head comparison against a novel anticoagulant in a post-operative DVT prevention study?
3. Would surrogate markers such as thrombus imaging, as is the case in the prevention and treatment of VTE, be considered for the basis of approval for new antithrombotics in other indications such as prevention of stroke in atrial fibrillation patients?

Clinical Development of New Therapies for Atherosclerosis

We additionally recommend a breakout session on the use of biomarkers and surrogate endpoints utilizing new imaging technologies in guiding drug development for new therapies for cardiovascular disease. Discussion focused on “plaque regression” and “plaque composition” together as (a) validated biomarker(s) or surrogate marker(s) for a clinical endpoint in atheropathogenesis may be a way to accelerate the development of new therapeutic options in vascular disease prevention and treatment.

For example, beneficial changes in plaque morphology (e.g., demonstration of plaque regression along with beneficial changes in plaque composition) could potentially reflect treatment changes in meaningful clinical vascular endpoints in lieu of a large-scale cardiovascular outcome study. Specific questions and topics that could be addressed in this session include the following:

1. Would imaging technologies [e.g., intravascular ultrasound (IVUS), intravascular MRI (IVMRI), cIMT, or other technologies] that provide

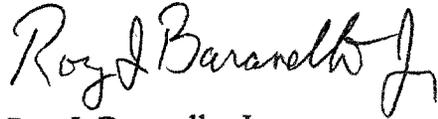
tomographic images that permit visualization of the lumen, vessel wall structure, and atherosclerotic plaques be an acceptable tool to determine plaque size and acceptable measure of plaque composition? What would be the acceptable imaging technology and measurement criteria for such technologies?

2. Would changes in plaque regression by these emergent sensitive imaging technologies be considered an acceptable biomarker of changes in atherosclerosis? What studies would be required to qualify plaque regression as a surrogate endpoint? Do studies focused on "plaque regression" need to be conducted in parallel with more traditional long-term outcome studies that measure major vascular endpoints? Could a new cardiovascular therapy attain approval for marketing on the basis of demonstrating plaque regression without accompanying changes in lipid biomarker data (e.g. minimal changes in LDL-C)?
3. Should a change in plaque volume/size be complemented by changes in plaque composition (e.g., lipid content, macrophage number and state of activity, size of 'fibrous cap', increased amount of collagen and cells over lipids/foam cells etc.)? What statistical modeling would need to be applied to measure these changes and determine changes in overall plaque burden?
4. What patient populations and trial designs should be considered to evaluate plaque regression/composition as an acceptable surrogate endpoint(s)? Would either parallel or subsequent traditional long-term outcome studies measuring incidence rates of major vascular adverse events still be required to gain approval of novel new therapies? Could surrogate endpoints (plaque regression and composition) be useful as bridging criteria to standard endpoints as suggested in an article authored by Dr. Robert Temple, FDA, (JAMA 1999; 282; 8; 790-795) who noted that *"Improvement in an intermediate endpoint is of value to patients even if this does not lead to reduced mortality or morbidity and would ordinarily be a basis for market approval by the FDA. At the same time, an effect on an intermediate endpoint may also be taken as reason to expect a favorable ultimate outcome; in that sense, the intermediate endpoint plays a role of the surrogate."*
5. If plaque regression and/or plaque composition is an acceptable biomarker for clinical and regulatory decision-making, drug development and approval will proceed more quickly/efficiently by basing initial conclusions regarding efficacy on vascular imaging results, reserving long-term morbidity and mortality for phase 4. If plaque regression becomes an acceptable surrogate clinical endpoint, would outcome studies still be required for initial approval for marketing, or could they be conducted post-marketing as post-approval commitments?

Wyeth

We are submitting the enclosed comments in duplicate. Again, Wyeth appreciates the opportunity to comment on the planned Critical Path workshop, and trusts that the Agency will take these comments into consideration.

Sincerely,

A handwritten signature in cursive script that reads "Roy J. Baranello, Jr." with a stylized flourish at the end.

Roy J. Baranello, Jr.
Assistant Vice President
Regulatory Policy & Operations