Prepared for ACT-AD
(Accelerate Cure and Treatments for Alzheimer’s Disease)

Avalere Health is a leading advisory company focused on business strategy and public policy. It serves a diverse client base, which includes Fortune 500 healthcare technology companies, federal government agencies, and major medical foundations. The company is organized into seven substantive areas - Medicare, Medicaid, Reimbursement, Long-Term and Post-Acute Care, Health Information Exchange, Evidence-Based Medicine, and Education. Anchored by a comprehensive research engine and staffed by experts in business, medical product commercialization, and health policy, Avalere provides strategic guidance, objective analytic research, and quality educational programs focused on the full range of healthcare issues facing our nation.

ACT-AD is a growing coalition of 50 national organizations representing patients, providers, caregivers, consumers, older Americans, researchers and employers seeking to accelerate development of potential cures and treatments for Alzheimer’s. The Coalition is directed by an Advisory Council made up of representatives from Alliance for Aging Research (AAR), Alzheimer’s Foundation of America (AFA), American Society on Aging (ASA), National Alliance for Caregiving (NAC), National Association of Area Agencies on Aging (n4a), National Consumers League (NCL), Research!America, and the Society for Women’s Health Research.

Grant funding provided by Wyeth Pharmaceuticals.
Executive Summary

Alzheimer’s disease poses a unique and burgeoning threat to the U.S. public health system in that age is the number one risk factor for developing the disease. With the steady aging of the Baby Boomers, the impact of Alzheimer’s will grow dramatically, imposing an increasing burden on federal and state entitlement programs. An estimated five million people have the disease in the United States alone, and the direct and indirect costs of Alzheimer’s and other dementias amount to more than $148 billion annually.¹

Current treatments for Alzheimer’s offer some symptomatic relief, but none affect underlying disease progression. As a result, there are currently no Alzheimer’s survivors. The speed at which new treatments may be available for patients depends on several critical factors, including medical innovation and the Food and Drug Administration (FDA) review process.

Alzheimer’s at a Glance

<table>
<thead>
<tr>
<th>Condition description</th>
<th>Progressive and fatal neurodegenerative disorder manifested by cognitive deterioration, with resultant impact on many areas of function (e.g., memory, judgment, progressive impairment of activities of daily living, a variety of neuropsychiatric symptoms, behavioral disturbances)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current prevalence</td>
<td>5 million US, 18 million worldwide</td>
</tr>
<tr>
<td>Average age of onset</td>
<td>The disease usually begins after age 60, and risk goes up with age. While younger people also may get Alzheimer’s, it is much less common. About 5 percent of men and women ages 65 to 74 have Alzheimer’s, and nearly half of those age 85 and older may have the disease.²</td>
</tr>
<tr>
<td>Average life expectancy</td>
<td>8-10 years³</td>
</tr>
</tbody>
</table>
| Current pharmaceutical treatments | Aricept (donepezil)  
Cognex (tacrine)  
Exelon (rivastigmine)  
Namenda (memantine)  
Reminyl/Razadyne (galantamine) |

Given the critical nature of the FDA review process on access to therapies, and the lack of standards governing this process through the 1980s, Congress passed the Prescription Drug User Fee Act (PDUFA) in 1992. This law served as an avenue to secure deeper financial resources for the FDA, and in turn expedite the review process.
Comparative Analysis of FDA Review Times for Alzheimer’s, HIV/AIDS, and Cancer Therapies

for medical therapies. Post-PDUFA, much work has been published on how many therapies have been reviewed for approval, but few studies have attempted to compare the review time of different therapeutic classes that represent both current and looming public health threats.

The purpose of this study is to assess FDA review times for Alzheimer’s therapies as compared to other diseases. This paper selects several diseases widely considered to be among the nation’s most pressing clinical challenges—Alzheimer’s disease, cancer, and HIV/AIDS—and seeks to compare the speed at which therapies that treat these diseases receive FDA approval. It presents an initial identification of potential differences in the FDA review process and thus speed to market for Alzheimer’s products as compared to other therapies.

An analysis of FDA review times is complicated by the fact there is no single repository of data or an abundance of public records to assess FDA review time for therapies. We used a number of public and proprietary databases that compile information on new drugs and their FDA approval status to determine estimated FDA review times per product. We also compared review times with the respective annual PDUFA goals to determine if the FDA met its review endpoints per product.

We found that the FDA met PDUFA review timelines for all drug categories examined. However, there were differences among HIV/AIDS, cancer, and Alzheimer’s categories in regard to the number of Priority Review designations and first-cycle approvals, which also affect the speed to market for new products.

Therefore, while the FDA met its target PDUFA goals with respect to Alzheimer’s therapies, therapies for HIV/AIDS and cancer were consistently reviewed more expeditiously because the FDA exceeded its target goals. A deeper understanding of the FDA review process and any potential barriers that continue to block expeditious review of new products can help policymakers, industry, patients, and their advocates work together to make improvements for future evaluation of emerging medical technology.

Background on the Drug Development and FDA Approval Process

The FDA is the government agency that regulates the sales and marketing of medical products and is charged with evaluating products for “safety and efficacy.” FDA approval for a product clears the path for new therapies to enter the marketplace.

When a pharmaceutical company discovers a compound that they believe will become a medically-viable product for a certain disease, the first step is to test that product in an “preclinical” model. After these preclinical experiments have been conducted, the company submits an Investigational New Drug (IND) application to the FDA, requesting permission to test the product in humans.
Once a drug’s IND has been approved, the company completes three phases of “clinical” review, or trials, designed to test safety and efficacy. The company has the ability to meet with the FDA throughout this process to ensure the appropriate design of their clinical trials.

Once the company completes the appropriate clinical trials, they submit the data supporting their claims to the FDA. This submission is called either a New Drug Application (NDA) or a Biologic License Application (BLA), depending on whether the compound is a drug or a biologic. The FDA then reviews and takes appropriate action on the application, deeming it either approved, not-approvable, or “approvable.”

Congress passed The Prescription Drug User Fee Act (PDUFA) in 1992 in an attempt to expedite FDA review for medical therapies, given the lack of standards governing this process through the 1980s. Recognizing that the FDA did not have the resources to speed review, the law created user fees that companies are required to pay for the review of their therapy. In exchange, the law sets target timelines for review of a NDA or BLA. These timelines have decreased over time to increase the speed of FDA review. For example, PDUFA set the FDA goal of acting on 70 percent of complete NDA submissions within 12 months during fiscal year 1995, 80 percent during fiscal year 1996, and 90 percent during fiscal year 1997. PDUFA requires the FDA to submit an annual report to Congress regarding its obtainment of these targets. PDUFA appears to have markedly improved FDA review time relative to the 23-month median review time typical of the early 1990s.

PDUFA also served to affect time to market in other areas that are not measured or reported publicly by the FDA. Notably, the PDUFA created the Priority Review designation to expedite reviews of products that address unmet medical needs. A drug receiving Priority Review must be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a disease. FDA review times for standard applications are slower than for compounds receiving a Priority Review, with standard review time currently set at 10 months and Priority Review set at 6 months.

It is important to note, however, that PDUFA’s creation of the Priority Review designation was not the first time that the FDA attempted to prioritize its review efforts by the perceived benefit of a product. Prior to PDUFA, applications were designated “A,” “B,” or “C” based on whether the product seemed to be a “major,” “modest,” or “no real” advance over existing therapies. Interestingly, HIV/AIDS utilized an entirely different classification system for FDA review. In 1987, the FDA created the “AA Priority” category specifically to classify all applications for potential AIDS therapies to ensure that these products received the highest priority in the review process.

An important nuance in regard to the PDUFA timeline targets is that they merely mandate the FDA to perform one of three actions on an application within the time
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allotted. In addition to approving or rejecting a product, the FDA can deem a product “approvable.” A product receiving an approvable letter necessitates further investigation by the FDA for full approval. For instance, the FDA may request additional data from the company to support the application, or may wish to clarify language on the product’s label. An approvable action moves the product into another review cycle, in effect “resetting” the review clock for another six months without affecting the FDA’s “score” in its annual PDUFA timeline report to Congress (i.e., an approvable decision still counts as a positive score in FDA’s obtainment of its PDUFA goals). For the purposes of this paper, products which did not receive any approvable letters before their approval are referred to as “first-cycle approvals.”

Figure 1 below illustrates the Drug Development and FDA Approval Processes relevant to this analysis.

Figure 1: Drug Development and FDA Approval Process

Analysis

Avalere selected HIV/AIDS and cancer as the comparator groups to Alzheimer’s for this analysis, as they are considered clinically challenging, life threatening illnesses. The analysis involved gathering FDA review information regarding all products on the market for the selected diseases. The products included were limited to the first approved indication per product (e.g., if a product was approved initially for breast cancer, it was included in the analysis; however, if breast cancer was the third indication for a product it was not included in the analysis).  

These specific analysis criteria resulted in the inclusion of 5 therapies for Alzheimer’s, 26 for HIV/AIDS, and 18 for the selected cancers. While none of the existing Alzheimer’s
therapies are considered disease-modifying, there are disease-modifying agents on the market for HIV/AIDS and the selected cancers.

Once the products for analysis were identified, we conducted a detailed comparative analysis of FDA’s review of all included products. We analyzed the drug development and approval history for the selected products, obtained from the following databases:7

- NDA Pipeline (FDC Reports, Inc.)
- Investigational Drugs Database (IDdb3) (Thomson Scientific, Ltd.)
- Adis R&D Insight (Adis Data Information BV)
- IMS R&D Focus (IMS Health)
- Pharmaprojects (PJB Publications)

We extracted information from every database for every product. The databases were analyzed for specific date references as to when a drug passed a specific FDA review milestone (IND submission date, NDA submission date, approval date, etc.) to determine the length of time each product spent between review milestones.8 The analysis did not consider clinical differences between and among products, focusing solely on FDA review times per product.

FDA’s obtainment of PDUFA timelines comprised one portion of our analysis to ensure that each product’s review was placed within the context of the year in which its NDA was submitted. In addition to evaluating review timelines, we assessed the use of additional review metrics across disease categories to determine if the frequency of occurrence of these designations differed across disease states. Therefore, we incorporated information as to which drugs in the analysis were given a Priority Review, as this designation affects speed to market for new products. In addition, as requiring two or more review cycles can greatly affect how expeditiously a product reaches the market, we determined whether products received approval in the first review cycle or a later cycle.

Discussion

We found that the FDA met PDUFA review timelines for all drug categories; there was no evidence of a slower or delayed FDA review time for Alzheimer’s. For the drugs selected for this study, the FDA appears to have met its PDUFA review time in virtually every instance. For those products approved prior to the passage of PDUFA in 1992, there is no standard metric against which to measure review times.

Interestingly, however, the analysis found that there were differences among HIV/AIDS, cancer, and Alzheimer’s categories in regard to the number of Priority Reviews and first-cycle approvals. In this context, HIV/AIDS products appear more successful than Alzheimer’s products at obtaining both Priority Review and approval in the first review
cycle. Therapies for the selected cancers also appear to have obtained first-cycle approvals more frequently than Alzheimer’s drugs. To put these statistics in context, approximately half of all products submitted to the FDA for any disease condition are completely reviewed in the first cycle, which is more consistent with the Alzheimer’s observation than the 94 percent success rate observed for cancer, or the 96 percent success rate observed for HIV/AIDS. Overall, given that Priority Review and complete first-cycle review affect the speed at which a new product reaches the market, this analysis indicates that the increased frequency of Priority Review and first-cycle approvals for HIV/AIDS and cancer drugs has accelerated market entry for products in these disease areas.

Figure 2: HIV/AIDS Drugs Obtain Priority Review Status More Often than Comparator Disease States

1Alzheimer’s: All Alzheimer’s drugs were approved after 1992.

2HIV/AIDS: This analysis does not distinguish between those HIV/AIDS products approved pre-and post-PDUFA, due to the “AA Priority” classification discussed above.

3Cancer: Selected Cancers include prostate, ovarian, and breast. Four of the 18 oncology products reviewed were approved pre-PDUFA: of these, one product was classified as Category A (the ovarian cancer therapy Hexalen®), one was classified as Category B (the prostate cancer therapy Lupron®), one was classified as Category C (the prostate cancer therapy Zoladex®), and one had no data available regarding its designation (the breast cancer therapy NOLVADEX®).
There are many possible explanations for these findings. One could be that because few drugs are currently on the market for Alzheimer’s, the analysis is based on a limited sample size. Some of the observed discrepancies in review may stem from the office in which Alzheimer’s products are reviewed; a similar analysis for multiple sclerosis products—which undergo similar review pathways as Alzheimer’s products—revealed similar results as Alzheimer’s. Another explanation is that press releases and conference materials were often the sources of information for the databases used in the analysis, as formal FDA information is not always publicly available.

An additional consideration is the strength and completeness of companies’ initial FDA submissions. Whether products submitted to the FDA to date met the thresholds for Priority Review depends upon whether the drugs met an unmet medical need (i.e., they treated the disease, but did not cure or alter the course of the disease). It is also possible that products submitted to date have failed to obtain first-cycle approval due simply to the completeness of the initial company submission. While to the extent possible the review controlled for NDA submission date by matching the review timeline with the corresponding PDUFA annual report to Congress, this did not eliminate all potential sources of bias, such as changing public perception or increased scientific or social understanding of a particular disease, which could have affected FDA focus.
Conclusion

Alzheimer’s disease poses a unique and burgeoning threat to the U.S. public health system in that age alone is the number one risk factor for developing the disease. Currently prescribed treatments do not affect underlying progression of Alzheimer’s.

Given the confluence of an aging society and the current state of medical technology, the impact of Alzheimer’s will grow dramatically in the coming years, imposing an increasing burden on federal and state entitlement programs, families, and the entire U.S. healthcare system.

This study assesses FDA review times for Alzheimer’s therapies in comparison to those for HIV/AIDS and selected cancers. While the FDA is meeting its mandated timelines for review across all of these categories of drugs, our analysis revealed differences in review times between the categories. The rate of expeditiousness at which these products are reviewed has a significant impact on the subsequent speed to market for the various therapies.

Our analysis represents an initial identification of differences in how products are reviewed by the FDA, but more research is warranted to understand the reasons that underpin the incongruities. A deeper understanding of the FDA review process and any potential barriers that continue to block expeditious review of new products can help policymakers, industry, patients, and their advocates work together to make improvements for future evaluation of emerging medical technology.

2 http://www.nia.nih.gov/Alzheimers/AlzheimersInformation/GeneralInfo/
3 http://www.nia.nih.gov/Alzheimers/AlzheimersInformation/GeneralInfo/
5 FDA Manual of Policies and Procedures 6020.3: Priority Review Policy. Note that this is the Priority Review Policy for the Center for Drug Evaluation and Research (CDER); a biologic drug reviewed by the Center for Biologic Evaluation and Research (CBER) must be a significant improvement in the safety or effectiveness of the treatment diagnosis or prevention of a serious or life-threatening disease.
6 This distinction was made because the FDA handles applications for supplemental indications differently and therefore their timelines would not provide valid comparisons.
7 These databases are available via subscription. Access was provided by Wyeth Pharmaceuticals on November 22, 2005, January 20, 2006, and April 7, 2006.
8 The data required for the analysis were not captured consistently within the databases, requiring the data to be processed manually. When a conflict arose between two or more databases, the date that appeared most consistently was selected in creating a review timeline for each approved drug; if no date appeared twice, an average was taken.
9 Avalere interviews with various FDA experts, conducted Fall 2005.