ENGELBERG CENTER for Health Care Reform at BROOKINGS

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Discussion Guide

Expert Workshop: Expedited Drug Development for Promising Therapies

Workshop Background

The Kefauver-Harris Amendments of 1962 established the foundation of modern drug development and regulation. These amendments required drug manufacturers to prove that drugs were not only safe, but also effective before they could be sold. Following passage of the amendments, the U.S. Food and Drug Administration (FDA) began requiring manufacturers to conduct adequate and well-controlled studies to produce substantial evidence of effectiveness.

Over the last few decades, FDA has recognized the importance of speeding patient access to new and promising treatments, especially in cases where the potential therapy represents a major step forward in the treatment of a serious disease. To speed access, FDA has several approaches to expedite the development and review process. These include Priority Review, Fast Track, and Accelerated Approval. These are useful approaches, and there may be further opportunities to expand the use and application of these programs to expedite the development and approval of promising therapies for patients who need them.

Current approaches for expediting review are the direct result of efforts that began in conjunction with passage of the Prescription Drug User Fee Act (PDUFA) in 1992. Among other objectives, PDUFA set new goals for FDA to reduce the drug review time and resulted in the formulation of two review categories: Priority Review and Standard Review. While Standard Review must currently be completed within a 10-month timeframe, under Priority Review status, FDA strives to complete the review process within six months. A Priority Review designation is granted if the drug represents a substantial improvement over existing treatments or the first demonstrated treatment for a disease. Priority Review only applies to the FDA review timeline following submission of a New Drug Application (NDA) and does not alter the evidentiary requirements for drug approval.

While Priority Review only influences FDA review time after NDA submission, FDA also established a Fast Track mechanism designed to both facilitate development and speed review. Sponsors may apply for this designation at any point during the development process for drugs intended for the treatments of serious or life-threatening conditions and that demonstrate the potential to fulfill an unmet medical need. Receiving a Fast Track designation facilitates increased communication with FDA in order to more quickly address issues as they arise. While distinct from Priority Review, Fast Track eligibility often overlaps with the likelihood of Priority Review status being granted.

The third approach to expedite drug development employed by FDA since PDUFA authorization in 1992 is the Accelerated Approval pathway. Designed for drugs that fulfill an unmet medical need in the treatment of serious diseases, Accelerated Approval utilizes surrogate endpoints that are reasonably likely to predict clinical benefit or clinical endpoints other than survival or irreversible morbidity. Accelerated Approval is important because a drug's effect on the surrogate endpoint or other clinical endpoints can typically be shown much sooner than the drug's effect on the actual clinical benefit, thus shortening the time to marketing approval. Accelerated Approval is only granted, however, under the condition that the drug's sponsor continues to collect evidence on key safety and clinical outcomes through confirmatory phase IV trials in order to verify and describe the clinical benefit. Traditional approval may be granted only after clinical benefit has been confirmed.

Approval Pathway	Application	Actions
Standard Review	Post-NDA filing	Provides approval decision within 10 months of NDA filing
Priority Review	Post-NDA filing	Provides approval decision within six months of NDA filing
Fast Track Status	During development process	Facilitates increased, real-time communication between sponsor and FDA during development
Accelerated Approval	During development process	Permits approval based on surrogate or other clinical endpoints and requires post-approval confirmatory trials to verify clinical benefit

Historically, these approaches have been applied to accelerate access to treatments for many serious diseases. One of the driving forces behind development and review pathway reform in the early 1990s was the urgent need to address the lack of treatments available for HIV/AIDS. Many important drugs to combat HIV/AIDS were approved for marketing quickly in the wake of PDUFA, with products such as the protease inhibitor Kaletra (lopinavir/ritonavir) benefiting from an expedited review process of 3.5 months.[1] Recent approvals of treatments for hepatitis C serve as examples of Priority Review: Merck's Victrelis (boceprevir) was approved as a first-in-class drug under priority designation in five months, followed closely by Vertex's Incivek (telaprevir), which was approved within a six-month timeframe. An important example of a drug granted Accelerated Approval and Priority Review is Pfizer's Xalkori (crizotinib), used in the treatment of late-stage non-small cell lung cancer. Xalkori was granted approval after two single-arm studies were conducted utilizing objective response rate (based on tumor shrinkage) as a surrogate endpoint.[2]

There is now great interest in reviewing and potentially building upon these existing approaches in order to more broadly implement effective processes for expedited development and review of promising therapies. Indeed, there have been discussions including legislators, industry, and the FDA in recent months to address this subject. Such an undertaking raises many questions regarding trial design, how best to define and verify promising results, how to deal with products studied in very targeted indications, and how to ensure that the post-market setting is equipped to support continued development of evidence on safety and benefit of therapies approved through an expedited pathway. Answering these questions and laying groundwork for a path forward to support the FDA's mission of the protection and promotion of public health will require broad input from key stakeholder groups, including patients, medical product developers, regulators, payers, clinicians, and other communities.

Workshop Objectives and Overview

This workshop, convened by the Engelberg Center for Health Care Reform at the Brookings Institution in cooperation with FDA, seeks to facilitate discussion regarding the scope, design, and implementation of an expedited drug development pathway. To facilitate conversation on these topics, this workshop is organized into five sessions.

Panel 1: Existing Approaches for Expedited Market Access

This panel will review lessons learned through the application of current approval pathways in specific disease areas. These concrete examples will both illustrate the pathways and may help to inform future expedited development approaches. Any new approach will need to be developed in the context of existing approaches, capitalizing on opportunities for improvement without creating redundancies. Discussion questions in this session will include the following:

- What are current and historical approaches to facilitating rapid development and review?
- What has been FDA's experience in applying these approaches for specific therapeutic areas (e.g., HIV, HCV, oncology)?

[1] http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm

[2] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm269856.htm

- What are the lessons learned through these experiences that may have implications for a new expedited pathway for promising therapies?

Panel 2: Opportunities to Improve and Expand Existing Pathways
After exploring current approval pathways in Panel 1, this session will focus on opportunities to expand these pathways and to address current challenges. Discussion questions will include the following:

- Are existing expedited development and review pathways and methodologies being applied as broadly as they could be across disease areas? If not, how can these tools be successfully applied to new therapeutic areas?
- What challenges exist in current pathways and how could these challenges be addressed?
- Are there issues that will need to be considered in order to ensure that an expedited drug development program is fully utilized by industry?
- What are the international regulatory considerations that need to be considered as new expedited drug development pathways for promising therapies are explored?

Panel 3: Focus Areas for Expedited Drug Development Informed by Patient and Public Health Needs
Harnessing the potential of an expedited development and review pathway will require identification of those therapeutic areas where early access to new effective treatments may be vital to improved patient outcomes. Discussion regarding the following types of questions is likely to be relevant to this process:

- What therapeutic areas are most likely to benefit from more rapid market access?
- What criteria should be used to determine which therapies have exceptional promise?
- Are there special considerations for therapies that are promising for particular subpopulations?
- How can patient preferences be incorporated into regulatory considerations and trial design for new and promising therapies?

Panel 4: Innovative Methodologies for Expedited Evidence Development
Development, refinement and use of innovative methodologic approaches for evaluating the safety and effectiveness of new therapies will be essential for expedited drug development. This session will explore the benefits and challenges of such methodologies and strategies to increase collaboration among stakeholders during drug development. Specific discussion topics may include the following:

- What approaches could enable the drug development timeline to be compressed for therapies with exceptional promise?
    - Utilization of different data sources (e.g., natural history data)
    - Novel trial designs (e.g., adaptive trials)
    - Alternative endpoints (e.g., surrogate endpoints)
    - Earlier timing of regulatory review (e.g., at the end of Phase 2 trials or after the first Phase 3 trial with expectation of further data from post-marketing studies if necessary)
    - Benefit-risk assessment methods
- What methodological challenges may be associated with these approaches?
- How can FDA encourage collaboration among all stakeholders, which was so successful in the past with the HIV epidemic, to further the goal of expedited drug development of promising therapies?

Panel 5: Post-Market Considerations to Ensure Safe Use and Continued Evidence Development Following Expedited Development and Approval
Expedited development and approval of promising therapies may involve generation of a different quantity or type of evidence in the pre-market period. For example, trials may be conducted on particular populations or using different types of endpoints than in traditional pre-market drug development. While these approaches may be appropriate to meet patient needs for rapid access to innovative therapies, expedited development may create or add to evidence gaps that would need to be addressed in the post-market environment. As we consider approaches for expedited development and review of drugs, we must recognize opportunities to better address these gaps and ensure the safety of these products. This session will bring together stakeholders to discuss this and other post-market topics, including the following:

- In light of the approaches discussed previously, what evidence gaps are likely to exist in the post-market setting? Are current tools and methodological approaches capable of addressing these gaps?
- To the extent that products approved in an expedited fashion have a different quantity or level of evidence, how could this influence decisions regarding coverage and payment?
- Are additional tools (e.g., ability to restrict access to specific patient populations, stronger withdrawal provisions for FDA) needed to enable the safe use of products approved under these expedited pathways?
- How can health care professionals and insurance providers help ensure appropriate use of promising therapies that are approved under an expedited drug development program?