ENGELBERG CENTER for Health Care Reform at BROOKINGS

December 15, 2011

Meeting Summary

Expedited Drug Development and Review for Promising Therapies

Introduction

Although biomedical innovation has offered many important advances in the treatment of illness, critical gaps remain in available treatments for patients with certain serious or life-threatening diseases. For drugs that demonstrate very early signs of providing promising treatment for these conditions, it is important to ensure that the U.S. Food and Drug Administration (FDA) collaborates with manufacturers so that they can efficiently gather the needed data to demonstrate safety and efficacy and get such therapies to the patients who need them. Indeed, FDA has begun to outline its thinking in these areas through its November 2011 report, "Driving Biomedical Innovation: Initiatives to Improve Products for Patients," in which the agency identified potential steps to develop an expedited drug development pathway for treatments that demonstrate considerable early promise in clinical trials. Targeting such promising treatments for fast, efficient approval that does not compromise the safety and efficacy standards underpinning FDA approval decisions presents FDA with distinct challenges and opportunities to review, define, and potentially augment existing tools such as Priority Review, Fast Track, and Accelerated Approval.

On December 15, 2011, the Engelberg Center for Health Care Reform at the Brookings Institution held an expert workshop that brought together a diverse group of stakeholders, including patient advocacy organizations, medical product developers, regulators, payers, clinicians, academic researchers, and other communities, to consider these issues. Key themes from the day-long discussion are summarized below.

Important Components of Expedited Development and Review

1) Achieving clarity on the use and application of existing tools for expedited development and review

As expedited pathways continue to be utilized, it is important to work toward achieving better clarity on how existing tools for expedited development and review can be more broadly and appropriately applied to therapies that demonstrate early promise. There is great potential in how current tools are applied to product development and review, but an understanding among all stakeholders of how to utilize these tools in a clear, consistent, and proactive manner is generally lacking. Some participants suggested that such confusion may hamper efficient application of the tools and could be alleviated through a reexamination of current guidance to identify areas where greater clarity could benefit patients, providers, developers, and regulators. It is especially important for FDA to provide clear, concise guidance on the expedited approval tools in order to ensure a level playing field that fosters biomedical innovation on the part of development firms of all sizes and degrees of institutional experience navigating regulatory pathways. Stakeholders at the workshop cautioned, however, that product development and review processes are not one-size-fits-all, and any efforts to better clarify application of current tools will need to ensure that an emphasis on case-by-case examination of the evidence and data supporting a drug application is maintained.

It may be useful for efforts to clarify existing tools for expediting development and review to be accompanied by a broad-based, collaborative discussion among all stakeholders to both define what it means for a drug to show early promise and to establish a systematic process for identifying and prioritizing treatments that fit that definition. Such an effort could begin by developing a process for bringing stakeholders, including patients, consumers, providers, regulators, payers, and manufacturers, together in a common forum in order to understand the clear medical needs of patient communities and to actively delineate benchmarks and achievements that would represent major steps forward in treatment. Starting with a focus on disease-specific areas could increase the effectiveness of this effort. With this type of process in place, it may be possible to foster greater collaboration between regulatory teams and developers in order to rapidly identify a drug as promising and respond as quickly and efficiently as possible to move safe, effective new treatments to market. Workshop participants note that it is important to see such collaborative mechanisms as aiding FDA in establishing clear processes for the expansion of its expedited review capabilities and not an effort to change or dilute evidentiary standards: through input and engagement all stakeholders will be able to help FDA plan for application of an expanded expedited pathway.

2) Use of surrogate endpoints and development of novel, adaptive trial designs
While biomedical advancements increasingly identify subpopulations of patients with chronic diseases who respond better to targeted therapies, strides in identifying and validating surrogate endpoints, including biomarkers, and the design of adaptive clinical trials for targeted therapies are critical. Some suggested that FDA's ability to efficiently evaluate studies that use surrogate markers is potentially limited due to lack of historical evidence supporting the biomarker or surrogate's ability to be reasonably likely to predict clinical benefit.

Bringing an increasing number of biomarkers to bear in expedited development while maintaining the evidentiary standards for approval will require collaboration among all stakeholders to assess and potentially validate candidate biomarkers as they arise. Such collaborations could include pooling resources in basic scientific research, clinical trials, and data infrastructure in order to move toward validation in a comprehensive and concerted manner. Importantly, this may allow stakeholders to harness a much greater breadth and depth of data to explore the basic biologic questions underpinning use of a biomarker as a surrogate endpoint. Pre-competitive collaboration within industry could also be well-suited for such exploration, as manufacturers, academics, and others vested in the research can work together to identify and understand the use of a biomarker. Examples of such an approach mentioned during workshop discussion include the Coalition Against Major Diseases (CAMD) at the Critical Path Institute. CAMD has been able to foster development of data sharing standards, disease progression models, and biomarker identification between collaborators that represent industry, regulators, providers, patient advocacy groups, and others. This model could be readily applied to many scientific or therapeutic areas to create a reliable and systematic approach to evaluating novel biomarkers for use in expedited drug development.

The relative dearth of biomarkers and surrogate endpoints that are validated or reasonably likely to predict clinical benefit may also limit the ability of manufacturers to make use of efficient, novel trial designs, which could be instrumental in refining or expanding expedited development and review. This includes adaptive designs that allow for efficient review and approval of therapies with companion diagnostics. Some participants pointed to such biomarker-adaptive Phase II or III trials as designs that could not only allow for flexible, responsive study of treatments and companion diagnostic markers but will enable greater targeting to specific subpopulations with the potential for promising response, establishing a basis for application of an expedited pathway. An important example of the power of

adaptive trial designs to address treatments and biomarkers is emerging in the I-SPY 2 trial, which has created an adaptive Phase II framework for treatments in breast cancer.

3) Addressing the potential for off-label use

As clarifying and defining pathways for expedited development and review may result in broader use, concerns about the potential for off-label use may be amplified. Though FDA clearly defines an approved drug's indication based on the evidence generated in the development and review process, FDA does not regulate the decisions of physicians, who may exercise medical judgment and expertise to prescribe drugs to those not included in the approved indication. Off-label use is especially complicated for drugs or biologics that have arrived to market through an expedited pathway, as supporting data are often targeted to narrow indications.

Participants considered potential mechanisms to restrict off-label use, suggesting that one option would be to include contraindications for use outside of the narrow indication for which approval is granted. Under this approach, documentation that a patient is being prescribed the treatment for this narrow indication would be required. However, it is unclear who (e.g., prescriber, payer) would ultimately be accountable for ensuring the narrow indication is met. Payers have existing tools, such as prior authorization requirements, that could help limit use to only approved indications. Comprehensive provider education could further reduce the potential for off-label use. However, from the patient perspective, this may serve to position the payer as the industry sector that is standing in the way of the patient-provider relationship. Therefore, broad collaboration between FDA, payers, manufacturers, patient advocacy organization, providers, and other groups will be needed to address these issues.

4) Harnessing a robust, reliable post-market infrastructure for evidence generation

The extent to which any expedited approval pathway will be used, and its ultimate success, may depend on confidence in an effective system for developing further evidence in the post-market setting. To date, there have been challenges with developing post-market evidence on safety and in confirming the relative benefits and risks of these products in the intended populations or in the other populations that might be treated and in gaining a timely understanding of how approved drugs—especially those approved based on evidence in relatively narrow populations—are actually being used in practice.

It is technically possible to develop more post-market evidence for treatments that receive expedited approval by building on recent progress in electronic data systems, FDA's investments to date in public-private networks such as the Sentinel Initiative for active medical product safety surveillance and other efforts such as the Health Maintenance Organizations Research Network (HMORN). These efforts have made important contributions to the infrastructure for post-market evidence development and have elucidated many practices (e.g., use of a common data model) that facilitate rapid analyses of electronic health care data. Building on this foundation, participants recommended that consideration should be given to the applicability of these tools to generate evidence for post-market surveillance of any product approved under an expedited pathway.

5) Establishing consistent, collaborative funding sources

Finally, funding mechanisms may need to be established in order to address some of the challenges identified above during both pre- and post-market phases to harness the full potential of expedited development and review pathways. Increased collaborative funding through the National Institutes of Health, for example, could be directed toward answering the basic science questions surrounding identification and validation of surrogate endpoints that are reasonably likely to predict clinical benefit validation of biomarkers and surrogate endpoints. Such pre-competitive research would similarly benefit

from potential matching funds or contributions from vested patient groups, industry, or other academic organizations. Core financing to bolster the strength of a post-market network could also make use of the infrastructure that is already being supported for post-market safety surveillance.

Conclusion

Addressing these challenges will be important in order for regulators and developers to meet the goal of enabling promising therapies to be identified in early phases of clinical trials and quickly brought to market for patients who need them without compromising established safety and efficacy standards. Existing tools could be useful to meet this goal; however, defining a clear and efficient pathway that acknowledges scientific advances in targeted therapies may prove essential. A systematic approach to identifying and prioritizing promising therapies; establishing pre-competitive collaborations to identify biomarkers and surrogate endpoints that are reasonably likely to predict clinical benefit; continuing advances in novel trial designs; and advancing the application and expansion of a national post-market research infrastructure are broad steps needed to achieve this goal.