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FDA's expedited approval programs: addressing premarket flexibility with enhanced postmarket evidence generation

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We would like to thank Drs. Janet Woodcock, Robert Califf, and Richard Schilsky for their thoughtful comments on our review article.¹ When the editors of *Clinical Trials* solicited our review on the U.S. Food and Drug Administration's (FDA) expedited development and review programs, we anticipated there would be accompanying commentaries from other academics with differing opinions, or perhaps from the perspectives of industry or venture capital. We hardly expected to initiate a discussion among the former Commissioner of the FDA, the current Director of the Center for Drug Evaluation and Research (CDER), and the Chief Medical Officer of the American Society of Clinical Oncology on the advantages and disadvantages to patients and clinicians of FDA's expedited approval programs. But we appreciate the opportunity to have done so. To be clear, the goal of our review was to engage in constructive dialogue, discussing the implications of expedited approval programs on premarket and postmarket evidence generation, highlighting some specific concerns, and offering our recommendations for robust medical product evaluations that ensure high-quality clinical evidence is available to inform patient care and clinical decision-making.

The FDA faces the challenging task of striking the right balance between ensuring that novel therapeutics are safe and effective and allowing promising new drugs to enter the market as quickly as possible. We agree with Dr. Califf that FDA's regulatory approach should not 'revert back to the strategy of the 1970s'.² Likely in response to the desires frequently expressed by patients and clinicians, the U.S. Congress has enacted laws requiring the FDA to develop expedited development and review pathways to accelerate the availability of novel therapeutics. Some of these pathways necessarily offer potential flexibility with respect to the evidentiary standards that are required to demonstrate medical product safety and effectiveness and secure approval. Accordingly, we believe there is a need for corresponding efforts to strengthen the clinical evidence that is generated after market approval.¹

Premarket flexibility and robust postmarket evidence generation

Over the last decade, the expedited development and review programs have increasingly led to products being approved on the basis of fewer or less robust studies.³ As we outline in our review,¹ this trend corresponds with FDA's adoption of a 'lifecycle evaluation' strategy, where the assumption is that once certain drugs are approved, additional safety and efficacy data will be generated in the postmarket setting.⁴ However, there is currently significant variation in the quantity and quality of postmarket clinical evidence for therapeutics approved on the basis of limited premarket evidence.⁵⁻⁷ We believe that additional efforts are necessary to strengthen postmarket clinical evidence generation, in particular for drugs approved via the Accelerated Approval pathway on the basis of surrogate markers of disease.

Dr. Woodcock states that 'the real issue requiring discussion is how frequently' failures of trials to confirm endpoints used for accelerated approval (i.e., surrogate markers) should occur.⁸ This question warrants significant debate and the answer will likely differ among regulators, industry, clinicians, patients, and the research community. One recent study demonstrated that fewer than 5% of new drug indications approved by the FDA on the basis of surrogate markers of disease are followed by at least one randomized, controlled, double blind postmarket trial published in the peer-reviewed literature, after an average of 5.5 years, that shows superior efficacy for the same clinical indication on the basis of clinical outcomes.⁷ Even more recently, FDA scientists published a review of all new drugs indicated for the treatment of malignant hematology and oncology diseases approved by the FDA over the last 25 years using the Accelerated Approval pathway.⁹ This review found 40% of the indications do not have completed confirmatory trials and 5% of the indications have been withdrawn.⁹ Although a 5% withdrawal rate appears to be reasonable for drugs that target unmet medical needs, these results imply that for 45% of accelerated cancer drug approvals, benefits assumed on the basis of surrogate markers have yet to be, or were not, confirmed.⁹

Recently, concerns have been raised about the FDA's lack of enforcement and drug sponsors' lack of completion of required confirmatory trials.^{5,10,11} Drug sponsors play an important role in generating postmarket clinical evidence. However, it is possible that once drug sponsors receive an Accelerated Approval for their product, the incentives to generate additional evidence, which may undermine previous efficacy and safety claims, may be minimal.⁶ Furthermore, drug sponsors are often performing trials in other therapeutic areas in parallel with their FDA-approved indications,⁶ which may indicate that sponsors prioritize new approvals instead of pursuing additional research focused on the originally-approved indications. In order to ensure that postmarket clinical evidence is generated, some have called for greater reliance on FDA's existing enforcement authority, including fines and other penalties on sponsors.¹⁰

Although our review recommended that the predictive validity of surrogate markers should be assessed using a three-part process,¹² as Drs. Woodcock and Schilsky note in their commentaries, randomized controlled trials are difficult to conduct for diseases that lack effective treatments.^{8,13} We agree with Dr. Califf about the importance of working 'together to devise trial designs that are informative and acceptable to patients in the postmarket phase.'² Although we outline certain limitations related to using real-world evidence and non-clinical trial data sources to support regulatory decisions, we also recognize their potential and suggest ways these study designs can help effectively and efficiently address questions that are unanswered at the time of approval.¹ For instance, rigorous pragmatic clinical trials, which leverage patient data from electronic health records or clinical registries, can be a valuable source of postmarket clinical evidence.¹⁴ However, we agree with Dr. Schilsky that real-world evidence should be used as a complement to clinical trial data, not as a substitute, for drug evaluation.¹³ As we continue moving into an era where expedited development and review programs are leveraged to secure earlier market approval, and real-world data are increasingly available for research and evaluation efforts, our interests are focused on how

to strengthen the clinical evidence that is generated after market approval to inform patient care and clinical decision-making.

Clarifications and comments

Dr. Woodcock states that ‘contrary to the assertions of Wallach et al., Fast Track designation does not entitle designated drugs ‘to be approved based on a single phase 2 study’ nor influence approval standards in any way, and Fast Track drugs do not receive priority review or ‘accelerated approval’ unless otherwise eligible for it on their merits’.⁸ To be clear, our intention was to convey that ‘when an agent receives Fast Track designation, it can still be eligible for Accelerated Approval and Priority Review,’¹ not that one designation leads to the other. Further, we did not think that our claim about Fast Track designation allowing therapeutic agents to be approved based on a single phase 2 study was controversial. Previous articles discussing Fast Track designation have included similar statements^{15, 16} and our review of the 1998 “Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review,” under section IV (“Programs For Expediting Development and Review”)¹⁷ suggested the same, stating:

“...the first phase 2 controlled trials in life-threatening or severely debilitating illnesses may provide sufficient data on safety and effectiveness to support approval, with later development of more extensive safety data, dose response information, and other information in post marketing studies.”

While more recent guidance documents, including “Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics”,¹⁸ do not include similar statements, neither do they establish that these prior standards are no longer acceptable.

In addition, we appreciated Dr. Woodcock's clarification that all New Drug Applications 'are required by law to contain all information and studies that sponsoring companies have conducted or are aware of.'⁸ The language we used in our review, suggesting that 'it is possible that drug sponsors only submit individual trials with the largest treatment effects to the FDA',¹ was poorly worded. Rather, what we had intended to suggest is that perhaps it is possible that controlled trials with larger treatment effect sizes, selected from among all studies submitted by the sponsoring company, are more likely to be designated as pivotal and support the product's approval. To our knowledge, this is an empirical question that has not been examined.

Dr. Woodcock also questioned our summary of the evidence suggesting that expedited regulatory approvals were associated with an increased likelihood of the FDA taking safety-related actions after market approval. Of the 3 studies we discussed, including one led by FDA scientists examining every new small molecule approval between 1997 and 2009,¹⁹ priority review and expedited pathway approvals were consistently associated with specific safety actions.¹⁹⁻²¹ Dr. Woodcock referenced a new study by Pinnow and other FDA scientists, published after we had submitted our review to *Clinical Trials*, that found no relationship between review times and subsequent safety label changes.²² However, the authors of that study note that 'differences in statistical modeling likely explain' the differences between the previous and present studies.²² Overall, we believe that the preponderance of evidence suggests that safety-related actions by the FDA are more likely among therapies that receive expedited approval. Nevertheless, these findings do not necessarily suggest that expedited regulatory approvals are 'dangerous'. On the contrary, when approvals are based on fewer or less robust premarket studies, it is expected that new and important information will be learned only after market approval, particularly with respect to safety. In some respects, it is reassuring to have found that FDA took major safety-related actions for one-third of recent novel therapeutic approvals,²¹ as it suggests that the agency is actively engaging in

postmarket safety surveillance efforts and acting upon and communicating with clinicians and patients when concerns are identified and deemed serious. Continued collaborations between the FDA, industry, clinicians, patients, and the research community are needed to ensure that medical product safety evaluations are routinely and rigorously conducted after marketing approval.

Dr. Schilsky discusses how improvements in the field of precision medicine have allowed for more accurate identification of patients likely to benefit from a targeted drug.¹³ We agree that trial participants should reflect the population of patients that are expected to benefit from the therapeutic agent being evaluated.¹ However, it is also worth noting that precision medicine enables drugs to be approved for narrower indications based on smaller trials. While these more ‘precise’ approvals can effectively address unmet medical needs, there are potential concerns as well if the drugs are then prescribed for broader indications, beyond those formally evaluated by the FDA. Postmarket clinical evaluations will be needed to understand whether drugs are being appropriately used and to confirm their safety and effectiveness in real-world settings.²³

Furthermore, as Dr. Woodcock states in her commentary, many Breakthrough Therapies designations arise from drug sponsors focusing on ‘targeted therapies’ or ‘precision medicine’.⁸ Considering that ‘more-than-expected’ Breakthrough Therapy designations have been made and that a number of Breakthrough Therapy ‘designated drugs have been approved based on early results, and with short review times,⁸ it will be important to closely monitor the products designated as Breakthrough Therapies and determine how often postmarket clinical evaluations are performed and the strength of the evidence generated.

In conclusion, although our review partly focused on the limitations of FDA’s expedited development and review programs, we agree with Dr. Califf that ‘the cup is half-full’.² The FDA has a successful track record of working with industry, clinicians, patients, and the research community to advance the public’s health by helping to speed innovations that make medicines more accessible,

while simultaneously working to assure the safety and efficacy of all medical products for which it maintains oversight. While expedited approval programs offer the FDA continued opportunities to build upon its prior premarket regulatory innovations, there are also opportunities for the agency to lead efforts that ensure robust medical product evaluations are taking place after market approval so that high-quality clinical evidence is available to inform patient care and clinical decision-making.

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