

Expediting drug development for serious illness: Trade-offs between patient access and certainty

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Drug development can be described as the progressive reduction of uncertainty about the effects of a molecule in people. For over a hundred years, controversy has raged over how much uncertainty should be accepted when allowing a drug to be marketed in the United States. In 1962, 26 years after a requirement for pre-market safety testing was instituted, Congress mandated that drug effectiveness must also be demonstrated prior to Food and Drug Administration (FDA) approval. The statutory language called for “substantial evidence” consisting of “adequate and well-controlled” studies showing effectiveness. This standard, interpreted by FDA as two adequate and well-controlled clinical trials each with a *p* value less than 0.05, was debated and litigated over the next two decades. Concurrently, voices were raised, first from the cancer community and later, very forcefully, from those impacted by the surging HIV epidemic, about whether a uniform standard of certainty was appropriate, given indications ranging from minor symptom relief to treating rapidly fatal diseases. In this issue of *Clinical Trials*, Wallach et al.¹ review the various “expedited programs” that have subsequently been created to address drug development for serious and life-threatening diseases and offer cautions and suggestions on improving evidence generation when such programs are used. This commentary offers an historical perspective, some factual corrections, and a response.

In the face of growing concerns about seriously ill patients’ access to innovative therapies, Congress established the first expedited program, the “Fast Track” designation, in 1988. Companies studying a drug to treat an unmet medical need in a serious or life-threatening disease could apply for and receive this designation, which conferred special FDA attention and the ability to have a “rolling review,” that is, submit parts of their application before the complete submission was ready. 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 does it influence approval standards in any way, and Fast Track drugs do not receive priority review or “Accelerated Approval”

(AA) unless otherwise eligible for it on their merits. FDA has issued authoritative guidance on the characteristics of the various expedited programs.² Today, Fast Track designation identifies drug development programs targeting serious unmet needs.

In 1992, Congress put into statute FDA’s existing “priority review” approach, establishing a 6-month review period for applications which purport to demonstrate a substantive improvement over available therapy in a serious disease (this program was modified in 2012 to include a 2-month pre-filing period, giving FDA 8 months to evaluate the application). This goal was part of the Prescription Drug User Fee Act (PDUFA) agreements, which provided FDA increased resources tied to review time frames. Eligibility for priority review is evaluated by FDA staff at submission, based on the evidence documented in the application. A few applications, per recent Congressionally mandated incentive programs such as “Priority Review Vouchers,” must receive a priority review.² Wallach et al. voice concern that priority review timelines may result in less safe drugs being approved, presumably because FDA does not have a chance to review the evidence thoroughly. This concern may have been more salient in 1992, when massive amounts of paper data files were delivered to the Agency via forklift through a loading dock. Today, standardized safety and efficacy data sets are submitted electronically through the FDA “Gateway,” in addition to the internationally harmonized “common technical document,” containing complete reports on manufacturing, toxicology testing, pharmacology, and clinical studies. These documents and data sets are exhaustively

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reviewed by large, multidisciplinary teams of scientists. If important questions cannot be fully resolved by the end of the review period, FDA can, and does, miss the goal date. (The PDUFA agreements call for meeting 90%, not 100%, of review timelines.) Contrary to concerns raised by Wallach et al., applications are required by law to contain all information and studies that sponsoring companies have conducted or are aware of.

Much concern about establishing review time frames was voiced at the initiation of PDUFA. Multiple academic analyses of the relationship between review speed and postmarket safety have been published, without reaching consistent conclusions. Some claim that completion well before the goal date (arguably “faster review”) results in fewer postmarket safety changes; others correlate shorter review times with a greater number of postmarket safety issues. Drugs approved well before formal goal dates are almost always those intended to treat serious or life-threatening illnesses, thereby confounding any association with review times. Pinnow et al.³ recently published a comprehensive analysis of postmarket safety changes over a 14-year period and found no relationship between review times and subsequent safety label changes. These results make sense, given that extending review time, per se, cannot make a drug any safer, unless the wait is so long that additional experience is generated, for example, as a result of marketing in another country. The extent of understanding of a new drug’s safety, and the limitations of that understanding, is largely a property of the development program. The most significant improvements in pre-approval drug safety evaluation over the past 30 years have come from better scientific insight into both the pathogenesis (e.g. of cardiac repolarization abnormalities) and the clinical signal detection (e.g. of drug-induced liver toxicity) of drug side effects. FDA has been a leader in these scientific efforts. The Center for Drug Evaluation and Research at FDA is currently working to further increase the rigor and consistency of its safety reviews.

In 1992, in the face of the HIV epidemic, FDA implemented regulations establishing “Accelerated Approval,” the third “expedited program” discussed in the Wallach et al. article. These regulations enable FDA to approve a drug for a serious or life-threatening condition based on a surrogate endpoint judged “reasonably likely to predict clinical benefit”; however, “substantial evidence” is still required. The drug sponsor is generally required to conduct with “due diligence” further studies after approval to confirm such benefit. By 1992, FDA had already approved multiple drugs based on “validated” surrogate endpoints, that is, surrogate endpoints expected to correlate with clinical outcomes (e.g. blood pressure reduction): such approvals do not use AA. AA was particularly applicable to HIV (surrogates of CD4 cell counts and then HIV viral load) and cancer (surrogates such as

radiographic tumor response or progression-free survival) and was used primarily in these diseases for the first decade, with 22 HIV drugs, 14 cancer drugs, and 8 drugs for any other condition approved using AA in the first 10 years. The use of AA in HIV, while highly controversial at the time, arguably led to the relatively rapid development of HAART (highly active antiretroviral therapy) and control of the epidemic in the United States, since requiring large outcome trials for each new antiretroviral agent (as some called for) would have very substantially slowed development and availability. Subsequently, AA has been used more broadly, particularly in rare diseases.

Wallach et al. voice a number of concerns about AA. First, they worry about the lesser amount of information generated by a development program using a surrogate endpoint. It is clear that there will be more uncertainty about a drug’s impact on clinical outcomes, particularly efficacy but often safety as well, when it is approved using AA. In some sense, this is the point. Individuals with serious, life-threatening diseases (and their families, and the physicians who care for them) have repeatedly stated their desire and willingness to tolerate more uncertainty, including about effectiveness, in a trade-off for faster access. They point out that their lives may be the cost of waiting for definitive clinical outcomes trials to be completed. The “unmet medical need” stipulation, combined with the “serious or life-threatening disease” requirement, usually means that AA is used for very dire disease states where patients and physicians have run out of, or lack entirely, options to treat a fatal illness. Thus, for example, AA is not used in “first-line” treatment for common cancers, where FDA-approved treatments are available. Instead, it is most frequently used in metastatic cancer when multiple types of therapy have been exhausted, or in rare tumors where accumulating patients in a randomized controlled trial (RCT) would be impossible or take decades.

The “reasonably likely to predict clinical benefit” standard for AA surrogate endpoints clearly acknowledges the possibility of error. Commentators are quick to point out the occasional drug withdrawals as signs of the program’s problems; however, the failure to have an AA endpoint confirmed by a later clinical trial is occasionally expected in a program that seeks to trade-off more certainty in exchange for earlier access. The real issue requiring discussion is how frequently these should occur. If AAs resulted in the same error rate regarding efficacy as traditional approvals, the AA program would be setting a higher-than-intended bar.

Even “gold standard” clinical outcome endpoints have limitations, and conversely, some surrogates provide fairly robust evidence of benefit. Traditional efficacy endpoints, while intended to measure clinically relevant outcomes, may not reflect the full picture of a drug’s effects. Since the drug approval decision is a

judgment that expected benefits will exceed expected harms in the intended population, reliance on a clinical endpoint can lead to statistical certainty but unclear overall value. For example, one might question the net benefit of a cancer drug that statistically improves the “gold standard” of overall survival for a few months in an RCT but results in a miserable quality of life. On the other hand, certain surrogate endpoints, such as rapid lowering of a toxic agent’s blood levels, demonstrated pharmacodynamic effects in enzyme replacement, or evidence of eradication of infectious agents have high face validity. Finally, the failure of an outcomes trial to confirm the predictive validity of a surrogate endpoint does not necessarily mean that the surrogate is invalid: there are multiple well-known controversies in medicine where two large, well-conducted, randomized trials had divergent outcomes: in some cases, even a third trial did not settle the dispute. Additionally, Wallach et al. are concerned that surrogate endpoints may overestimate effectiveness. This is true. In cases that lack treatment alternatives, this uncertainty about magnitude may be acceptable to patients and clinicians; however, it must be taken into account in any benefit/risk assessment. It is also plausible that use of a surrogate endpoint will underestimate benefit. In fact, an RCT using a clinical outcome measure that evaluates a single domain in a multidimensional disease may similarly over- or underestimate drug impact.

Wallach et al. offer recommendations to assess the predictive validity of surrogate endpoints using a three-part process. Unfortunately, several of these steps are predicated on the availability of RCTs using effective therapies. This evidence is never available for diseases that lack effective treatment.

Citing a number of studies, Wallach et al. also raise concerns about the timeliness and completion rate of required postmarket confirmatory trials after AA. This is a serious and problematic issue, as lack of additional evidence prolongs the period of uncertainty. There are practical and ethical challenges to carrying out outcome trials in serious diseases that have only a single treatment option. These challenges have been addressed in many cancer approvals by doing a comparative confirmatory trial in an earlier tumor stage that has a current, evidence-based treatment. Success in this trial is used to confirm that the drug is also effective in the more advanced setting. In other cases (e.g. HIV and some cancer agents), longer observation of the same subjects exposed in the surrogate endpoint trial confirmed durability of effect (viral load reduction or tumor stability, respectively), and thus clinical impact. Wallach et al. suggest doing randomized outcome trials in regions where the drug is not yet approved. While this may sometimes be possible, most development programs are carried out simultaneously worldwide in economically advanced countries, and some ethicists have raised strenuous objections to trials being conducted in

populations that will never have a chance to obtain such therapy in their healthcare system. Nevertheless, despite the challenges, it is critical that confirmatory trials be completed. As part of FDA evaluation of an application under AA, the proposed confirmatory trial is carefully assessed for feasibility and proper design. These assessments can be found in FDA reviews posted online.

The FDA Modernization Act of 1997 codified another type of regulatory flexibility by clarifying that FDA had statutory authority to approve a drug based on a single clinical trial and “confirmatory evidence.” FDA issued guidance in 1998 to expand on this standard.⁴ Confirmatory evidence could come from pre-existing FDA approvals when pursuing new dosage forms, expanded populations, or related indications for a drug. In other situations, including rare diseases and very convincing trials demonstrating improved survival, a single trial was deemed acceptable based on practical or ethical reasons, when bolstered by mechanistic data or animal studies. Wallach et al. imply that FDA has the authority to require additional efficacy trials (for the approved indication) after approval; however, this is only the case for AA or “animal rule” approvals.

The most recent expedited program is the “Breakthrough Therapy” (BT) designation, created by Congress in 2012. Like Fast Track designation, this new program does not automatically confer any other expedited features, or change the FDA standards for safety or effectiveness, but does allow for “rolling review.” Like Fast Track, BT designation requires study of a serious disease but has a higher bar of “preliminary clinical data” that indicates the drug “may demonstrate substantial improvement on a clinically significant endpoint” compared to available therapies. This language has been interpreted by FDA to mean that—in early studies—the drug has shown an impact on a clinical outcome (or convincing surrogate endpoint) that would be “game-changing” for people with the disease if verified.

Given that BT designation does not create any new approval standards, why has there been controversy about it? Understanding this requires an appreciation of the profound changes in drug development that have occurred over the past 15 or so years. In the 1980–2000 period, drug developers largely concentrated on the “blockbuster” model, seeking indications with large populations. With the rise of formulary management and drug cost-consciousness, and as these therapeutic areas became crowded with competitors and generic copies, this strategy became less tenable. After a period of transition, drug developers, while not wholly abandoning prevalent diseases, began focusing on what has been called “targeted therapies” or “precision medicine,” utilizing advances in genomics, other basic sciences, and related technologies. These newer

therapeutics often target molecular subsets of disease, resulting in small populations enriched for those likely to respond, with substantially larger treatment effects (as those believed unlikely to respond are not enrolled). Many BT designations arise in this context, particularly in cancer. Similar progress is now being made in many other areas of unmet medical need.

While it was believed at the time of BT designation enactment that there would be only a handful of eligible candidates each year, the numbers have been much higher than expected. Targeted cancer therapies are highly represented but there are designations in most disease areas, including psychiatry and neurological diseases. It is true that a number of BT-designated drugs have been approved based on early results and with short review times. These actions were due to the often dramatic nature of the clinical results, not the BT designation per se. In fact, if later studies (or subsequent approvals of other drugs) do not uphold major promise for the therapeutic, then BT designation can be (and has been) withdrawn.⁵ Overall, the reported trends toward shorter development programs, faster pre-market reviews, higher numbers of orphan-designated new drugs, and more-than-expected BT designations are primarily attributable to major advances in biomedical science, including precision medicine, not to significant shifts in FDA policy.

A final caveat raised by Wallach et al. relates to non-randomized (single-arm) trials. They point out that it is more difficult to make causal inferences based on non-randomized data. Of course, this is true, and FDA urges drug developers to initiate randomization early in their programs and expects it in efficacy trials whenever feasible. For most diseases and treatment effect sizes, randomization provides the fastest method of obtaining persuasive results. However, there are a number of settings—short-term, dire prognoses, unrelenting natural history—where external (historical) controls can be adequate and randomization to placebo can be challenging or ethically questionable. External controls are acknowledged as acceptable, under certain circumstances, in FDA regulations concerning the characteristics of adequate and well-controlled trials. Many of the “game-changing” BT approvals have been based on outcomes from non-randomized trials that, on their face, would never have occurred spontaneously, such as prolonged regression of widely metastatic tumors in patients who had received multiple types of chemotherapies. The Agency frequently draws upon data from recent clinical trials or case series, using rigorous methods, to establish the current natural history of serious, relatively untreatable diseases.

In summary, in response to patient need, FDA operates a number of programs intended to speed the development of drugs for serious or life-threatening diseases lacking effective treatments. Some of these programs result in less-than-usual certainty about drug safety and

effectiveness while maintaining statutory evidentiary standards. Ongoing evaluation of the trade-off between earlier access and confidence in drug performance is needed, and FDA has likely not been as transparent as possible in communicating around these issues. While patient groups and the treating physician community generally regard the Agency’s approach as either appropriate or overly conservative, some academic commentators have raised concerns about the consequences of these trade-offs. Clearly, more open dialogue on this issue is needed.

The 1962 amendments represented a triumph for scientific evidence in medicine. Over the ensuing decades, many ineffective medicines were withdrawn from the market, and newly approved drugs were accompanied by unprecedented amounts of data. We should not retreat from this standard. On the other hand, the revolution in biomedical science since that time cannot be ignored. RCTs are fundamentally empirical tests of hypotheses. In today’s drug development, these hypotheses emerge from literally hundreds of preceding experiments in vitro, in animals and in humans, that lead to a prediction of benefit. We should aim for a future where that prediction is robust and the empirical test “confirmatory.” Only then will drug development be able to deliver on its promise of accessible, safe, effective treatments for human disease.

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