

Benefit-Risk vs Substantial Evidence of Effectiveness: Considering a more dynamic model for approval of drugs addressing serious unmet medical need

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Introduction

Following the Thalidomide Tragedy of the late 1950s and early 1960s, the United States passed the Drug Efficacy Amendment (also known as the Kefauver-Harris Amendment) to the FDA Food Drug and Cosmetic Act in 1962, and in doing so ushered in a new era of drug regulation in the United States. In addition to generally increasing the scope of authority of the FDA (e.g. FDA authority over drug manufacturing), the amendment mandated that the FDA determine a drug is both effective and safe before marketing approval (previously, drugs only had to demonstrate safety)ⁱ. To determine a drug is effective, the amendment required that drug manufacturers provide “substantial evidence of effectiveness” from “adequate and well-controlled investigations.” While the regulatory and medical landscape has changed dramatically over the last 60 years, this statutory standard has remained largely unchanged (the Food and Drug Administration Modernization Act of 1997 modified the definition but only to clarify that one “investigation” may be sufficient), though it has been added to. Specifically, the Prescription Drug User Fee Act – V (enacted in 2013) specified that the “FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients.” In other words, in addition to generally determining a drug is effective (based on “substantial evidence”), the FDA must also make a benefit-risk determination. This may sound like an obvious expectation, but the updated requirement highlights the fact that a risk-benefit assessment (including *expected* benefits) may be separate from “substantial evidence” of effectiveness. In light of the FDA’s increasing focus on making decisions in the context of benefits and risks, and the rapid increase in drugs developed to target Orphan Indicationsⁱⁱ (often with serious unmet medical need), now is the time for regulators and lawmakers to consider whether the current model for drug approval should be adapted to better serve the needs of patients in the US.

A more dynamic model for drug approval may be beneficial to patients with serious, unmet medical need. Specifically, the statutory requirements could be revised to allow drug marketing based on an earlier determination of a drug’s “benefit-risk” profile for patients with limited or no options, followed by a full approval based on substantial evidence of effectiveness. To qualify for this preliminary approval, the FDA and drug developers would have to agree on the clinical data required to support substantial evidence of effectiveness, as any new drug approval paradigm should not decrease the current rigor associated with drug development. If subsequent, confirmatory studies failed to demonstrate a drug’s effectiveness or revealed new safety signals that change the benefit-risk determination, the FDA would have the authority and responsibility to rescind the drugs’ preliminary marketing status. While there are many details of a new system that would need to be agreed upon and refined, **a review of (1) the current demand for investigational medicines; (2) the current time between the availability of evidence that could inform a valid benefit-risk assessment and drug approval; and (3) the potential feasibility of such a model all suggest that consideration of a more dynamic approval model is warranted.**

Access to Investigational Drugs – Current State

Under the existing regulatory framework, patients with “immediately life-threatening conditions” or “serious” diseases may access investigational therapies through FDA’s Expanded Access (also referred to as Compassionate Use) Programsⁱⁱⁱ if they are ineligible for clinical trials. These programs may be sponsored by pharmaceutical companies or treating physicians and can target individual patients, intermediate groups of patients, or large groups of patients (through a treatment protocol). However, all of these pathways still require “FDA’s review and authorization” and “cooperation of... drug companies and health care providers, in order to be successful.”^{iv}

Literature on the use of investigational drugs, FDA communications, and recent legislation all clearly indicate that (1) there is substantial demand in the healthcare community for drugs in advance of actual marketing approval and (2) the current mechanisms for access are still not optimal. Three reviews^{viviii} published between 2016 and 2018 all separately evaluated the Expanded Access pathways available for patients and all three generally concluded that the existing processes present significant challenges to patient access due to the burden and complexity of these pathways. While these articles were selected at random and are not necessarily representative of the current state of expanded access programs, the underlying concerns are corroborated by the FDA’s recent focus and statements on increasing access to investigational medicine. In May of 2018, the FDA published a comprehensive report on Expanded Access programs and largely echoed the sentiments of these reviews, citing “administrative burden” and the inherent complexities of managing all the stakeholders involved in the process^{viii}. In response to the report, Dr. Gottlieb (the outgoing FDA commissioner) has implemented and proposed steps to enhance the EAP process^{ix} and also indicated that the FDA would “incentivize” (though not compel) pharmaceutical companies to provide drug via expanded access^x. Separate from these programs, the US recently passed the “Right to Try Act” as another mechanism to provide earlier access to drugs, which further highlights the patient and health-care provider (HCP) demand for easier access to investigational therapies. While proponents of the law suspect that it will provide a more “direct route for access because it cuts out FDA oversight and paperwork^{xi},” the requirements for patient participation are similar and physicians and companies must still work together to provide the therapy on a case by case basis^{xii}. A year after the bill was passed, an ALS patient after whom the bill was named (Frank Mongiello) has not been able to access the investigational treatment he seeks^{xiii}.

While the current heightened awareness to the challenges of earlier access may drive some improvement, it is not clear these will address the fundamental issues that complicate early access to treatment for patients with no options. For example, even treatment protocols, which should be the most expeditious way to grant access to large groups of patients, still require designated clinical sites and IRB approval. No matter how streamlined the processes become,

this is an inherent complication that could preclude patient access. In addition, Dr. Gottlieb's comments to BioCentury are predominantly targeted at pharmaceutical companies, while Bunnik et al. concluded that "Physicians, patients and policy-makers should not shift the responsibility to address these issues to pharmaceutical companies, but work together to resolve them."^{vi} Finally, regardless of how effective additional pathways or modifications to existing pathways may be, there are now multiple mechanisms to get access to drugs outside of the statutory approval process. As almost all stakeholders agree this chance for access to investigational medicines is important, it is incumbent upon lawmakers to consider whether a statutory system that precludes access to these medicines (and requires the creation and implementation of regulatory loopholes) is truly necessary and in the public's best interest.

Availability of Data to Inform a Benefit-Risk Assessment in Advance of "Substantial Evidence"

While a dynamic approval model may require a movement away from the typical phases, it is likely that successful Phase 2 studies could be used to substantiate the benefit-risk assessment and preliminary approval. A review spanning drug development and approvals between 2004 and 2014 indicates that Phase 2 of drug development is actually the most crucial step in determining whether a new molecular entity (NME), i.e. new drug molecules without other approved indications, will be successful or not. Only 33% of new molecular entities (NMEs) that enter Phase 2 make it to Phase 3. However, 61% of these drugs are submitted for approval and 89% of these drugs are then approved^{xiv}. Therefore, an NME that reaches Phase 3 is more likely than not to have a favorable benefit-risk profile, as these drugs are approved by the FDA about 54% of the time.

In addition to the overall numbers, it is important to consider how often late stage molecules fail due to safety versus efficacy. Patient safety is paramount and making an ineffective drug available to a patient with no other options would not be as detrimental as providing drugs that cause a patient harm. A review of drugs that entered pivotal trials from 1998 to 2008 showed that these drugs failed due to safety 17% of the time, while lack of efficacy (57%) and commercial considerations (22%) were the cause of program failure in the vast majority of cases. While this frequency of safety concerns is far from negligible, it is important to note that safety is a focus of drug development throughout the entire lifecycle of a drug, and important safety concerns are identified post-approval for about one-third of new drugs^{xv}. Since the majority of drugs fail for reasons other than safety, and safety of a new drug is not guaranteed even after approval, these results indicate that safety concerns are not so substantial that preliminary marketing authorization could not be granted for patients with serious, unmet need.

The results presented are not meant to imply that the FDA could merely rely on a "successful" Phase 2 trial to grant preliminary approval; the FDA would have to exercise considerable judgment on a case-by-case basis to determine if the available data support such a favorable

benefit-risk determination for an indicated population (discussed further under feasibility below). Rather, these results (and the continued demand for Expanded Access) highlight that the information from Phase 2 studies could facilitate a scientifically valid benefit-risk assessment in many situations for patients with limited or no other therapeutic options.

The end result would be access to drugs much earlier than is typical of the current model. While “Accelerated Approval” decisions do offer some flexibility for approval decisions, these decisions are still based on substantial evidence of effectiveness. In these cases, pharmacologic effects demonstrated in clinical studies are linked to “a strong likelihood of clinical effectiveness” in situations where “when the pathophysiology of a disease and the mechanism of action are very well understood.”^{xvi} Of course not all disease are “very well understood” (especially among rare diseases without alternatives), so this approval pathway does not facilitate benefit-risk based flexibility for many diseases and patients. Phase 3 trials are therefore often required to demonstrate substantial evidence of effectiveness. Phase 3 trials typically take anywhere from 1 to 4 years to complete^{xvii} (not counting the time spent on developing the study and aligning with the FDA through End of Phase 2 Meetings), and the time of filing to drug approval adds an additional 1.6 years^{xviii}. Of course, the preliminary review of the benefit-risk profile of a drug would take time (as would the development of the submission etc), but it is still reasonable to conclude that this new model would facilitate patient access to beneficial drugs anywhere from 2 to 6 years earlier than the current system facilitates. For patients who have diseases which cause irreversible damage and/or mortality, regulators and lawmakers must consider whether the current gap between informative (but inconclusive) clinical data is acceptable.

Feasibility of a Dynamic Approval Model

The substantial demand for investigational medicines and availability of informative clinical data in advance of drug approval support consideration of a more dynamic model from a logical perspective. However, to inform wise regulatory decisions in the interests of bringing safe and effective medicines to patients, practical ramifications must be considered. Specifically, a dynamic approval model would require (a) increased judgment from the FDA in terms of both scientific evidence and patient needs, (b) a mechanism for withdrawal post-initial approval, and (c) robust drug development after a drug is on the market to generate substantial evidence of effectiveness. Ultimately though, none of these concerns is totally unique to the proposed model and do not preclude further consideration of the phased approach to approval.

Regarding the greater discretion from the FDA in benefit-risk decisions, it is important to keep in mind that the FDA is currently charged with exercising “the broadest flexibility in applying the statutory standards,” when evaluating Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses ([21 CFR Sec 312.80](#)). However, they must do so “while preserving

appropriate guarantees for safety and effectiveness.” In other words, Americans are already asking the FDA to use their discretion in reviewing drugs which would address the needs the dynamic model would be designed to address, but because the “statutory standards of safety and effectiveness apply to all drugs,” FDA reviewers must still conclude that a drug has demonstrated substantial evidence of effectiveness. This is an almost impossible task, and of course any drug that “guarantees” safety and effectiveness for the target population should be approved. Therefore, these somewhat conflicting charges likely present more complications in drug development than they solve. Instead, the dynamic model would simply ask the FDA reviewers to determine whether they can conclude that the benefit-risk profile for a drug is favorable for an indicated population with serious, unmet need based on the information submitted to them while giving the FDA a more clear mechanism to eventually obtain substantial evidence of effectiveness for full approval.

Regarding the second consideration, decisions to approve and then subsequently withdraw marketing authorizations could present difficult situations to navigate between pharmaceutical companies, the FDA, patients, and prescribers. However, these dynamics are already in play for drugs approved under Accelerated Approval, in which manufacturers can market a drug based on a “surrogate endpoint” (the “pharmacologic effects” referred to above) but still have to demonstrate clinically significant changes post-approval. This approval framework has led to tension between patients and the Agency in the past. For example, when the FDA revoked the approval of Avastin for use as a breast cancer drug, there were protests outside the FDA hearings and many patients “pleaded for [Avastin’s] continued approval.^{xix}” While these can be difficult scenarios to manage under any model, they may be better addressed by a regulatory framework that explicitly prioritizes the benefit-risk for patients instead of standards of scientific evidence.

Finally, the new model would require robust drug development to continue in parallel with drug marketing. Therefore, the FDA would need to hold companies accountable to agreed-upon timelines and objectives. As mentioned above though, post-approval studies are already required for drugs marketed under Accelerated Approval and when there are unanswered questions about a drug’s safety or effectiveness after the drug review. In addition, the “conditional approval” paradigm in Europe offers a reasonable comparison (though the proposed model would be more flexible than the Conditional Marketing Authorisation Application standards). In both cases, the effectiveness of these post-approval programs is controversial. A review of post-approval studies for drugs approved between 2005 and 2010 in both the US and EU concluded that “some of [the] findings can be seen as reassuring” while “others underline the lack of global coordination of postmarketing research for novel drugs.”^{xx} In addition, a 2018 article specific to the US noted that “the majority [of post-approval studies] are not fulfilled by the date set by the FDA, and that... the agency is not equipped to adequately keep track of them^{xxi},” while a review of European post-approval studies found that, “about 70% of specific obligations” (i.e. the post-marketing requirements) are completed on time^{xxii}. In light of this potentially conflicting

evidence, it is reasonable to be wary about increasing reliance on post-approval studies. At the same time, it is possible a new model which codifies and standardizes expectations for post-approval studies could increase the rigor and timeliness of post-approval studies.

Discussion and Conclusions

Further consideration and exploration of a dynamic drug approval model, that includes a preliminary marketing authorization status based on a benefit-risk assessment followed by a full approval based on substantial evidence of effectiveness (and a re-evaluation of the benefit-risk in light of any new safety findings) is warranted. The current state of the Expanded Access programs in the United States is clear evidence that there is a medical need for access to investigational drugs, and that the currently available pathways have not fully addressed this need. While FDA's proposed improvements to this system may improve patient access to investigational medicines, they will likely be unable to address many of the fundamental concerns with expanded access. Therefore, regulators and lawmakers should consider whether statutory frameworks that prevent or complicate access to investigational therapies are in the public's best interest. Furthermore, a high-level of analysis of the drug development approvals in relation to clinical trial success / failure indicates that clinical data that could reasonably inform a benefit-risk assessment is available years before a drug is approved by the FDA. Finally, none of the practical challenges that this paradigm presents are unique to the ones that the FDA, pharmaceutical companies, HCPs, and patients currently manage.

While the current review indicates that the dynamic approval may be beneficial for patients in the US, further exploration of this topic is necessary before recommending any specific changes to the statutory framework for drug approval. Systematic evaluation of the kinds of data that could facilitate the preliminary approval are required, and additional consideration would have to be given to the feasibility concerns briefly summarized herein. The most pressing practical issue would be to determine whether increased reliance on post-approval studies for critical scientific data might adversely impact the high-level of rigor currently ensured in drug development. There are also likely practical considerations not identified in this paper which would need to be considered. Finally, economic implications are not strictly under the purview of the FDA and were therefore outside the scope of this review. However, private insurers and government payers play a critical role in patient access to medicine, so whether or not patients would actually gain access to drugs with a preliminary approval should be investigated.

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