Key points:

- Securing access to promising new drugs for seriously ill patients without good treatment options is an important priority, as is confirming drug safety and effectiveness.
- The proposed Conditional Approval pathway for FDA approval of new drugs is similar to the existing Accelerated Approval pathway and suffers from many of the same concerns, including the likelihood of reliance on weak confirmatory trials.
- Accelerated Approval could be improved by strengthening requirements for confirmatory trials to use meaningful endpoints and be completed in a reasonable timeframe.
- Postapproval studies face important limitations on confirming safety and effectiveness.
- Where it is possible to secure patient access to promising drugs while continuing to study them preapproval, that is often the preferable approach.
- This can be achieving by continued improvement of the existing Expanded Access pathway, including by pursuing approaches to make it more palatable to companies developing new drugs.

February 3, 2020

The Honorable Bruce Westerman
United States House of Representatives
209 Cannon House Office Building
Washington, DC 20515

The Honorable Mike Braun
United States Senate
374 Russell Senate Office Building
Washington, DC 20510

The Honorable Mike Gallagher
United States House of Representatives
1230 Longworth House Office Building
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The Honorable Lisa Murkowski
United States Senate
522 Hart Senate Office Building
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The Honorable Tim Burchett
United States House of Representatives
1122 Longworth House Office Building
Washington, DC 20515

Re: The Conditional Approval Act

Dear Congressmen and Senators,

We are a group of experts in bioethics, health policy, and FDA law and regulation writing to express our concern regarding your recent bicameral bill, the Conditional Approval Act.[1]

We share your goal of helping patients access potentially life-saving medicines as quickly as possible. Many patients facing serious or life-threatening diseases and conditions for which there are no proven therapies have an understandably heightened tolerance for risk. As such, we agree that they should have pathways to try promising new drugs even before safety and efficacy has been fully established. We also believe that the Food and Drug Administration (FDA) is right to consider both the severity of the condition and the availability of treatment alternatives when deciding whether to grant marketing approval for new medical products.

[1] S.3133, H.R. 5497, Dec. 19, 2019, https://www.congress.gov/bill/116th-congress/senate-bill/3133/text.

However, drugs that are not ultimately demonstrated to be sufficiently safe and effective are of no use to patients; the same is true for promising drugs that remain out of reach because insurers will not pay for them. As we seek ways to facilitate patient access, we cannot overlook the critical need to collect rigorous evidence about the safety and effectiveness of new drugs.[2] This evidence is essential to allowing patients and their clinicians to make informed treatment decisions, facilitating coverage decisions by payers, and promoting progress in developing improved treatment options. Unfortunately, gathering this evidence after approval can be difficult, despite the best intentions. If we hinder the ability to understand whether new drugs are truly safe and effective, the risks currently accepted by patients out of necessity due to the lack of better options – risks of bodily harm, financial harm, and time wasted with ineffective products – will extend in perpetuity. This is bad for patients today and for patients tomorrow.

Therefore, instead of new approaches to marketing approval, we recommend steps to improve the existing Accelerated Approval pathway, which already achieves many of the Conditional Approval Act's aims by temporarily adjusting approval standards to accommodate patients in need. In addition, because data collection in the preapproval period is often preferable to postapproval study, we encourage attention to improving Expanded Access. This is a decades-old pathway that permits preapproval access outside clinical trials for patients willing to take risks for a chance of medical benefit, while preserving the ability to rigorously study new drugs before they are made available for marketing. Finally, while urging a different approach, we note several areas of ambiguity in the proposed Conditional Approval Act.

Learning from and Improving Accelerated Approval

The Conditional Approval Act would allow sponsors of new drugs intended for the treatment, prevention, or diagnosis of serious, life-threatening, or chronic diseases or conditions to seek "provisional and time-limited approval" for marketing when the following criteria are satisfied:

- The drug's expected benefits outweigh its potential risks to patients
- The sponsor will likely be able to provide "comprehensive clinical data" after approval
- Confirmatory clinical trials are difficult or costly to conduct
- There are no (or no more than 2) meaningful treatments for the disease or condition

Conditional Approval status would be required to be renewed annually and renewal would be capped at 5 years. If the sponsor did not secure marketing approval based on a "full demonstration of safety and effectiveness" during this time, Conditional Approval would expire and the product would presumably automatically revert to the status of unapproved drug, the continued marketing of which would violate the federal Food, Drug, and Cosmetics Act.

Importantly, Congress has already authorized a similar conditional approval pathway called Accelerated Approval. Accelerated Approval allows the FDA to grant marketing approval of a new drug that is expected to offer a meaningful therapeutic benefit over existing treatments for a serious or life-threatening disease or condition "upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the

[2] Sharfstein JM. Déjà vu at the FDA. *Milbank Quart.* 2017. https://www.milbank.org/quarterly/articles/deja-vu-fda/

severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."[3] Although there are some diseases and conditions that do not yet have compelling surrogate endpoints that could support Accelerated Approval, in 2012, Congress added the provision allowing this pathway also to be used on the basis of an intermediate clinical endpoint, potentially extending its scope to more diseases and conditions.

Sponsors of drugs that secure Accelerated Approval may be required to conduct "appropriate postapproval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit."[4] If they fail to do so "with due diligence" – or if a required study fails to verify the predicted benefit or other evidence "demonstrates that the product is not safe or effective under the conditions of use" – the FDA may withdraw approval.[5]

Given this existing approval pathway, as well as the fact that the FDA already has – and is actively exercising – the authority to approve new drugs relying only on Phase 1 or 2 trials,[6] there does not appear to be a compelling need for yet another approval pathway. In addition, experience with Accelerated Approval to date gives reason for concern about conditional approval approaches.[7]

First, although the FDA has authority to pull Accelerated Approval drugs off the market if sponsors fail to confirm the product's safety and effectiveness in postapproval studies, it has rarely invoked this withdrawal authority,[8] while simultaneously demonstrating a willingness to accept weak confirmatory evidence. For example, only 5% of the 93 oncology indications granted Accelerated Approval between 1992-2017 were withdrawn in light of postapproval trial results.[9] Some – including the FDA – have interpreted this low rate of withdrawal as demonstrating that Accelerated Approval is largely achieving its goal of getting good drugs to patients quickly. However, the same report indicated that postapproval evaluations remained ongoing for 40% of those Accelerated Approval oncology indications, precluding assessment of their quality (although some of these may have only recently been approved).[10] Moreover, of the 55% of oncology indications that FDA reported as having complete confirmatory trials verifying clinical benefit, only 30% of these demonstrated improvement in overall survival. The remaining 70% demonstrated changes in surrogate measures, with about half of these using the *exact same* surrogate measure in the confirmatory trials as used in the preapproval trial leading to Accelerated Approval.[11] Postapproval trials conducted after Accelerated Approval are also often missing design characteristics that contribute to scientific confidence, such as blinding, randomization, and comparator groups.[12] Rather

[3] 21 U.S.C. § 356(c)(1)(A).
[4] 21 U.S.C. § 356(c)(2).
[5] 21 U.S.C. § 356(c)(3).
[6] Darrow JJ, Avorn J, Kesselheim AS. The FDA breakthrough drug designation—four years of experience. *N Engl J Med*. 2018;378(15):1444-1453.
[7] Miller FG, Joffe S. Balancing access and evaluation in the approval of new cancer drugs. *JAMA*. 2011;305(22):2345-2346.
[8] Herder M. Pharmaceutical drugs of uncertain value, lifecycle regulation at the US Food and Drug Administration, and institutional incumbency. Milbank Quart. 2019. https://onlinelibrary.wiley.com/doi/full/10.1111/1468-0009.12413
[9] Beaver JA, Howie Lynn J, Pelosof L, et al. A 25-year experience of US Food and Drug Administration accelerated approval of malignant hematology and oncology drugs and biologics: a review. *JAMA Oncol.* 2018;4(6):849-856.
[10] Id.
[11] Id. See also Gyawali B, Hey SP, Kesselheim AS. Assessment of the clinical benefit of cancer drugs receiving accelerated approval. *JAMA Intern Med.* 2019;179(7):906-913.
[12] Naci H, Smalley KR, Kesselheim AS. Characteristics of preapproval and postapproval studies for drugs granted accelerated approval by the US Food and Drug Administration. *JAMA.* 2017;318(7):626-636.

than producing genuine confirmation of safety and effectiveness, these approaches risk entrenching the uncertainty that was intended only as a temporary tradeoff for earlier access.[13] Finally, it is worth recognizing that on the single occasion the FDA took steps to unilaterally withdraw approval of an Accelerated Approval indication, it faced harsh public criticism and required a substantial outlay of time and resources, potentially influencing its willingness to exercise this option in the future.[14]

The second concern is that confirmatory trials are often delayed. Accelerated Approval assumes that there will be at least some gap during which products with only signals of clinical benefit are available to patients, but this gap can be substantial. For example, a study examining indications approved via Accelerated Approval between 2009-2013 found that only half of the required confirmatory studies had been fulfilled by 2017, with about 20% of the remainder either delayed by more than a year or terminated altogether. Recruitment challenges were cited as the primary reason for reported delays.[15] These delays, alongside often weak confirmatory data in trials that are completed, raise concern that patients are exposed for too long to drugs that may not be safe and effective, risking harm beyond disease progression, wasting time and money, and distracting from participation in trials of products that may be better or pursuit of other alternatives.

Notably, similar concerns have been demonstrated with regard to the European Union's Conditional Marketing Authorisation (CMA).[16] In addition, analysis of the CMA pathway indicates that companies have not used it as a prospectively planned pathway to secure early access to promising new drugs for patients, but instead as a "rescue option" after regulators raised major objections regarding the possibility of granting standard marketing authorization.[17]

Rather than develop a new conditional approval pathway that risks replicating many of Accelerated Approval's shortcomings, we urge you to strengthen the existing pathway. We view Accelerated Approval as an important option for patients who cannot wait for products to demonstrate safety and efficacy on the strongest measures, but who nonetheless deserve to eventually have confidence in the products they are buying and using. We therefore recommend:

1) Adjusting the Accelerated Approval pathway in line with your bill's proposal to require brief, renewable terms alongside a maximum period for Accelerated Approval status, followed by automatic expiration of approval absent satisfactory confirmation of safety and effectiveness during that period;

2) In confirmatory trials for drugs that have received Accelerated Approval, precluding the use of unvalidated surrogate endpoints (i.e., surrogates *reasonably likely* to predict clinical benefit, but

[13] Herder, supra note 8.
[14] Vitry A, Nguyen T, Entwistle V, Roughead E. Regulatory withdrawal of medicines marketed with uncertain benefits: the bevacizumab case study. *J Pharm Policy Pract.* 2015;8:25.
[15] Naci et al., supra note 12.
[16] Banzi R, Gerardi C, Bertele V, Garattini S. Approvals of drugs with uncertain benefit-risk profiles in Europe. *Euro J Intern Med.* 2015;26(8)572-584; Banzi R, Gerardi C, Bertele V, Garattini S. Conditional approval of medicines by the EMA. *BMJ.* 2017;357:j2062.
[17] Hoekman J, Boon WPC, Bouvy JC, Ebbers HC, de Jong JP, De Bruin ML. Use of the conditional marketing authorization pathway for oncology medicines in Europe. *Clin Pharmacol Ther.* 2015;98(5):534-541.

not known to do so) and accepting only clinical outcomes or surrogates specifically validated for the drug's indication (i.e., *proven* to predict clinical benefit);[18,19]

3) Requiring that confirmatory trials testing clinically meaningful endpoints be underway (i.e., at least fully approved and ready to enroll participants) at the time of Accelerated Approval;[20]

4) Encouraging the FDA to issue further guidance clarifying which intermediate clinical endpoints will suffice for Accelerated Approval.[21]

Challenges of Collecting Rigorous Data Postapproval

One of the defining features of Accelerated Approval (and similar proposals) is the reliance on postapproval trials. But this is also one of the pathway's biggest concerns, as there are often major challenges to completing these studies and limitations on the evidence that can be produced in the postapproval period. This does not mean that Accelerated Approval is not a useful tool. But it does suggest that where other approaches are possible, they may be preferable.

Sometimes studies that lack the traditional features of rigorous design, such as blinding, randomization, and concurrent control groups, as well as studies that have not yet been replicated, can nonetheless produce compelling evidence of safety and efficacy. This may be the case when there is a good understanding of the biology of the disease in question, strong evidence about the drug's mechanism of action, and clarity about the relationship between the two; when there is a large effect size in those patients receiving the agent; and when there are well-understood, consistent, typically poor outcomes for patients on current therapy or supportive care.[22] For example, one of the first clinical studies of imatinib (Gleevec) was a Phase I dose-escalation trial in patients with chronic myeloid leukemia, which demonstrated complete hematologic response (return to normal white blood cell range) in 53 of 54 patients, typically in the first 4 weeks of therapy.[23] In another example, 20 patients with severe rheumatoid arthritis were treated with infliximab (Remicade) in a brief Phase I/II trial and saw dramatic improvement (although the effect faded within weeks).[24] It is critical to understand, however, that these examples are extremely rare and few products show such compelling treatment effects early in development. Moreover, many conditions present with substantial variability within and across patients, raising concerns about evidence generated by trials that lack rigorous design features, including many that have been used to support FDA approval.[25]

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[18] Food and Drug Administration. Guidance: Expedited programs for serious conditions – drugs and biologics. 2017. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

[19] Attention is also needed to improving the validation process. Wallach JD, Ross JS, Naci H. The US Food and Drug Administration's expedited approval programs: evidentiary standards, regulatory trade-offs, and potential improvements. *Clin Trials*. 2018;15(3):219-229; Ciani O, Buyse M, Drummond M, et al. Time to review the role of surrogate end points in health policy: state of the art and the way forward. *Value Health* 2017; 20: 487-495.

[20] Gyawali B, Kesselheim AS. Reinforcing the social compromise of accelerated approval. *Nature Rev Clin Onc.* 2018;15:596-597.

[21] Food and Drug Administration, supra note 18.

[22] Miller FG, Joffe S. Equipoise and the dilemma of randomized clinical trials. *N Eng J Med.* 2011;364(5):476-480.

[23] Druker BJ et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344(14):1031-1037.

[24] Elliott MJ et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. *Arthritis Rheum.* 1993;36(12):1681-90.

[25] Darrow JJ, Avorn J, Kesselheim AS. FDA approval and regulation of pharmaceuticals, 1983-2018. *JAMA*. 2020;323(2):164-176; Zhang AD, Puthumana J, Downing NS, Shah ND, Krumholz H, Ross JS. Clinical trial

Weak preapproval evidence can be tolerable in order to get promising products to patients sooner, but only if we are ultimately able to confirm that the products' benefits outweigh their risks by continuing to study them. This is difficult to do preapproval and it becomes even more challenging postapproval. First, companies have little incentive to design postapproval trials that may call into question the product they are now permitted to sell for a profit, indicating an important role for the FDA in requiring – and holding companies accountable for conducting – the highest quality postapproval trials possible. Second, the quality of trials that are feasible to conduct postapproval can be limited in important ways. Once a product is available on the market, patients have little incentive to take on the added burdens of clinical trial participation. This is especially true for randomized controlled trials (RCTs), which provide the strongest evidence regarding safety and efficacy, but demand that some patients be willing to receive something other than the newly-approved, perhaps heavily-hyped product that may have been quickly adopted as standard of care.[26]

The following scenario is easy to imagine: a new drug for a life-threatening disease that currently lacks alternative treatment options is conditionally approved for marketing. Patients understandably flock to the new treatment, despite weak evidence of effectiveness. Concurrent controls become difficult or impossible for postapproval trials because patients are unwilling to forgo the new drug, in turn making it difficult to gather strong confirmatory evidence to support the product's use – and reimbursement by private insurers. For example, eteplirsen (Exondys 51) was approved for Duchenne Muscular Dystrophy on the basis of weak evidence that was not convincing to insurers, leaving some patients frustrated by lack of coverage for the costly drug, which might have been avoided with stronger data.[27] In another example, high-dose chemotherapy with autologous bone marrow transplant for breast cancer initially suggested dramatic improvement, leading to excitement and widespread use of this treatment regimen in the 1990s – alongside fights with insurers who refused coverage absent evidence from well-controlled trials. Randomized trials were derided as unethical and were difficult to enroll but, when finally completed, demonstrated that this treatment regimen offered no advantage over standard-dose treatment.[28]

Importantly, these concerns affect more than the drug approved for use on weak evidence. Now imagine that a second investigational drug for the same indication comes along, but can only feasibly be tested against the first, which still has only weak evidence supporting it, because patients are otherwise unwilling to enroll in a trial. Testing the second drug in this way, however, will not allow us to meaningfully evaluate the second drug's safety and efficacy because we remain uncertain about the safety and efficacy of the first drug. And so on. In this way, both Accelerated Approval and the proposed Conditional Approval risk hampering subsequent clinical progress, leaving patients facing

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evidence supporting FDA approval of novel therapeutic agents over three decades, 1955-2017: cross-sectional analysis. https://www.medrxiv.org/content/10.1101/19007047v1. Published Sep 23, 2019; Darrow et al., supra note 6; Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *JAMA*. 2011;305(22):2320-2326; Naci et al., supra note 12; Wallach et al., supra note 19.

[26] Huetteman E. Call for FDA to withdraw preterm birth drug divides doctors and insurers. *Kaiser Health News.* Jan. 27, 2020. https://khn.org/news/call-for-fda-to-withdraw-preterm-birth-drug-makena-divides-doctors-and-insurers/ (describing difficulty enrolling patients in a postapproval trial of a drug that had become standard of care); Miller & Joffe, supra note 7.

[27] Thomas K. Insurers battle families over costly drug for fatal disease. NY Times. June 22, 2017. https://www.nytimes.com/2017/06/22/health/duchenne-muscular-dystrophy-drug-exondys-51.html

[28] Mello MM, Brennan TA. The controversy over high-dose chemotherapy with autologous bone marrow transplant for breast cancer. *Health Affairs.* 2001;20(5):101-117.

serious and life-threatening diseases and conditions without truly meaningful treatment options, despite having products on the market.

The difficult reality is that part of the function of requiring FDA approval prior to marketing is to restrict whether and how patients can access investigational new drugs so that it is possible to conduct the rigorous clinical testing that becomes so challenging once a product is on the market.[29] This is difficult because it requires limiting the options available to current patients – i.e., they can participate in a trial, secure access via a non-trial preapproval pathway, or wait for approval – for the benefit of future patients. But it is important to acknowledge that current patients benefit from the contributions to clinical advancement made by patients who came before them, and future patients will also contribute to continuing this clinical advancement for those who come later. Everyone benefits from approaches that facilitate the generation of high-quality evidence.

The key is to balance two sets of interests: (1) those of seriously ill patients who wish to access promising, but unproven, products and are willing to forgo confirmation of safety and effectiveness because they lack meaningful alternatives, and (2) the longer-term interests of all patients in having products that they can be confident are safe and effective.[30] One approach to achieving this balance is to simply accept that early drug approval on weak evidence may permanently hamper the ability to gather the highest quality data via RCTs, while also seeking to narrow the evidentiary gap by demanding more rigorous postapproval studies than have been carried out to date. For example, this would involve selection of endpoints that more reliably demonstrate efficacy, as described above, as well as leveraging innovative trial designs.[31] Importantly, however, this approach will sometimes entail an unnecessary tradeoff between evidentiary confidence and patient access when it is instead possible to have both, protecting gold standard trials in the preapproval setting while simultaneously facilitating patient access.

Improving Expanded Access – and Research

FDA's existing Expanded Access pathway offers a preferable alternative to early marketing approval. It allows patients with serious or life-threatening diseases or conditions who have exhausted approved treatment options to access promising investigational drugs before they are approved, so long as this access will not interfere with clinical trials or otherwise derail clinical development.[32] We encourage you to consider shifting your attention to efforts that could potentially improve this pathway's reach. These might include ideas such as:

- Encouraging the FDA to require sponsors to include product-specific Expanded Access plans (whether willing to offer Expanded Access or not) with their IND submissions prior to moving into Phase II trials. Early planning before receipt of the first patient request could help in cases where a sponsor is in principle willing to provide Expanded Access but would otherwise find that they cannot make necessary arrangements in time to help a patient (or patients).[33]

[29] Kapczynski A. Dangerous times: the FDA's role in information production, past and future. *Minn L Rev.* 2018;102:2357-2382.
[30] Miller & Joffe, supra note 7.
[31] Wallach et al., *supra* note 19.
[32] 21 C.F.R. 312, Subpart I.
[33] Food and Drug Administration. Expanded Access Program Report. May 2018. https://www.fda.gov/media/119971/download

- Providing stable funding for and extending Project Facilitate, FDA's Oncology Center of Excellence pilot program offering "concierge" services that help physicians navigate Expanded Access for investigational products, including liaising with companies and assistance with forms.[34] Broadening this program to other disease areas, as well as creating a permanent staff and budget, can help promote equitable access for patients by improving physician awareness of the Expanded Access pathway and their ability to navigate it.

- Encouraging dialogue between the FDA and industry, especially with smaller companies, about how to address financial and other constraints and concerns that may inhibit their willingness and ability to offer Expanded Access, including potential clarification of the FDA's existing rules concerning what expenses companies may charge for,[35] as well as ideas for how to address relevant personnel, supply, and logistics issues.

Apart from Expanded Access, we also urge attention to financial incentives to encourage sponsors to conduct trials with broader eligibility criteria, including platform trials, facilitating the dual benefit of allowing more patients to access products that appear promising while collecting data likely to more meaningfully inform clinical use postapproval. Finally, increased funding for research to address devastating diseases and conditions that currently lack treatment options should be a top priority.

Troubling Ambiguity

Finally, we note that the Conditional Approval Act as currently written contains substantial textual ambiguity. Sometimes statutory ambiguity allows useful regulatory flexibility, but here it risks creating loopholes that could be harmful to patients individually and collectively.

The proposal currently includes no specification as to whether any clinical trial phase must have been completed before requesting Conditional Approval. The bill also includes contradictory clauses, in one location stating that there must be no existing meaningful treatments for the disease or condition in question, and in another saying that there may be no more than 2. The bill does not specify what it means for confirmatory clinical trials to be difficult or costly to conduct, descriptors that could be applied to virtually any drug study. It is also unclear what it would mean for a sponsor to be "likely" able to provide "comprehensive" clinical data after conditional approval. Relatedly, the bill envisions that sponsors will be required to "complete in a timely manner clinical investigations to provide full demonstration of safety and effectiveness," but does not specify what would constitute a "full demonstration," whether unvalidated surrogate endpoints will suffice, and whether a drug could move from Conditional Approval to Accelerated Approval or whether traditional approval would be the required next step. The bill also includes no restriction on how much patients may be charged for a conditionally approved drug, although the press release references "an acceptable market rate."[36] Unfortunately, market rates are often beyond the reach of patients and payers, and given experience with drugs like eteplirsen, it is likely that some insurers would balk at paying for drugs approved conditionally with weak evidence.

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[34] Food and Drug Administration. Project Facilitate. Aug. 28, 2019. https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate

[35] 21 C.F.R. 312.8.

[36] Press release: Westerman, Gallagher, Burchett, Braun Introduce Bicameral Prescription Drug Legislation. Dec. 19, 2019. https://westerman.house.gov/media-center/press-releases/westerman-gallagher-burchett-braun-introduce-bicameral-prescription-drug

Conclusion

We agree that it is critical to get promising products to patients facing serious and life-threatening conditions as quickly as possible, and we commend your attention to this problem. But we are concerned about undermining the ability to rigorously demonstrate the safety and efficacy of new drugs. An indication of promise after a small, uncontrolled Phase I study or even a somewhat larger Phase II without randomization or a concurrent comparison group can offer support for extending preapproval access to patients without other options. Short of extraordinary outcomes, however, these early trial results should not be considered the equivalent of having "real, meaningful, life-extending treatments sit[ting] on the shelf."[37] These early stage trials typically do not "establish and confirm safety," nor do they regularly predict successful confirmatory trials. Ultimately, we must balance securing early access with securing meaningful evidence and treatment options.

A new conditional approval pathway is not the right solution. Even if the substantial ambiguities in the proposed bill were remedied, it is not clear that Conditional Approval would be a superior or necessary addition beyond Accelerated Approval or the FDA's existing authority to approve many new drugs without waiting for Phase 3 trials. Experience with Accelerated Approval to date raises concerns that the weak evidence supporting early marketing approval is too infrequently replaced with acceptable confirmatory evidence. We recommend clarifying when Accelerated Approval may be used in the absence of surrogate endpoints, buttressing the requirements for confirmatory trials, and making the approval truly temporary, pending adequate supporting evidence of safety and effectiveness. Given the difficulty of securing high-quality evidence postapproval, we also recommend emphasizing the development of such evidence in the preapproval period, while facilitating Expanded Access for patients unable to enroll in rigorous clinical trials.

The problems are complex and require both short- and long-term vision; there is no silver bullet. We would be happy to work with you to make progress for all patients in need.

Sincerely,

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