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June 30, 2026

The Honorable Jake Auchincloss
United States House of Representatives
1526 Longworth House Office Building
Washington, DC 20515

Attn: Nikita Varman, Health Policy Advisor

RE: Comments on Legislative Discussion Draft "Next-Generation U.S. Clinical Development to Accelerate Cures"

Dear Ms. Varman,

As core members of the Program On Regulation, Therapeutics, And Law (PORTAL) at Brigham and Women's Hospital and Harvard Medical School, we appreciate the opportunity to provide feedback on Congressman Auchincloss' discussion draft, entitled "Next-Generation US Clinical Development to Accelerate Cures." Based in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital and Harvard Medical School, PORTAL is one of the largest academic research centers in the United States dedicated to investigating the regulation, use, evidence, and cost of prescription drugs. Our research program is independent of the pharmaceutical industry.

We share the Congressman's goal of modernizing the US clinical trial process to improve efficiency and retain US competitiveness in clinical research. At the same time, we believe it is essential that reforms preserve the FDA's robust evidentiary standards and regulatory authority to protect patients and the integrity of the drug approval process. Below, we offer section-by-section comments highlighting both the strengths of the proposal and areas we believe warrant further consideration:

Sections 2-4. Point-of-care platforms

a. Precision oncology as a model for point-of-care clinical research

Recent studies have shown improved outcomes with targeted therapies in phase 1 oncology trials, with progressively higher objective response rates between 2015 and 2023.[1] Genome-targeted cancer therapies have also demonstrated higher response rates and lower toxicity compared with non-genome-targeted therapies, and precision medicines now account for around 40% of FDA oncology drug approvals.[2] However, the implementation of precision oncology remains limited by unequal access to next-generation sequencing (NGS), underuse of molecular profiling, and fragmentation between clinical research and routine care.[3] Patients with low socioeconomic status, Black or Hispanic patients, and those

[1] Rossi A, Braña I, Vieito M, et al. Evolving Landscape of Targeted Therapies in Early Phase Clinical Trials. *Eur J Cancer*. 2026;240:116745. doi:10.1016/j.ejca.2026.116745
[2] Tibau A, Hwang TJ, Molto C, Avorn J, Kesselheim AS. Clinical Value of Molecular Targets and FDA-Approved Genome-Targeted Cancer Therapies. *JAMA Oncol*. 2024;10(5):634. doi:10.1001/jamaoncol.2024.0194
[3] Roberts TJ, Kesselheim AS, Avorn J. Variation in Use of Lung Cancer Targeted Therapies Across State Medicaid Programs, 2020-2021. *JAMA Netw Open*. 2023;6(1):e2252562. doi:10.1001/jamanetworkopen.2022.52562

covered by Medicare or Medicaid experienced meaningful delays in access to NGS across several tumor types.[4]

The integration of clinical research into routine care ("point-of-care trials") is particularly relevant for precision oncology, since patients are often identified through molecular biomarkers during standard clinical practice. Universal molecular prescreening programs embedded within routine care could facilitate earlier identification of eligible patients for precision oncology trials, improve trial efficiency, and reduce barriers to participation. Together, these findings support expanding molecular prescreening to optimize patient selection, improve equitable access to trials, and accelerate the development of targeted therapies while reducing disparities in trial enrollment.

Positives in the Discussion Draft: Investment in validating biomarkers.

***Areas of Concern*:** A new regulatory pathway may not be required, as existing FDA flexibilities already support many pragmatic and point-of-care trial approaches. Ongoing monitoring is essential since moving to "embedded clinical trials in routine care" can increase the risk of bias.

b. Integrating patient-reported outcomes into point-of-care platforms

Several studies have shown that the systematic monitoring of *patient-reported outcomes* (PROs) — defined as information on symptoms, health status, or quality of life reported directly by patients — when integrated into routine oncology care, can improve symptom control, reduce emergency visits and hospitalizations, and even improve survival outcomes.[5] In this context, electronic PRO monitoring illustrates how systematically incorporating the patient perspective into routine care can simultaneously improve clinical outcomes and generate meaningful real-world evidence for drug development. Despite the growing importance of PROs and quality of life in oncology, quality-of-life data remain limited and are often methodologically inconsistent in the trials supporting regulatory approvals.[6,7] In a recent analysis of oncology indications approved by the FDA and EMA between 2020 and 2023, we found that only around 13% of indications met the methodological criteria required to receive quality-of-life benefit credit according to validated tools such as the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) Quality of Life checklist,[8] while most studies showed no statistically significant benefit in PROs.[9] These findings suggest that, despite the increasing clinical and regulatory recognition of PROs, the integration of PROs into oncology trials remains late, heterogeneous, and often limited to exploratory endpoints.

In this context, several initiatives have been proposed to move toward a more patient-centered model of drug development starting from the earliest stages of clinical research. Key recommendations include the early identification of patient-relevant outcomes through direct patient feedback, the involvement of

[4] Hage Chehade C, Ozay ZI, Jo Y, et al. Trends and Disparities in the Use of Next-Generation Sequencing in Patients With Cancer in the United States. *JAMA Netw Open*. 2026;9(4):e265585. doi:10.1001/jamanetworkopen.2026.5585
[5] Basch E, Deal AM, Dueck AC, et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *JAMA*. 2017;318(2):197-198. doi:10.1001/jama.2017.7156
[6] Tibau A, Romano A, Liu ITT, Han J, Cliff ERS, Kesselheim AS. Assessing Outcomes Emerging After Conversion to Regular Approval for Cancer Drug Indications Granted Accelerated Approval, 1992-2021. *JNCI: J Natl Cancer Inst*. 2025;117(10):2103-2111. doi:10.1093/jnci/djaf195
[7] Liu ITT, Kesselheim AS, Cliff ERS. Clinical Benefit and Regulatory Outcomes of Cancer Drugs Receiving Accelerated Approval. *JAMA*. 2024;331(17):1471. doi:10.1001/jama.2024.2396
[8] Oosting SF, Barriuso J, Bottomley A, et al. Methodological and Reporting Standards for Quality-of-Life Data Eligible for European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) Credit. *Ann Oncol: Off J Eur Soc Med Oncol*. 2023;34(4):431-439. doi:10.1016/j.annonc.2022.12.004
[9] Tibau A, Romano A, Kesselheim AS. Will I Feel Better? Raising the Bar for Quality of Life in Oncology. *Nat Rev Clin Oncol*. 2025;22(4):235-236. doi:10.1038/s41571-025-01002-4

PRO experts from the initial phases of clinical development, structured discussions between developers and regulators on clinically meaningful endpoints, and the prospective incorporation of PROs into phase 1-2 studies (not only phase 3 trials) with predefined statistical plans and strategies to minimize missing data. Additional proposals include increasing patient involvement in study design and facilitating the inclusion of PRO data in regulatory labels to support shared decision-making.[10]

In parallel, initiatives aimed at integrating clinical research into routine care, such as the "point-of-care" platforms recently proposed in the US, could facilitate a more systematic and practical integration of PROs into both oncology care and clinical research.

Positives in the Discussion Draft: Point-of-care platforms could support routine collection of PROs, improving patient care while generating meaningful patient-centered evidence for clinical development.

***Areas of Concern*:** Without standardized collection, analysis, and reporting methods, expanded use of PROs may generate heterogeneous and difficult-to-interpret evidence.

Sections 5-8. Modernize Preclinical and Early-Stage Clinical Development

a. Lessons from Australia for reforming the US IND process

The US early-phase clinical testing process begins with consultations and ultimately leads to the filing with FDA of an Investigational New Drug (IND) application collecting the preclinical data and setting out a research plan for human clinical testing. By contrast, in Australia, notification of the Therapeutic Goods Administration (TGA) may be all that is needed to supply an unapproved drug in a clinical trial, while local Human Research Ethics Committees (HRECs) supply detailed evaluation of the preclinical data. Institutional Review Board (IRB) approval, which is also required to set up early-stage trials in the US, focuses primarily on ethical review. One major difference between HRECs and IRBs is that after the National Health and Medical Research Council reviews and certifies committees as multi-site HRECs, scientific and ethical review by one certified HREC is then recognized by HRECs at other institutions (efficient mutual recognition for early-stage trials is not common among US IRBs). Importantly, the regulatory components are not the only differences between the US and Australian system; for example, Australia offers less expensive health care costs and a publicly funded health system that covers many standard tests.

A pathway modeled on the Australian system that removes the IND could risk usurping the FDA's authority to pause or halt an early-phase study for safety or other issues. The TGA retains authority to question and stop a trial even under its notification scheme. Australia can also rely on notification because its HRECs perform scientific validity and product-safety review, a role that US IRBs are neither designed nor resourced to assume.

To reform the IND process, new legislation could:

- Empower the FDA to standardize communications from the pre-IND stage through IND review and evaluation.

[10] Basch E. Toward patient-centered drug development in oncology. *N Engl J Med*. 2013;369(5):397-400. doi:10.1056/NEJMp1114649

- Provide funding for FDA to train and hire additional IND reviewers to reduce the time between a sponsor's initial engagement with the FDA and IND authorization.
- Introduce mandatory recognition (or incentives for recognition) of IRB approvals across sites to reduce duplication and accelerate trial activation.
- Provide regulatory or financial incentives for companies conducting early-stage development in the US, such as tax credits or other benefits similar to those available in Australia.

***Positives in the Discussion Draft*:** Pre-competitive cooperation among sponsors. Expanded authority for foreign inspections.

Areas of Concern: IRBs are not equipped to assume the scientific review responsibilities being proposed. Requiring clinical data to be generated in the US may undermine the global nature of clinical development.

b. Maintaining FDA oversight of first-in-human trials

Delegating Phase 1 trial oversight to pre-certified third parties could accelerate study initiation, but raises concerns about safety, independence, and regulatory authority that must be addressed if this proposal is going to proceed:

- *Reduced FDA authority*: The FDA should not lose the discretion to directly oversee certain studies or the ability to rapidly halt studies when safety concerns arise. Depending on how Section 6 is drafted, the FDA could lose its authority to impose a clinical hold if there is no IND in place.
- *Unpredictable safety risks*: Serious adverse events can occur even in seemingly low-risk first-in-human studies, making robust oversight essential.[11] It is difficult to know in advance whether a Phase 1 is truly "high risk," which makes inherently unanticipated adverse events hard to predict. Catastrophic safety failures occurred in trials of agents that were regarded as low risk (e.g., TGN-1412 in 2006 and BIA 10-2474 in 2016), and the safety reforms that followed those cases, reinforced the need for meaningful regulatory oversight of first-in-human studies.
- *Conflicts of interest*: Third-party reviewers may depend on industry funding, potentially compromising independent safety assessments. Pre-certification programs are ripe for capture by industry and regulated entities that they review; a third-party certifier that relies on sponsors to fund its reviews may be slower than the FDA to halt a trial or designate a study as "high risk." Such potential conflicts of interest must be legislatively prohibited.
- *Liability concerns*: If a third party authorizes a study that later harms participants due to insufficient oversight, the third-party organization should be able to be held legally responsible for the harms.

Unlike the proposed US approach, Australia's regulator retains authority to intervene in an ongoing study and can compel the sponsor to provide documentation needed for an objective, unbiased review of safety issues. Some concerns with third-party review could be mitigated through legislative drafting, but important trade-offs related to safety, independence, and accountability are unlikely to be resolved

[11] Bonini S, Rasi G. First-in-Human Clinical Trials - What We Can Learn from Tragic Failures. *N Engl J Med*. 2016;375(18):1788-1789. doi:10.1056/NEJMe1609006

through drafting alone. Thus, it is important that the FDA maintain some responsibility and that this be organized as a pilot subject to review.

Positives in the Discussion Draft: Could streamline Phase 1 trial initiation and reduce FDA workload.

Areas of Concern: May weaken independent safety oversight, reduce FDA authority, and introduce conflicts of interest and liability concerns.

c. Global regulatory alignment

Inspired by Project Orbis in oncology,[12] but focused on early-stage clinical development.

Proposal: Establish a coordinated review pathway among the FDA, EMA, MHRA, TGA, Health Canada, and other trusted regulatory agencies for first-in-human and Phase I clinical trials.

Positives in the Discussion Draft: Harmonizes regulatory expectations across major jurisdictions. Reduces the need for sequential Phase I studies across multiple regions. May accelerate global drug development and patient access to innovative therapies.

Areas of Concern: Requires substantial coordination among participating regulators. May be challenging to achieve alignment on scientific, ethical, and operational standards.

d. US clinical trials and foreign data acceptance

The FDA already has the authority to reject foreign clinical data if the data are not considered generalizable to US patients. Following this principle, the FDA has previously raised concerns about China-only studies. [13]

- It remains unclear what the proposed legislation would require. If it mandates that part of clinical development be conducted in the US, development costs and timelines would likely increase, as US-based trials are substantially more expensive.
- This approach would also run counter to international trends. Countries such as China, Japan, India, and South Korea have increasingly accepted foreign clinical data to accelerate patient access to new therapies, moving away from local data requirements. Notably, the historical justification for such local data requirements was at least partially scientific (for example, the potential for differing drug responses/interactions in East Asian populations).
- There is also a risk of reciprocal action. If the US requires domestic clinical data, other countries may adopt similar policies, forcing sponsors to conduct additional regional studies and increasing global development costs and delays.
- One of the main concerns among sponsors is that innovative approaches accepted by the FDA may not be accepted by other regulatory agencies. This uncertainty can reduce sponsors' willingness to invest in novel clinical trial designs.

Less burdensome alternatives could include:

- Requiring at least one US site in pivotal trials;

[12] Tibau A, Kesselheim AS. Global Cooperation and Early Access—Clinical Outcomes Matter. *The Lancet Oncology*. 2024;25(6):687-688. doi:10.1016/S1470-2045(24)00210-9
[13] Li G, Liu Y, He R, Su L, Chen X. FDA Decisions on New Oncological Drugs. *Lancet, Oncol*. 2022;23(5):583-585. doi:10.1016/S1470-2045(22)00136-X

- Requiring postmarketing studies in representative US populations;
- Requiring FDA review or certification of whether pivotal trial control groups reflect the US standard of care;[14]
- Encouraging international regulatory collaborations, such as the Project Orbis initiative in oncology.[15]

***Positives in the Discussion Draft*:** May increase confidence that pivotal trial results are applicable to US patients.

Areas of Concern: Could increase development costs and timelines and encourage other countries to impose similar local data requirements.

Sections 9-11. Enhancing FDA Transparency to Support Modernization

a. Resolving clinical holds and improving trial efficiency

Regulatory uncertainty remains a key barrier to innovation.

- FDA could improve predictability by providing more structured and transparent feedback, particularly for novel trial designs.
- The proposal could lead FDA to publish anonymized examples of common deficiencies leading to clinical holds (e.g., reasons for clinical holds, time required to resolve holds) and successful mitigation strategies (resolution pathways). This could improve predictability and reduce avoidable delays.
- FDA could regularly publish key performance indicators, including: time to safe-to-proceed notification, time required to resolve clinical holds, pre-IND response timelines, variability across FDA review divisions.

Positives in the Discussion Draft: Facilitates collective learning across sponsors, contract research organizations (CROs), and regulators. Reduces repetition of common mistakes and avoidable deficiencies. Improves transparency and predictability in the IND review process.

Areas of Concern: May create incentives to prioritize speed over review quality and scientific rigor.

Section 12. Evidence-Based Regulatory Reforms for Follow-On Product Sponsors

12a. Directs FDA to improve the Competitive Generics Pathway through engagement of health care stakeholders

Improving the FDA's Competitive Generic Therapy pathway may further encourage generic manufacturers to quickly enter the market for products for which there is limited competition, which could have positive effects on price and drug supply.[16,17]

[14] Molto C, Tibau A, Bujosa A, et al. Association Between Control Group Therapy and Magnitude of Clinical Benefit of Cancer Drugs. *Sci Rep*. 2022;12:21342. doi:10.1038/s41598-022-25983-9
[15] Tibau A, Kesselheim AS. Global Cooperation and Early Access—Clinical Outcomes Matter. *The Lancet Oncology*. 2024;25(6):687-688. doi:10.1016/S1470-2045(24)00210-9
[16] Chahal HS, Fowler AC, Patel R, Shimer M. Characteristics and Outcomes of Products Seeking Competitive Generic Therapy Designation and Exclusivity. *JAMA*. 2021;326(18):1863-1865. doi:10.1001/jama.2021.14595
[17] Kho K, Patel R, Chahal HS. US Food and Drug Administration Competitive Generic Therapy Approvals and Drug Competition. *JAMA Intern Med*. 2026;186(1):136-138. doi:10.1001/jamainternmed.2025.6072

Proposed measures:

- The FDA could more clearly identify which products are eligible for the Competitive Generic Therapy designation. For example, by explicitly flagging eligible products on its list of off-patent and off-exclusivity drugs, or by determining whether insufficient competition exists before an application is submitted.
- The current 180-day market exclusivity incentive for the first approved Competitive Generic Therapy generic should be maintained, including the existing 75-day forfeiture provision if the product is not marketed within the required timeframe.
- In some very small or otherwise low-revenue markets, the 180-day exclusivity period may not be sufficient to encourage manufacturer entry. Therefore, additional policy measures may be needed to promote competition in these settings.

***Positives in the Discussion Draft*:** Greater clarity on Competitive Generic Therapy eligibility could accelerate generic competition and improve drug affordability and supply.

Areas of Concern: Competitive Generic Therapy incentives alone may not be sufficient to attract manufacturers in low-revenue markets in which competition is most limited.

12b. Strikes the interchangeability legal designation for biosimilar products

Removing the interchangeability designation for biosimilars could simplify the regulatory framework, reduce unnecessary evidentiary requirements, and promote broader biosimilar uptake in the US, consistent with recent FDA efforts to streamline biosimilar development and approval.[18] However, such a step should be paired with additional guidance and outreach from FDA on the general safety and effectiveness of switching between biologics and biosimilars to encourage changes in state-level pharmacy substitution laws and to improve prescriber and patient comfort with using biosimilars.[19]

Positives in the Discussion Draft: Removing the interchangeability designation could simplify the regulatory framework and promote broader biosimilar uptake.

Areas of Concern: Without adequate FDA guidance and education, this change could create uncertainty and limit its impact on biosimilar adoption.

12c. Establishes a 505b(2) pathway for follow-on biologics

Creating a 505b(2)-like pathway for follow-on biologics could lower the cost and time of bringing to market products that fall somewhere between a biosimilar and a wholly new biologic (e.g., "biobetters"). The FDA should be explicit about the evidence required to establish the safety and efficacy of such products, scaled to the degree of deviation a product has from its reference product. Such requirements would likely differ from those for small molecules and biosimilars.

[18] FDA. Considerations in Demonstrating Interchangeability with a Reference Product: Update. Draft Guidance FDA-2017-D-0154. Published June 20, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-demonstrating-interchangeability-reference-product-update

[19] Rome BN, Bhaskar A, Kesselheim AS. Biosimilar Interchangeability and Substitution in the US: What Comes Next? *Am J Manag Care*. Published online October 31, 2025:1-4. doi:10.37765/ajmc.2026.89826

If this provision is intended to promote market competition, it remains unclear whether it would do so as effectively as further improvements to the biosimilar approval pathway, since follow-on biologics would be unlikely to be freely substituted for their reference products. Stand-alone biologics could face less favorable incentives under current policy frameworks, including earlier eligibility for Medicare drug price negotiation and exclusion from policies designed to encourage biosimilar uptake, such as enhanced Medicare Part B reimbursement add-on payments and exemptions from inflation-based rebates. It is also unclear how products approved through this pathway would fit within the existing biologic exclusivity framework. Taken together, these factors may limit the pathway's ability to enhance competition and reduce prices, while potentially discouraging biosimilar development.

Positives in the Discussion Draft: A 505(b)(2)-like pathway could reduce the cost and development time of improved biologics (*biobetters*) and promote incremental innovation.

Areas of Concern: This new pathway is unlikely to increase competition or lower prices as much as biosimilars, and need to clarify how it would interact with the current biologic exclusivity framework and Medicare drug price negotiation program.

We appreciate the opportunity to share our perspective on this important legislative effort and would welcome the opportunity to further discuss these issues with your office. Please do not hesitate to contact us with any questions.

Sincerely,

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