COLLABORATION FOR REGULATORY RIGOR, INTEGRITY AND TRANSPARENCY

Written Testimony of Reshma Ramachandran, M.D., M.P.P., M.H.S. of Yale School of Medicine

Hearing on "The Future of Biotech: Maintaining U.S. Competitiveness and Delivering Lifesaving Cures to Patients"

Senate Health, Education, Labor, and Pensions (HELP) Committee

October 29, 2025

Chairman Cassidy, Ranking Member Sanders, and distinguished members of the committee, thank you for the opportunity to testify. My name is Reshma Ramachandran. I am an Assistant Professor at Yale School of Medicine where I co-direct an interdisciplinary research and policy program called the Yale Collaboration for Regulatory Rigor, Integrity, and Transparency (CRRIT). Our CRRIT team conducts research on how medical products are evaluated, regulated, and covered with the aim of advancing policies that improve patient health and healthcare. I am also a primary care physician, taking care of patients at a federally qualified health center in New Haven, Connecticut. As an unpaid volunteer, I sit on the Board of Directors for Doctors for America, an independent, non-partisan, and non-profit organization representing over 42,000 clinicians of all specialties across the country who are committed to prioritizing and advocating on behalf of patients, above all else.

I receive no research funding support or personal fees from any pharmaceutical, biotechnology, or medical device companies nor any health insurers or pharmacy benefit managers. The views expressed in this testimony are my own and not that of my employer nor the organizations I work with.

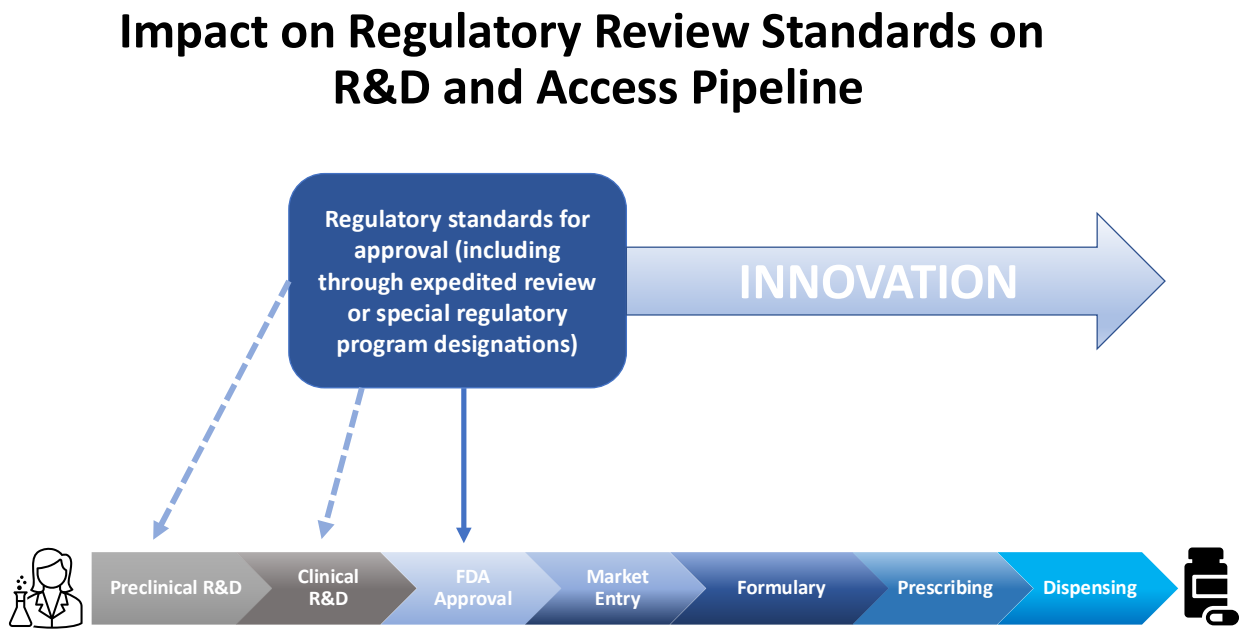
As a practicing physician, I am often concerned about whether I can provide assurance to my patients that the treatment I am prescribing is not only safe, but also will work meaningfully for them. This is why I have dedicated my research and clinical career to studying and advancing policies that shift the burden of uncertainty around new treatments away from my patients and instead, enable public health agencies in collaboration with other stakeholders to generate robust, scientific evidence to address this uncertainty. I am supportive of any effort to ensure that my patients and others will have timely access to cures that are truly lifesaving.

What does the "Future of Biotech" depend on?

The future of the biotechnology industry within the U.S. is dependent on the foundational infrastructure that has historically undergirded the discovery, development, and accessibility of novel treatments. This not only includes the enabling environment that the U.S. government has created to support a thriving biomedical industry, but most importantly, the various federal health agencies that are intended to align public health priorities with innovation and access. Funding from the National Institutes of Health (NIH), the world's largest biomedical research agency, has contributed to almost every new drug or biologic approved by the U.S. Food and Drug

Administration (FDA) over the past decade.[1] Additionally, these public investments have buoyed the development of drugs considered to be first-in-class, for rare disease indications, and those that have received expedited review designations by the FDA, signaling their novelty and use for an unmet medical need.[2]

While the NIH and other federal agencies have been instrumental in enabling these discoveries, the FDA has also played a significant role in shaping and advancing the biotechnology industry. Following passage of the 1962 Kefauver-Harris Amendments, the agency outlined specific regulatory standards for novel therapeutics (and subsequently, other medical products) to ensure that robust studies were conducted by manufacturers ahead of approval to provide reassurance to patients and clinicians that once approved, a treatment had been determined by the FDA to not only be safe, but also effective for the intended population. While many focus on the role of the FDA in enabling access to novel treatments, the more significant role that the agency plays as a regulator is that of shaping innovation intended to promote public health and protect patients.



The FDA's standards for ensuring safety and efficacy of new medical products before approval, and increasingly, evaluating safety and efficacy after approval have implications for various stakeholders:

[1] Galkina Cleary E, Jackson MJ, Zhou EW, Ledley FD. Comparison of Research Spending on New Drug Approvals by the National Institutes of Health vs the Pharmaceutical Industry, 2010-2019. *JAMA Health Forum*. 2023;4(4):e230511. doi:10.1001/jamahealthforum.2023.0511

[2] Zhou EW, Jackson MJ, Ledley FD. Spending on Phased Clinical Development of Approved Drugs by the US National Institutes of Health Compared With Industry. *JAMA Health Forum*. 2023;4(7):e231921. doi:10.1001/jamahealthforum.2023.1921

- Payers including private insurers as well as Medicare and Medicaid look to the FDA's evaluation of novel medical products when making coverage decisions.[3,4]
- Clinicians including those who author clinical practice guidelines look to the FDA's evaluation of novel medical products when developing such guidelines or in making individual prescribing decisions, relying on the agency's assessment of safety and efficacy when doing so.[5]
- Patients, especially those affected by the disease indication for which a particular medical product has been approved, rely on the FDA's evaluation of safety and efficacy in making informed decisions about their health, often in consultation with their clinicians.
- Other pharmaceutical companies look to the FDA's rationale for its decisions as a precedent for how they should also design a clinical trial and the degree of evidence that is necessary to obtain FDA approval and market authorization.

Patients and clinicians often have inherent trust that the FDA is acting as a scientific regulator in making approval decisions. Now, however, patients, clinicians, and other stakeholders are facing an inflection point as to whether such trust can be granted blindly to the agency. Longstanding concerns have been invoked regarding the rigor of FDA approval standards for new medical products with calls for increased transparency, removal of industry conflicts of interest, and the need to adhere to strong scientific standards in regulatory decision-making. However, these stated principles have been overshadowed by policies advancing opposite goals and prioritizing industry interests and politics ahead of scientific integrity. In my written testimony, I outline a few of the underlying principles necessary to enable the "Future of Biotech" and policy proposals for how these might be advanced as well as ongoing threats that would hinder the U.S.'s ability to delivery truly lifesaving cures to patients.

What are the underlying principles to enable the "Future of Biotech" and maintain U.S. competitiveness in delivering truly lifesaving cures to patients?

1. Not just more new medical products, but new medical products that are meaningfully, clinically beneficial for patients and are safe.

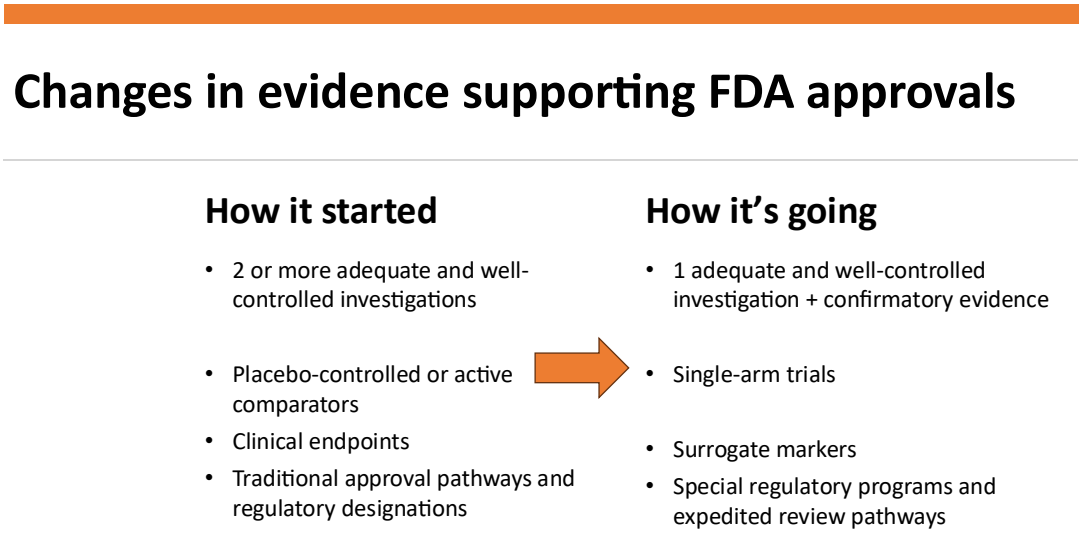
In making regulatory decisions around new medical products, the FDA faces a tension between enabling speedy access while also ensuring certainty for patients and clinicians that these new approvals are meaningfully effective and safe. However, over time, the FDA has increasingly relaxed regulatory standards for approval. Although the FDA had historically

[3] Dhruva SS, Ramachandran R, Ross JS. Medicare's National Coverage Determination for Aducanumab — A One-Off or a Pragmatic Path Forward? *New England Journal of Medicine*. 2022;387(17):1539-1541. doi:10.1056/NEJMp2210198

[4] Rathi VK, Johnston JL, Ross JS, Dhruva SS. Medicare's New Device-Coverage Pathway — Breakthrough or Breakdown? *New England Journal of Medicine*. Published online March 10, 2021. doi:10.1056/NEJMp2101874

[5] Mooghali M, Mitchell AP, Skydel JJ, Ross JS, Wallach JD, Ramachandran R. Characterization of accelerated approval status, trial endpoints and results, and recommendations in guidelines for oncology drug treatments from the National Comprehensive Cancer Network: cross sectional study. *BMJ Med*. 2024;3(1):e000802. doi:10.1136/bmjmed-2023-000802

required two or more adequate and well-controlled investigations to be the basis of new drug approval, the agency has stated it would allow for a single clinical trial along with confirmatory evidence such as in vitro data, animal studies, real-world evidence derived from electronic health records, insurance claims, or registries, and other sources outside of clinical trials.[6] As of 2024, two-third of new drug approvals are based on single pivotal trials compared to less than a third in 2011.[7] Additionally, the FDA has approved new drugs despite pivotal trials failing to achieve one or more primary endpoints and often without additional requirements after approval to further address these missed endpoints.[8] Other shifts in FDA approval standards are as follows:[9]



Zhang et al. *JAMA Netw Open*. 2020;3(4):e203284.

While regulatory flexibility for certain diseases or conditions may be necessary, particularly for rare diseases where there are limited or no adequate treatment options available, such flexibility should be granted as an exception, not as a rule. **Use of regulatory flexibility must also be coupled with requirements after approval for manufacturers to generate**

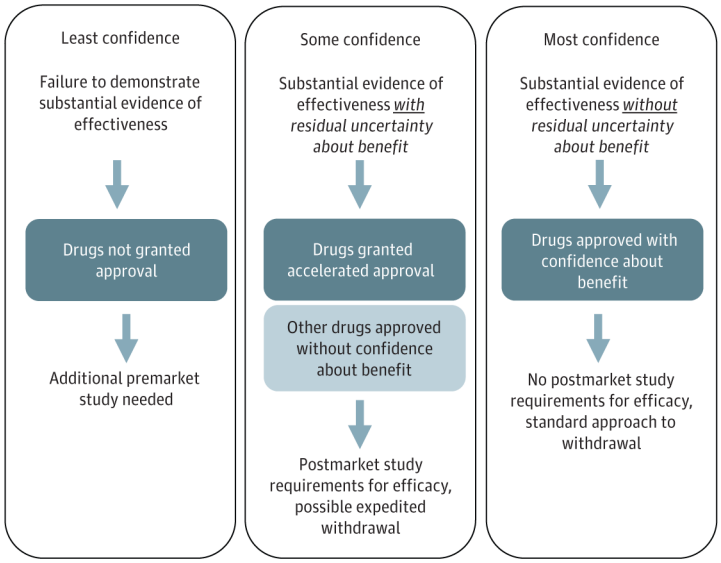
[6] Godoy CB, Ramachandran R, Sapre P, Ross JS. Confirmatory evidence supporting single pivotal trial new drug approvals by the Food and Drug Administration, 2015 through 2023. *Clinical Trials*. Published online October 15, 2025:17407745251376620. doi:10.1177/17407745251376620

[7] Conti A. Analysis: The majority of novel drugs approved by FDA rely on evidence from a single pivotal trial | AgencyIQ by POLITICO. AgencyIQ. February 7, 2025. Accessed October 28, 2025. https://www.agencyiq.com/blog/analysis-the-majority-of-novel-drugs-approved-by-fda-rely-on-evidence-from-a-single-pivotal-trial/

[8] Johnston JL, Ross JS, Ramachandran R. US Food and Drug Administration Approval of Drugs Not Meeting Pivotal Trial Primary End Points, 2018-2021. *JAMA Internal Medicine*. Published online February 13, 2023. doi:10.1001/jamainternmed.2022.6444

[9] Zhang AD, Puthumana J, Downing NS, Shah ND, Krumholz HM, Ross JS. Assessment of Clinical Trials Supporting US Food and Drug Administration Approval of Novel Therapeutic Agents, 1995-2017. *JAMA Netw Open*. 2020;3(4):e203284. doi:10.1001/jamanetworkopen.2020.3284

evidence confirming that the drugs are truly clinically beneficial and are safe.[10] A balance can be struck between enabling timely access and uncertainty at the time of FDA approval such that allowing for premarket uncertainty should be matched with requirements for postmarket certainty. Otherwise, patients and clinicians will continue to not have assurance of the approved product's benefits and risks.



Congress and the FDA have taken such steps to improve completion of required postapproval studies for pathways such as accelerated approval. Under accelerated approval, drugs are granted early market authorization based on unvalidated surrogate endpoints in lieu of clinical outcomes that directly measure how patients feel, function, or survive. In exchange, manufacturers are required to complete a study after approval confirming the drug's predicted clinical benefit.[11] Should the required postapproval study not be completed or fail to demonstrate clinical benefit, the FDA may withdraw the drug from the market. Under the Food and Drug Omnibus Reform Act of 2022, FDA was granted necessary authorities to have greater oversight of these postmarketing requirements and clarify to manufacturers the process for withdrawing drugs with unproven clinical benefit. Nevertheless, the agency has exercised flexibility with these new authorities; the FDA has allowed for continued market authorization for certain accelerated approval drugs despite failed postapproval studies or continued use of surrogate endpoints within postapproval studies, leaving unknown whether the therapeutic has meaningfully clinical benefit for patients.[12,13,14]

---

[10] Fernandez Lynch H, Sachs RE, Lee S, Herder M, Ross JS, Ramachandran R. Extending the US Food and Drug Administration's Postmarket Authorities. *JAMA Health Forum*. 2023;4(6):e231313. doi:10.1001/jamahealthforum.2023.1313

[11] U.S. Department of Health and Human Services. Review of the FDA's Accelerated Approval Pathway. Office of the Inspector General. August 4, 2021. https://oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000608.asp

[12] Gyawali B, Kesselheim AS, Ross JS. The Accelerated Approval Program for Cancer Drugs — Finding the Right Balance. *New England Journal of Medicine*. Published online September 14, 2023. doi:10.1056/NEJMp2306872

Such flexibility is not limited to drugs, but has also impacted medical device clearance or authorization. Studies examining premarket evidence for novel moderate-risk and high-risk medical devices have shown that several received FDA clearance despite not being supported by clinical studies or studies with missed primary endpoints.[15] Among those moderate-risk devices without premarket evidence supporting efficacy, the FDA often did not require postapproval studies. These devices would later become the basis of subsequent 510(k)-cleared medical devices.[16] Devices granted breakthrough designation under a 2016 program intended to facilitate access to innovative health technologies have also been found to have significant residual uncertainty around their benefits and harms at the time of FDA approval.[17]

Studies have also suggested that when the FDA favors speed and regulatory flexibility in their approval decisions, tradeoffs can occur beyond uncertainty related to efficacy, including safety. Prior analyses have found associations between postmarket drug safety events such as withdrawals, black box warnings, and safety communications to health professionals and the public with therapeutics receiving accelerated approval or when decisions were made near the regulatory deadline.[18] Other studies have found that under the 510(k) pathway, which allows for market entry based on predicate devices that were previously authorized, over 40% used predicates with a Class I recall, an FDA designation that indicates a significant likelihood of causing serious harms or death.[19] These devices were also over six times as likely to be subject to a Class I recall compared to those that used predicates without recalls. Moreover, when the FDA has allowed manufacturers to submit supplements to original applications for high-risk devices that previously underwent the premarket approval (PMA) process, these were associated with a 30% higher increased risk of any recall and Class I recall.[20]

---

[13] Abrams M, Ramachandran R, Steinbrook R. Report: Failed Trials, Yet Full FDA Approval of a Duchenne Muscular Dystrophy Gene Therapy. Public Citizen. February 26, 2025. Accessed October 28, 2025. https://www.citizen.org/article/failed-trials-yet-full-fda-approval-of-a-duchenne-muscular-dystrophy-gene-therapy/

[14] Mehta GU, Pazdur R. Oncology Accelerated Approval Confirmatory Trials: When a Failed Trial Is Not a Failed Drug. *J Clin Oncol*. 2024;42(32):3778-3782. doi:10.1200/JCO-24-01654

[15] Johnston JL, Dhruva SS, Ross JS, Rathi VK. Assessment of FDA Approval for New High-risk Therapeutic Devices Not Meeting Pivotal Study Primary End Points, 2016-2020. *JAMA Intern Med*. 2021;181(10):1409-1412. doi:10.1001/jamainternmed.2021.3042

[16] Johnston JL, Dhruva SS, Ross JS, Rathi VK. Clinical Evidence Supporting US Food and Drug Administration Clearance of Novel Therapeutic Devices via the De Novo Pathway Between 2011 and 2019. *JAMA Intern Med*. 2020;180(12):1701-1703. doi:10.1001/jamainternmed.2020.3214

[17] Kadakia KT, Dhruva SS, Ross JS, et al. FDA Authorization of Therapeutic Devices Under the Breakthrough Devices Program. *JAMA Intern Med*. 2025;185(8):996-1004. doi:10.1001/jamainternmed.2025.2235

[18] Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *JAMA*. 2017;317(18):1854-1863. doi:10.1001/jama.2017.5150

[19] Kadakia KT, Dhruva SS, Caraballo C, Ross JS, Krumholz HM. Use of Recalled Devices in New Device Authorizations Under the US Food and Drug Administration's 510(k) Pathway and Risk of Subsequent Recalls. *JAMA*. 2023;329(2):136-143. doi:10.1001/jama.2022.23279

[20] Dubin JR, Enriquez JR, Cheng AL, Campbell H, Cil A. Risk of Recall Associated With Modifications to High-risk Medical Devices Approved Through US Food and Drug Administration Supplements. JAMA Netw Open. 2023;6(4):e237699. doi:10.1001/jamanetworkopen.2023.7699

Thus, a better balance must be struck at the FDA in prioritizing robust evidence generation of new medical products to ensure certainty for patients and clinicians with ensuring timely access. To do so, Congress and the FDA should consider the following:

- **The FDA should only exercise regulatory flexibility in premarket approval standards in limited circumstances, particularly for diseases or conditions of truly unmet need where there are no available or suitable treatment options.**
- **The FDA must apply the principles of replicability/reproducibility being pursued by other federal health agencies to evidence supporting FDA approval of medical products.[21] As originally intended, unless under rare circumstances or with support of robust confirmatory evidence, the FDA should require more than one "adequate and well-controlled investigation" – ideally, well-designed clinical trials that have enrolled participants reflective of those who would be administered the treatment – to be the basis of approval.**
- **While there may be diseases or conditions for which regulatory flexibility related to the quality of premarket evidence may be necessary, the FDA should ensure that robust postapproval studies are completed to verify the predicted clinical benefit of the drug or device. The parameters for these studies, which will inform the quality of evidence generated, should be set by the FDA in collaboration with other stakeholders including payers.[22,23,24]**
- **The FDA should also ensure the clinical validity and rigor of novel data sources including real-world evidence derived from electronic health record, insurance claim, and registry data, particularly when using such data to evaluate efficacy of novel medical products. These data sources, while promising, must be made more robust and re-designed to yield conclusive and actionable results to support medical product approvals and confirm clinical benefit of novel treatments.[25,26,27]**

---

[21] National Institutes of Health. LEADING IN Gold Standard Science. Published online August 22, 2025. https://www.nih.gov/sites/default/files/2025-08/2025-gss.pdf

[22] Abbasi AB, Curtis LH, Fleisher LA, Califf RM. Why Evidence Generation Should Matter to Payers and How They Can Help. *JAMA*. 2024;332(5):412-417. doi:10.1001/jama.2024.7616

[23] Mooghali M, Moneer O, Janda G, Dhruva SS, Ross JS, Ramachandran R. Assessing Medicare's Coverage With Evidence Development Program. *Health Affairs*. 2025;44(1):32-39. doi:10.1377/hlthaff.2024.00814

[24] Dhruva SS, Ramachandran R, Ross JS. Medicare's National Coverage Determination for Aducanumab — A One-Off or a Pragmatic Path Forward? *New England Journal of Medicine*. 2022;387(17):1539-1541. doi:10.1056/NEJMp2210198

[25] Wallach JD, Zhang AD, Skydel JJ, et al. Feasibility of Using Real-world Data to Emulate Postapproval Confirmatory Clinical Trials of Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval. *JAMA Network Open*. 2021;4(11):e2133667. doi:10.1001/jamanetworkopen.2021.33667

[26] Dhruva SS, Ross JS, Desai NR. Real-World Evidence: Promise and Peril For Medical Product Evaluation. *P T*. 2018;43(8):464-472.

[27] Janda GS, Wallach JD, Dhodapkar MM, Ramachandran R, Ross JS. Feasibility of Emulating Clinical Trials Supporting US FDA Supplemental Indication Approvals of Drugs and Biologics. *JAMA Intern Med*. 2023;183(11):1271-1273. doi:10.1001/jamainternmed.2023.4073

2. Not just new products, but new products based on standards rooted in robust regulatory science

The FDA has increasingly allowed for approvals to be based on novel endpoints including surrogate markers that are intended to be proxy measures for clinical outcomes directly measuring how patients feel, function, and survive.[28] Use of surrogate makers has been shown to reduce the duration, size, and total cost of clinical trials when compared to clinical outcomes. Surrogate endpoints are considered to be "validated" where there has been substantial, robust evidence demonstrating a strong association with the predicted clinical outcome. Others are "unvalidated" such that the surrogate markers are "reasonably likely to predict clinical benefit." However, even for surrogate markers considered to be validated, studies have suggested a lack of available or sufficient evidence showing an association with a clinical outcome.[29]

The FDA has increased transparency of which surrogate markers the agency would accept to support regulatory approval of drugs through publicly posting and updating a list of surrogate endpoints that had been the basis of approval. However, missing within this list is a justification for the selection of these specific surrogates as well as evidence supporting their validation. Without such information, patients, clinicians, and payers continue to be uncertain of the clinical benefit of drugs approved by the FDA based on surrogate endpoints. Moreover, as inclusion of a surrogate marker in this list signals to manufacturers FDA's acceptance of such endpoints, drug developers will continue to use these endpoints in their clinical trials supporting potential approval of future therapeutics despite the lack of evidence around clinical benefit available.

Thus, for surrogate markers and other novel endpoints that have been accepted by the agency to support regulatory approval, the FDA should take the following steps to strengthen their underlying evidence:

- **The FDA within their lists of surrogate endpoints should make more transparent the strength of evidence, providing a summary of evidence for each included surrogate marker and which clinical outcomes the surrogate is thought to predict.**
- **The FDA should regularly convene advisory committees of independent experts to routinely review and vote on the use of new surrogate markers for disease indications. Such committees should also be regularly convened to re-evaluate the use of surrogate markers based on current evidence, especially those that had been previously unvalidated or where there had been no high-quality evidence when initially accepted for regulatory approval.**

---

[28] Ramachandran R, Wallach JD, Ross JS. *Validating Surrogate Endpoints to Support FDA Drug Approval*. Federation of American Scientists; 2025. Accessed July 24, 2025. https://fas.org/publication/validating-surrogate-endpoints/

[29] Wallach JD, Yoon S, Doernberg H, et al. Associations Between Surrogate Markers and Clinical Outcomes for Nononcologic Chronic Disease Treatments. *JAMA*. Published online April 22, 2024. doi:10.1001/jama.2024.4175

- **The FDA should collaborate with other federal research agencies including the NIH, Centers for Medicare and Medicaid Services (CMS), Patient Centered Outcomes Research Institute (PCORI), and others to generate evidence to examine whether surrogate markers are appropriate for regulatory approval. These publicly funded studies can inform discussions at FDA advisory committees when reviewing proposed or existing surrogate markers to determine if they should be accepted to support FDA approval or sunset.**

Besides this, the FDA as well as federal agencies have historically collaborated with researchers at academic institutions to strengthen regulatory science and policy. This research has directly informed regulatory standards for approval, which has led to innovation that is better aligned with available scientific evidence, improved patient outcomes, and enhanced access to both novel and existing treatments. Through these collaborations, researchers from academic institutions and other organizations have brought a wide breadth of expertise to the FDA ranging from postmarket safety surveillance methods, manufacturing and compounding practices, the role of patients in regulatory decision-making, effective use of real-world data sources for assessing efficacy and safety, and more. The future of this government-academic partnership remains uncertain despite the immense benefit it offers not only to the agency, but also to patients and clinicians in ensuring that the FDA and federal health agencies continue to pioneer advancements in regulatory science that are critical for rigorously evaluating novel medical products. Such collaborations should be maintained to ensure that the FDA has continued access to specialized, independent expertise in shaping medical product regulation and surveillance.

3. Not just new products, but also new products that patients can afford and access

Novel medical products continue to be out of reach for patients, often due to high prices that are commanded by the pharmaceutical industry despite significant government investment into the research and development and unrelated to the product's therapeutic benefit.[30,31] Even for drugs approved by the FDA with known uncertainty at the time of approval, manufacturers are able to set prices that are independent of their value. Allowing manufacturers to set such prices has further disincentivized the completion of studies comparing their products to other available options or from confirming clinical benefit after approval, even when required to do so. If a manufacturer can set a price that the market will bear, why would they conduct an additional study after approval that may demonstrate a lack of clinical benefit or inferiority compared to other available treatments?

[30] Wouters OJ, Berenbrok LA, He M, Li Y, Hernandez I. Association of Research and Development Investments With Treatment Costs for New Drugs Approved From 2009 to 2018. *JAMA Netw Open*. 2022;5(9):e2218623. doi:10.1001/jamanetworkopen.2022.18623

[31] Jiang TE, Ramachandran R, Vokinger KN, Ross JS. Therapeutic benefit of the most expensive drugs covered by Medicare and Medicaid. *Journal of Pharmaceutical Policy and Practice*. 2025;18(1):2564405. doi:10.1080/20523211.2025.2564405

The Inflation Reduction Act of 2022 allowed Medicare for the first time to consider factors such as therapeutic value as well as public investment in negotiating prices of a limited basket of prescription drugs. However, recent passage of provisions within the One Big Beautiful Bill Act have diluted Medicare's ability to negotiate lower drug prices for drugs indicated for rare diseases and often priced staggeringly high by manufacturers.[32,33] This coupled with the FDA's increased adoption of flexible regulatory standards, making unclear the clinical efficacy and safety of therapeutics at the time of approval, leaves Medicare and its beneficiaries with limited opportunity to ensure that prices of approved treatments are fair.

Proposed solutions such as creating platforms to directly sell select prescription drugs to patients will not meaningfully lower drug prices. Instead, the lack of affordability and access will only be further exacerbated by the loss of health insurance coverage for millions as well as the anticipated rise in health insurance premiums.[34,35] Many of my own patients have already begun to make difficult decisions about rationing certain medications or forgoing them altogether as they face these sudden, yet preventable shocks. **As an initial step, CMS must be empowered to negotiate the prices of more drugs as other similar countries already do and authorized to make publicly available the rationale including their assessment of therapeutic value as well as the contribution of public and private investment into individual drugs' discovery and development.**[36] Without more transformative policies to lower prices of treatments, new biotechnology discoveries will be of no use to any patients if they are unable to afford them.[37]

What are ongoing threats to the "Future of Biotech"?

1. *Diminishing investment, resources, and personnel at federal health agencies that serve as the core infrastructure for novel biomedical research and innovation*

The continued loss of scientists, technical experts, and regulators across federal health agencies has raised significant concerns around U.S. capacity to maintain and enhance the nation's competitiveness in delivering lifesaving cures. An estimated 21% of FDA's workforce

---

[32] Chen JC, Kaltenboeck A. The Blockbuster Orphan Paradox: Consequences Of Special Treatment Of Rare Disease Drugs In Medicare Negotiation. doi:10.1377/forefront.20250826.624663

[33] Althobaiti H, Seoane-Vazquez E, Brown LM, Fleming ML, Rodriguez-Monguio R. Disentangling the Cost of Orphan Drugs Marketed in the United States. *Healthcare (Basel)*. 2023;11(4):558. doi:10.3390/healthcare11040558

[34] Lo J, Levitt L, Ortaliza J, Cox C. ACA Marketplace Premium Payments Would More than Double on Average Next Year if Enhanced Premium Tax Credits Expire. KFF. September 30, 2025. Accessed October 28, 2025. https://www.kff.org/affordable-care-act/aca-marketplace-premium-payments-would-more-than-double-on-average-next-year-if-enhanced-premium-tax-credits-expire/

[35] Sullivan J, Rapfogel N. *Five Key Changes to ACA Marketplaces Amid Uncertainty Over Premium Tax Credit Enhancements*. Center on Budget and Policy Priorities; 2025. Accessed October 28, 2025. https://www.cbpp.org/research/health/five-key-changes-to-aca-marketplaces-amid-uncertainty-over-premium-tax-credit

[36] Qureshi O, Ramachandran R, Ross JS. Medicare Part B and Part D drug eligibility for center for Medicare and Medicaid Services price negotiation under the Inflation Reduction Act: estimates using 2016–2019 data. *Journal of Pharmaceutical Policy and Practice*. 2024;17(1):2312374. doi:10.1080/20523211.2024.2312374

[37] Qureshi O, Ramachandran R. Victory Over Big Pharma Will Take More Than the IRA. *MedPage Today*. https://www.medpagetoday.com/opinion/second-opinions/109495. April 4, 2024. Accessed August 15, 2024.

including over 900 scientists and health experts as well as 500 regulators, investigators, and compliance officers have either been fired or left the agency.[38] At FDA's Centers for Drug Evaluation and Research (CDER) and Biologic Evaluation and Research (CBER), key parts of the agency responsible for evaluating and regulating drugs and biologics, the FDA reported a loss of 1219 and 325 staff as of FY2025 at these centers, respectively compared to 287 and 72 the year prior.[39]

The impact of such attrition has detrimentally impacted FDA's review and approval operations. Industry analysts recently reported a decreased rate of drug approvals and increased rate of delays in meeting regulatory deadlines.[40] However, they also noted that the FDA has "attempted to take a more permissive approach to approvals for some medications, such as those related to oncology." Additionally, FDA officials "have also indicated a more expansive view toward rare disease drug approvals." This may indicate that the FDA, despite seeing a significant loss in technical expertise and scientific review staff, may further relax regulatory standards for approvals, further shifting the burden of uncertainty onto patients and clinicians.

2. Entrenching the infrastructure of federal regulatory agencies with the industries that are to be regulated

While leadership across federal health agencies including at the FDA have called for a removal of conflicts of interest and enhanced transparency, the agency has continued to facilitate privileged access to regulated industry seeking to advance policies to relax regulatory rigor and perpetuate continued uncertainty of novel medical products for patients and clinicians. Earlier this year, the Secretary of Health and Human Services as well as FDA leadership signaled the possibility of reform of the agency's user fee process.[41] User fees are fees collected from companies regulated by the FDA that further augment Congressional appropriations and fund FDA operations including hiring of review staff and supporting of data systems. As of FY2024, nearly half of the FDA's $7 billion budget came from user fees and funded nearly 70% and over 50% of the agency's prescription drug and biologics budget, respectively.

As the FDA's reliance on user fees has grown since the inception of the program in 1992, so has industry's influence on the FDA's priorities. The program has been successful in ensuring that the agency's has continued capacity to review a growing portfolio of new drug applications.

---

[38] Roberts B, Waldman A, Rebala P. Gutted: How Deeply Trump Has Cut Federal Health Agencies. *ProPublica*. Published online August 21, 2025. Accessed October 28, 2025. https://projects.propublica.org/federal-health-worker-cuts-rfk-trump-administration/

[39] 1U.S. Food and Drug Administration. Center for Drug Evaluation and Research & Center for Biologics Evaluation and Research Net Hiring Data (FY 2023-2027). FDA.gov. October 16, 2025. Accessed October 28, 2025. https://www.fda.gov/industry/fda-user-fee-programs/center-drug-evaluation-and-research-center-biologics-evaluation-and-research-net-hiring-data-fy-2023

[40] Silverman E. FDA review of drugs is slowing while application delays are growing, analysis finds. STAT. October 20, 2025. Accessed October 28, 2025. https://www.statnews.com/pharmalot/2025/10/20/fda-drug-approvals-slowing-rejections-rising/

[41] Ziaks TJ, Schwartz JL, Ross JS, Ramachandran R. Reforming the Prescription Drug User Fee Program. *N Engl J Med*. 2025;393(8):734-736. doi:10.1056/NEJMp2507648

However, negotiations ahead of reauthorization of the program every 5 years are conducted behind closed doors between the FDA and industry without participation from public stakeholders including patients and clinicians. Separately, public stakeholders are invited to listening sessions to provide the FDA with recommendations around commitments on how the fees should be used. However, these sessions do not include any information from the FDA on what is being negotiated with industry that would allow public stakeholders an opportunity to provide relevant recommendations.

Additionally, negotiated commitments around how the user fees will be spent by the FDA has led to the adoption of metrics for shortened regulatory review times, increased interaction between FDA reviewers and industry, and pilot programs that prioritize speed and flexible standards for approval instead of patient-centered metrics around efficacy and safety.[42] Despite calls for reform from current federal health agency leadership, no such changes to date have been made to make the FDA's negotiations with industry more transparent or inclusive of public stakeholders. Finally, no proposals have been advanced to ensure that the FDA remains truly independent of the industries it is meant to regulate. Rather, FDA leadership has provided additional, privileged access to pharmaceutical and biotechnology company executives without transparency to the public.[43]

3. Allowing for politics to supersede scientific integrity in making regulatory decisions

At its core, the FDA is intended to be a scientific regulator in making decisions that adhere to its core mission of promoting public health and protecting patients. While the agency across administrations may vary its priorities, scientific integrity at the FDA should and must supersede politics.[44] However, recent regulatory decisions seem to indicate the opposite causing conclusions and regulatory decisions to be made ahead of available or conclusive scientific evidence.[45] For example, in recent public announcements around safety actions related to acetaminophen, the FDA themselves noted in communications to health professionals that "a causal relationship has not been established and there are contrary studies in the scientific literature."[46] In their announcement related to the approval of leucovorin for a condition associated with autism, the FDA pointed to a few dozen case reports of a heterogeneous sample

---

[42] Mitchell AP, Trivedi NU, Bach PB. The Prescription Drug User Fee Act: Much More Than User Fees. *Medical Care*. 2022;60(4):287-293. doi:10.1097/MLR.0000000000001692

[43] Commissioner O of the. CEO Forums: An FDA Listening Tour to Engage Pharmaceutical and Biotech CEOs. FDA. August 11, 2025. https://www.fda.gov/industry/ceo-forums-fda-listening-tour-engage-pharmaceutical-and-biotech-ceos

[44] Zettler PJ, Ramachandran R, Lynch HF. Never Waste a Crisis: The Past, Present, and Future of FDA Reform. *J Health Polit Policy Law*. Published online October 8, 2025:12262664. doi:10.1215/03616878-12262664

[45] Fernandez Lynch H, Ramachandran R. Contributor: By loosening standards, the FDA isn't doing rare-disease patients any favors. *Los Angeles Times*. https://www.latimes.com/opinion/story/2025-10-19/fda-approval-rare-disease-drugs-treatments. October 19, 2025.

[46] Commissioner O of the. FDA Responds to Evidence of Possible Association Between Autism and Acetaminophen Use During Pregnancy. FDA. September 22, 2025. https://www.fda.gov/news-events/press-announcements/fda-responds-evidence-possible-association-between-autism-and-acetaminophen-use-during-pregnancy

of adult and pediatric patients as evidence to support such a decision.[47] Such a rationale based on anecdotal evidence in lieu of clinical trials is unprecedented and recent reporting has indicated that FDA leadership tasked reviewers to find evidence to support an already-made conclusion.[48]

Moreover, the agency's recent announcement of recipients of the new Commissioner's New Priority Voucher has raised significant concerns around tradeoffs the agency would undertake to demonstrate the program's success.[49,50] Qualifying drugs receiving this voucher would be eligible for shortened review times of 1 to 2 months compared to 10 months for standard review and 6 months for priority review. Such an expedited timeline may further siphon already reduced review staff and resources towards drugs receiving this voucher. Additionally, with such limited time for review, the FDA review teams may not be able to conduct as rigorous of an evaluation of the qualifying drug's efficacy or safety, particularly when reviewing a new therapeutic not previously evaluated by the agency. It also remains unclear as to how these specific products were chosen as the FDA has not disclosed their rationale for selection, raising questions as to how manufacturers may have influenced the FDA in the process. Ultimately, without further explanation from the FDA around the selection of voucher recipients coupled with continued rigorous evaluation of recipient drug applications, trust in the FDA review and approval process will only be further questioned by patients, clinicians, and payers.

Conclusion

A "Future of Biotech" that maintains U.S. standing as a leader in health technology innovation and in delivering truly lifesaving cures to patients is contingent on the U.S. having a public biomedical research and regulatory infrastructure that is well-resourced and well-staffed. Recent policies stripping federal public health agencies such as the FDA of scientific and technical staff, blurring the lines between the regulator and the industries needing to be regulated, and politicizing the scientific regulatory review process will only further jeopardize trust in these institutions and unfairly shift the burden of uncertainty onto patients and their clinicians. Strategic reform of agencies like the FDA is needed, but must be done in such a way that places patients at the center and aligns stated principles with actions that deliver not just more cures, but those that are truly safe, effective, and accessible.

---

[47] U.S. Food and Drug Administration. Approval of Previously Withdrawn New Drug Application for WELLCOVORIN (Leucovorin Calcium) Tablets. Published online September 24, 2025. https://www.federalregister.gov/documents/2025/09/24/2025-18510/approval-of-previously-withdrawn-new-drug-application-for-wellcovorin-leucovorin-calcium-tablets

[48] Lawrence L. Inside FDA, career staffers describe how political pressure is influencing their work. STAT. October 14, 2025. https://www.statnews.com/2025/10/14/fda-under-trump-rfk-jr-staff-describe-political-pressure/

[49] Karlin-Smith S. First Cohort Shows Many Routes To US FDA's Commissioner's National Priority Voucher. *Pink Sheet*. Published online October 18, 2025. https://insights.citeline.com/pink-sheet/agency-leadership/us-fda/first-cohort-shows-many-routes-to-us-fdas-commissioners-national-priority-voucher-XIXA5BZH5ZADVFPJHQTLWSDU4Y/

[50] Carpenter D, Hwang TJ, Kesselheim AS. Flaws in the FDA's New Priority Voucher Program. *New England Journal of Medicine*. 0(0). doi:10.1056/NEJMp2509215