PATIENTS AND FAMILIES FIRST:

BUILDING THE FDA OF THE FUTURE

Senate Committee on
Health Education Labor & Pensions
Senator Bill Cassidy, M.D., Chair

Introduction

Biomedical innovation holds enormous promise for the American people. More than twenty years since the human genome was first sequenced, Americans are starting to see a wave of therapies resulting from decades of advances in personalized medicine. These products are already treating, and even curing, previously intractable diseases, offering patients new hope. New tools using artificial intelligence (AI) can detect diseases earlier and more accurately. The growing use of biosimilars and generic drugs offers patients more options at lower costs.

But "innovation" is meaningless unless it creates products that actually help patients. Discoveries that never leave the lab help no one. The Food and Drug Administration (FDA) has enormous leverage over how to channel breakthroughs that can make Americans' lives better. President Trump's mandates to cut red tape and make America healthy again challenge FDA, Congress, stakeholders, and patients to work together to examine the extent to which FDA's regulatory framework works efficiently for American patients and families. While many parts of FDA work well, unnecessary bottlenecks slow patients and consumers getting the products they need.

Ultimately, it should be easier to make Americans healthy by empowering them with the tools and information they need to make healthy choices and live better lives. The Senate Health, Education, Labor, and Pensions (HELP) Committee plans to initiate a collaborative, bipartisan process for reforms to strengthen the FDA and get better and more affordable products to patients faster. This paper reflects initial input from a variety of stakeholders—patient advocates, academic researchers, clinical societies, manufacturers, FDA, and more.

I. FDA Review of New Applications and Evidence

A. The Need for a More Consistent, Predictable Review Processes

One of the greatest challenges innovators face, particularly small- and medium-sized companies, is that FDA's process for reviewing new products can be an unpredictable "black box." FDA teams can differ greatly in the extent to which they require testing or impose standards that are not calibrated to the relevant risks. The perceived disconnect between the forwardleaning rhetoric and thought leadership of senior FDA officials and cautious reviewer practice creates further unpredictability. This uncertainty dampens investment and increases the time it takes for patients to receive new therapies.

Companies report that they face a "reviewer lottery," where critical questions hinge on the approach of a small number of individuals at FDA. Some FDA review teams are creative and forward-leaning, helping developers design programs and overcome obstacles to get needed products to patients, without cutting corners. FDA's Oncology Center of Excellence (OCE), for example, is repeatedly identified as a model for providing predictable yet flexible options for bringing new drugs to cancer patients. OCE is now a dialogue-based regulatory paradigm that has facilitated efforts by academia, industry, the National Institutes of Health (NIH), and others to develop new cancer therapies and launch innovative programs and pilots like Project Orbis, Real-Time Oncology Review.

Unfortunately, not all review teams are equally collaborative or forwardthinking, creating an unpredictable path to market. This lack of predictability extends across multiple dimensions—the timeliness of communications, level of responsiveness to questions, and flexibility on designing preclinical studies and clinical trials, among others. When firms disagree with reviewers, often their only choice is to either acquiesce or pursue timeconsuming and expensive appeals. In 1997, Congress required FDA to take a "least burdensome" approach to regulating medical devices, which means the minimum information necessary to adequately address a regulatory question or issue, through the most efficient manner at the right time.[1] To improve predictability,

Congress and FDA should consider how to apply this principle to other product categories while maintaining patient safety and evidentiary standards. Additionally, as Congress considers reforms, proposals should ensure there is accountability, transparency, and flexibility in the review process to meet the agency's resources.

B. Assessing FDA's Approach to Clinical Trials and Alternative Evidence Models

Clinical trials are the cornerstone of gathering the evidence needed to ensure that new drugs and medical devices are safe and effective for patients. Novel clinical trial approaches can enable faster, smarter, and less expensive trials, driving better insights from studies with more participation from patients that more accurately reflect the populations with the relevant disease. The traditional clinical trial model is evolving – sponsors are increasingly moving away from three-phase, site-based studies towards decentralized trials with adaptive, concurrent, or other alternative designs to enable trials to yield actionable results earlier.

FDA has embraced more creative clinical trial approaches, with direction and support from Congress. Through the 21st Century Cures Act and Food and Drug Omnibus Reform Act (FDORA), Congress required FDA to update or issue guidance on the use of complex and novel clinical trial designs, decentralized trials, and digital health technologies in clinical trials, among others.[2] These provisions have pushed FDA to further support sponsors to adopt new trial designs and technologies, including to facilitate better international harmonization.

FDA, however, could do more to expand the use of novel trial designs and technologies to garner better data from trials, allow more patients to participate, and reduce costs. Longer timelines and comparatively higher regulatory burdens for low-risk, early-phase trials in the U.S. drive sponsors to initiate first-in-human studies abroad, excluding American patients from the benefits of this research and weakening domestic clinical research infrastructure. In recent years, companies report that they are increasingly looking to start trials in other peer countries such as Canada, Europe, Australia, New Zealand, and even adversarial nations like China. Alarmingly, in recent years China has surpassed the United States as the top venue for clinical trials.[3] Thus, the United States is increasingly losing its competitive edge in Phase I clinical trials to countries that streamline oversight by eliminating regulatory redundancies and focusing regulatory scrutiny on higherrisk studies, enabling trials to begin up to three times faster than in the U.S. FDA should consider a voluntary pilot program akin to Australia's model to demonstrate an approach for low-risk Phase I studies in the United States. Such a pilot could explore streamlined, notification-based oversight and generating evidence to inform longer-term policy and regulatory modernization.

FDA has also taken action to better articulate how sponsors can use real-world evidence (RWE) to support FDA review. Prompted by the 21st Century Cures Act, FDA has issued guidance documents on how the agency will use RWE for regulatory actions. Most recently, FDA issued new guidance on the use of RWE in medical device premarket and postmarket decisionmaking, which provides more concrete direction to sponsors on study design, data relevance, and data quality considerations. This guidance represents an important step toward translating high-level policy goals into actionable expectations for sponsors. As stakeholders respond to FDA's most recent guidance document, FDA should consider how this feedback may inform the development of related RWE guidance for review of drugs and biologics.

FDA should also continue removing barriers and further expanding the use of digital health technologies and other tools to conduct decentralized trials. Beyond agency-wide policies, FDA must apply these approaches in its review of specific trials and product application. Innovators, and ultimately patients, benefit when FDA proactively issues guidance and helps lay the groundwork for sponsors and FDA reviewers to embrace new approaches. One area deserving additional attention is the validation of these digital health technologies for use in clinical trials. Such technologies are a key enabler for decentralized trials, allowing sponsors to collect quality data without requiring participants to travel to an academic medical center and maximize the number of patients,

including from rural areas, who can benefit from promising treatment candidates.

FDA must appropriately tailor its review of digital health technologies to the relevant risks. In some cases, FDA expects products like monitors and sensors to meet medical device-like standards, despite the fact that most do not serve the function of a medical device. Even when FDA has approved or cleared certain remote patient monitors as medical devices, FDA resists their use for data collection in their trials. FDA requires re-validation of these tools from study to study, which creates unnecessary duplication. Agencies should align on risk-based validation requirements for use across studies.

Additional obstacles hamper the use of novel trial approaches. For example, trial participants could receive care from their local doctor and community hospital or use remote laboratory testing to reduce travel for study visits. The requirements for sponsors to supervise this work are cumbersome, and the responsibilities unclear between investigators at the trial sites and the sponsor running the trial.[4] New technologies and approaches are also ripe for greater use to fulfill obligations to collect data after FDA approval. Such tools can expand the pool of patients willing to participate in post-approval studies and better enable the more convenient collection of data from patients at home or in their communities, especially in rural areas.

FDA has taken important steps to modernize its approach to evidence generation and should continue to expand these efforts consistent with the statutory principle of relying on the "least burdensome" means of generating evidence. Building on FDORA's reforms to the nonclinical testing methods FDA may rely on for drug and biologics review, FDA released a Roadmap to Reducing Animal Testing in Preclinical Safety Studies in April 2025 that outlines near-term and long-term actions to promote fit-for-purpose alternatives, enhance validation and qualification pathways for animal testing alternatives when scientifically appropriate. FDA's recent actions acknowledge the promise of technological advances and recognize the need for more human-relevant approaches, including in vitro systems, organ-on-a-chip technologies, and computational models that can inform regulatory decision-making. To fully realize these reforms, FDA should more consistently coordinate expectations for alternative evidence types across centers and review divisions so sponsors receive clear, predictable signals about how FDA will evaluate such data.

C. Assessing FDA's Approach to AI

AI-powered tools have the potential to meaningfully improve product development and review and post-market surveillance.[5] As policymakers look to translate this feedback into actionable policy, a few principles should inform FDA's work in this nascent space. First, FDA should take a focused, risk-based approach to regulating AI that guards against mission-critical risks without stifling new discoveries. FDA should focus on areas where AI outputs directly inform regulatory submissions and benefit-risk assessments, and where existing processes do not already guard against critical risks. For example, FDA's Investigational New Drug (IND) review process already ensures that drugs are safe for testing in people. More FDA requirements over how AI is used in pre-IND research would likely be duplicative of existing safeguards. FDA should take a targeted approach to regulating AI directed at specific risks and that does not deter discovery.

FDA should also be clear about its expectations for AI, including for regulatory interactions and appropriate standards. Within its statutory authorities, FDA must provide clarity about how it scrutinizes particular uses of AI and the specific organizational elements at FDA that will be involved. For example, pilot programs, like the RWE pilot Congress created in the 21st Century Cures Act, may provide experience and data to inform future work. Sponsors who seek to use AI may run into obstacles as different teams at FDA have varying levels of familiarity with, or take different approaches to, regulating the use of AI in medical products. FDA should provide broadly applicable guidance to avoid delays and provide agency reviewers with the tools and expertise needed to oversee the deployment of AI-enabled technologies. Stakeholders note difficulty in understanding

the lines of authority and decision-making at FDA, especially between crosscutting initiatives like the Digital Health Technology Steering Committee and Digital Health Center of Excellence, and committees and teams within the product-based centers. Stakeholders also tout the need for international harmonization for AI through bodies like the International Conference on Harmonization, International Coalition of Medicines Regulatory Authorities, and others.

Finally, FDA must look to qualified experts and stakeholders, as the agency will need a sufficient team of experts with relevant acumen to fully harness AI.[6] FDA will not only need to use its current authorities to hire new personnel but will also have to expand or create programs to fill gaps. For example, FDA should look to creating more external fellowships, partnerships, or other programs grow the agency's talent pipeline.

II. Supporting the Development of Cutting-Edge and Rare Disease Therapies

A. FDA's Struggles Leveraging Groundbreaking New Authorities

Scientific breakthroughs decades in the making have enabled substantial growth in the number and promise of cell and gene therapies. Through December 2025, FDA has approved 48 cell and gene therapies, including, in 2023, the first therapy to use CRISPR gene-editing technology.[7] The research pipeline continues to expand rapidly: according to the American Society for Cell and Gene Therapy, over 4,000 gene, cell, and RNA therapies are in development, a 15% increase since just the beginning of 2021.[8] As the field advances at unprecedented pace, FDA should fully leverage its new authorities and resources to deliver more treatments and cures to patients.

Against this backdrop, where rare disease drug development depends on regulatory agility and collaboration, FDA's increasing use of clinical holds has raised concern among stakeholders. Despite funding increases, there has been a pronounced increase in Center for Biologics Evaluation and Research (CBER)-imposed clinical holds over the past five years. FDA can impose holds on IND applications if the agency finds that the product in question may lead to an unreasonable risk of injury, or other deficiencies in the application or clinical trial materials. A hold prevents a trial from starting or stops any further progress if the trial is ongoing. Although FDA has 30 days to review new INDs before trials may begin, the agency may impose a clinical hold and must justify a decision in writing within 30 days.[9]

Clinical holds are highly disruptive for innovators, clinicians, and patients, often derailing complex and costly trials. Sponsors report opaque and procedurally rigid interactions with FDA, including late-stage outreach urging IND withdrawal on day 29 of the 30-day review period with little explanation, holds imposed using boilerplate regulatory citations without explanations that are specific to the trial in question, and feedback on trial design that arrives long after trials are completed. When issuing clinical holds, FDA should judiciously pursue a more transparent and constructive dialogue with sponsors in order to more expeditiously address safety concerns, without major delays to patient access to new treatments.

In 2022, Congress also updated the accelerated approval pathway. First created to address the HIV/AIDS crisis, the accelerated approval pathway allows FDA to approve new drugs based on surrogate endpoints that are reasonably likely to predict clinical benefit, on the condition that sponsors conduct post-approval studies to verify the clinical benefit of the approved drug. While the accelerated approval pathway has been successful, some sponsors were not completing the required post-approval studies in a timely way, and FDA had to use a time- and resource-intensive process to withdraw approval for drugs that failed such studies.[10]

Additionally, accelerated approvals have appeared to be concentrated in singular disease areas, potentially to the detriment of other high-need patient populations: for example, over 80% of approvals in this pathway between

2010 and 2021 were to treat cancers.[11] FDA must use its new authorities carefully, maintaining the rigor of this pathway while expanding its use to new disease areas. To help accomplish this, Congress required FDA to create an inter-agency coordinating council to support the consistent and appropriate use of accelerated approval across FDA.[12] Congress also directed FDA to update its guidance updates FDA's policies and procedures for accelerated approval, particularly to address concerns over the lag time between initial approvals under the accelerated approval program and final approval following the successful completion of confirmatory trials. Unleashing the full potential of the accelerated approval pathway may necessitate agency action to administer guidance and accountability for drug sponsors.

B. Reviewing FDA's Rare Disease Approach

While individual diseases may only impact a small population, approximately 30 million Americans suffer from one of more than 7,000 rare diseases, approximately 95% of which currently have no treatment.[13,14] As scientific advancements in studying and diagnosing rare diseases continue, the total number of rare diseases will only grow.[15] The FDA framework has long recognized that treating rare diseases—defined as affecting fewer than 200,000 people in the United States— is a unique challenge.[16] Since Congress passed the Orphan Drug Act in 1983, ushering in the "orphan drug revolution," FDA has continued to approve more drugs for rare diseases every year.[17] Indeed, 51% of new drug approvals in 2023 were for rare diseases versus 34% in 2018.[18]

Despite the progress made in treating rare diseases, challenges remain. The current drug approval framework is ill-suited for personalized medicines and often fails to recognize meaningful difference between treating hundreds of thousands of patients and treating only a handful.[19] As a result, new therapies face onerous regulatory requirements that can make development cost-prohibitive, discourage investment in small-population therapies, and push this groundbreaking work overseas. These challenges are compounded by the significant financial costs to develop a rare disease therapy. These costs are often borne by small companies, which account for approximately 70% of rare disease therapies in Phase III trials.[20] Further, traditional approaches for running and evaluating clinical trials are not designed to accommodate "n-of-1+" products, underscoring the need for a review framework that can be better adapted for these therapies.

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Consider, for example, a medicine targeting a mutation in a specific gene in the liver that causes a debilitating disease in a single-digit number of patients. Under current frameworks, a researcher must effectively start from scratch to obtain FDA approval to adapt the drug to target a different mutation on the same gene, even if aspects of the drug are well-understood and unchanged. At the same time, onerous manufacturing requirements can substantially increase the cost of creating these drugs, as FDA's one-size-fits-all manufacturing requirements differ little between a therapy that treats thousands of patients and one that treats less than five.

FDA Commissioner Dr. Marty Makary has publicly acknowledged the need to modernize traditional regulatory pathways to better accommodate therapies intended for small-population medicines.[21] For example, in January 2025, FDA announced a renewed "flexible approach" to evaluating chemistry, manufacturing, and controls (CMC) requirements for cell and genetherapies to expedite product development.[22] These are positive steps, and Congress can do more to support FDA's efforts to keep pace, including through codifying or expanding such efforts.

Unpredictability in rare disease drug review, including across divisions and offices, creates unnecessary

obstacles to investing the time and capital needed to develop these products. The individual divisions responsible for reviewing applications have widely divergent experience when it comes to rare diseases. The OCE and Office of Oncologic Diseases have reviewed the majority of approved orphan drugs.[23] Other divisions and offices have far less experience with rare disease products. Similar to the "reviewer lottery" phenomenon noted above, there can be significant divergence in executing the same statutory standard for drugs aiming to treat different rare diseases. Thus, consistency and predictability in the FDA review process would help bring more drugs to patients with rare diseases. Encouragingly, in July 2024, FDA announced a Rare Disease Innovation Hub to improve coordination across the agency and act as a single point of contact for stakeholders on rare disease issues.[24] This Hub should help better facilitate rare disease drug development, and coordinate efforts to provide more helpful guidance to sponsors. As FDA stands up this Hub, Congress should ensure that the program ultimately results in better outcomes for rare disease patients.

III. Updating FDA's Framework to Increase Competition and Innovation

A. Aligning Biologics Pathways with Current Science

When Congress passed the Biologics Price Competition and Innovation Act (BPCIA) in 2009, it created two pathways for approving biologics: a "standard" Biologics License Application (BLA) and an abbreviated BLA for biosimilars.[25] Only biologics that match the mechanism of action, conditions of use, route of administration, dosage form, and strength of an existing reference product can use the abbreviated biosimilar pathway—all other biologics are treated the same, and require a standard BLA.[26] Below are examples of the types of products that are treated as standard biologics that must establish safety and efficacy from scratch, unable to build off of existing applications that could streamline FDA's review:

- "Biobetters" that are improved versions of existing biologics, such as products modified to treat new mutations or disease subtypes;
- Biosimilars with certain physical changes, such as new routes of administration (i.e. a subcutaneous version of an injectable product that is more convenient for patients);
- New combinations of drugs to treat additional diseases; and
- New versions of "missile-payload"-type drugs, like antibody-drug conjugates, that involve new versions of products intended to treat different versions of disease.

Despite the promise of biologics, regulatory pathways for these products are limited, stifling price and competition and delaying patient access. Creating a middle ground between a full BLA and an abbreviated BLA could help address this gap. There is already a comparable intermediate pathway for small molecule drugs called the 505(b)(2) pathway. This pathway permits sponsors, where appropriate, to rely on FDA's previous findings of safety and efficacy for other drugs and published literature, allowing new products, or products with new features, to launch without having to start from scratch. The 505(b)(2) pathway for drug is used for drugs with new routes of administration (such as moving from infusion to injection), new features (such as extended release formulations), or to rely on published literature or studies conducted by third parties.[27] One analysis found that the pathway "primarily serv[es] to increase competition."[28] Extending a similar intermediate pathway to biologics would allow appropriate biosimilars and modified biologics to partially rely on FDA's existing findings, streamlining review while preserving standards for safety and efficacy.

B. The Lengthy Path to Approval for Biosimilars

Biosimilars are of growing importance to the U.S. health care system and are projected to save more than $180 billion over the next five years. Biosimilars are products that are "highly similar" to an FDA-approved biologic, such that there are no "clinically meaningful" differences between the biosimilar and the reference biologic in

terms of safety, purity, and potency. Through October 2025, FDA has approved 75 biosimilars to 11 reference products, granting interchangeability to 16 products. At the same time, approximately half of the biologics expected to lose exclusivity over the next decade do not yet have biosimilars in development.[29] As FDA continues to update its regulatory frameworks to better reflect the science underlying biosimilar development, further improvements in development efficiency could help bring lower-cost options to patients more quickly and expand competition in biologic markets.

To obtain FDA approval as a biosimilar, sponsors must demonstrate to FDA that the biosimilar is "highly similar" to the reference product through clinical studies. While not mandated in the statute, FDA has interpreted this language to sometimes require that sponsors conduct comparative clinical efficacy studies—meaning studies that compare the efficacy of the product to treat the relevant disease against the reference product. In contrast, there is no analogous requirement for generic drugs. Instead, generic small molecule drugs rely on pharmacokinetic studies to show that the body absorbs the generic drug in the same way that it absorbs the reference drug.

In October 2025, FDA issued new guidance clarifying when confirmatory efficacy studies are, and are not, needed to demonstrate biosimilarity, marking a significant step toward aligning regulatory expectations with advances in analytical characterization and understanding of biologics.[30] The guidance makes clear that these studies are not routinely required and should be reserved for circumstances where uncertainty about biosimilarity cannot be resolved through analytical, functional, and pharmacokinetic data alone. This clarification represents a positive evolution in FDA's approach and reflects the growing scientific consensus that modern analytical tools are often more sensitive and informative than clinical efficacy trials for detecting meaningful differences between biologic products.

Biosimilars may also meet the statutory criteria to be interchangeable with the reference product, allowing automatic substitution at the pharmacy level under the laws of most states. To be interchangeable, the biosimilar sponsor must demonstrate that it "can be expected to produce the same clinical result" as the reference product and that switching between the biosimilar and reference product poses no greater risk than just using the reference product.[31] In 2019 guidance, FDA recommended that sponsors conduct switching studies to support interchangeability, involving at least two alternating periods with the proposed interchangeable biosimilar and reference product.[32] By comparison, FDA routinely assigns therapeutic equivalence ratings to generic drugs without requiring additional studies beyond those needed for approval, enabling automatic substitution and rapid market uptake. In contrast, biosimilar adoption has been slower and associated with more modest price reductions.

Questions remain regarding the position the current administration will ultimately adopt on whether a separate interchangeability designation is necessary to demonstrate substitutability with a reference product, given the accumulated evidence on biosimilar safety. During the press conference announcing the October 2025 guidance, Dr. Makary also stated his view that all biosimilars should be considered interchangeable, a notable signal that FDA leadership may be open to further reform in this area. To meaningfully increase biosimilar uptake and deliver sustained cost savings for patients, Congress should consider whether additional legislative action is warranted to codify FDA's current thinking regarding the types of studies needed to demonstrate biosimilarity and interchangeability.

C. Opportunities to Increase Competition from Generic Drugs

Generic drugs are an integral part of our health care system. Approximately 90% of all drugs dispensed in the United States are generics, and they generated $445 billion in health care savings in 2023.[33] The Hatch-Waxman Act created the current regulatory framework to facilitate the approval and launch of generic drugs

after a period of exclusivity for the brand drugs that generics seek to copy. While this framework has worked well for almost 40 years, abuses still occur that unnecessarily delay generic competition. The Senate HELP Committee has advanced legislation with broad bipartisan support that seek to limit some of these abuses: the Ensuring Timely Access to Generics Act, the Expanding Access to Low-Cost Generics Act, and the Increasing Transparency in Generic Drug Applications Act, which was recently enacted into law. These bills will reduce gamesmanship and speed drugs to market and are estimated to bring taxpayers billions of dollars in savings.[34]

Building on the measures that the HELP Committee passed last Congress, Congress should consider additional reforms to maintain and further increase generic drug competition. While the overall framework has been enormously successful in bringing generic drugs to patients, certain discrete problems can unnecessarily delay more competition. Targeted reforms could help speed competition without jeopardizing the balance of the Hatch-Waxman framework.

For example, the Hatch-Waxman framework that Congress created in 1984 was not created with complex drug-device combinations (such as auto-injector pens and inhalers) in mind. The complexities of drug-device combination products have run into statutory uncertainty that can limit FDA's consideration of relevant evidence. Additionally, recent litigation in which generic sponsors were found potentially liable for patent infringement related to "skinny" labels creates uncertainty for manufacturers to invest in bringing generics and biosimilars to market.[35] Finally, despite decades of requests for more certainty regarding patent listing obligations for drug-device combinations, FDA has not weighed in. Instead, the Federal Trade Commission has stepped into the void, usurping FDA's jurisdiction and creating harmful uncertainty in the process.[36] In each case, Congress may consider reforms to help protect and strengthen generic competition.

IV. FDA's Framework for Software, Medical Device Review, and Innovation

A. Challenges in Predictability and Transparency in Medical Device Review

The Medical Device Amendments (MDA), enacted in 1976, created the first regulatory framework for premarket and post-market regulation of medical devices.[37] Under this risk-based system, devices are classified according to the risk they pose to patients and are subject to corresponding regulatory controls to provide reasonable assurance of safety and effectiveness.[38] The two primary regulatory pathways are Premarket Approval (PMA) for high-risk Class III devices and Premarket Notification (510(k) clearance) for moderate-risk Class II devices. While there are other pathways for moderate-risk devices, such as De Novo review, the overwhelming majority (approximately 99% percent) of medical devices go to market through the 510(k) pathway.[39]

Nearly fifty years later, FDA struggles to keep up with device innovation. Device manufacturers report many of the same challenges faced by drug and biologic sponsors, including delays, inconsistent review practices, and limited opportunities for real-time engagement with FDA reviewers. Stakeholders report a disconnect between the innovation-forward posture of the Center for Device and Radiological Health's (CDRH) leadership and reviewers for individual applications. This misalignment poses challenges to quickly get new devices to patients.

Congress has directed FDA over the years to provide industry with guidance on best practices in selecting the appropriate premarket submission, yet stakeholders continue to note difficulties in deciding how to bring their devices to market. Sponsors incur financial and opportunity costs to comply with regulatory requirements for each marketing pathway, particularly for sponsors who must self-select between several options available for moderate-risk devices.[40] For example, stakeholders note that the De Novo pathway, created for novel

low-to-moderate risk products lacking a predicate device, can require a level of clinical data comparable to that of a PMA application – the most stringent and timeconsuming pathway. Stakeholders note how a lack of standardized guidance on the De Novo pathway results in challenges for developers in understanding FDA's expectations, delaying devices getting to patients.

Medical device developers, especially for rare diseases and special populations, face additional hurdles in reaching patients, often lagging their orphan drug counterparts.[41] Similar to drugs, sponsors design rare disease devices for very small patient populations, offering limited market incentives for manufacturers. Over the years, Congress has directed FDA to promote the development of cutting-edge medical devices, including through the creation of the Breakthrough Devices Program in the 21st Century Cures Act for patients with lifethreatening conditions and unmet clinical needs. Despite the advantages offered through the Breakthrough Devices Program, and the potential to leverage this program for pediatric and other special populations, fewer than 10 percent of breakthrough-designated products successfully transition from concept to commercialization – a gap referred to as the "Valley of Death."[42]

FDA must continue to adapt to the constant evolution of medical products to advance patient care. As health technologies become more interoperable, it is increasingly important for sponsors to market devices, electronic health record systems, and other technologies that can exchange clinically meaningful information in a secure way. Indeed, shortly after FDA published guidance in September 2023 on the marketing of secure and interoperable medical devices, GAO released a report highlighting the pervasiveness of cyber risks to interconnected devices and deficiencies in FDA's coordination with federal partners on cybersecurity oversight.[43] As FDA continues implementing new device authorities granted by Congress, the agency could strengthen coordination with key agencies, like the Office of the National Coordinator for Health Information Technology (ONC), and collaborate with manufacturers to ensure compliance with evolving requirements. Product developers are also eager see FDA fully embrace Congress' recent directive to leverage predetermined change control plans (PCCPs), which allow developers to make certain postmarket improvements to their devices with minimal disruption.[44] This approach holds tremendous potential to expedite getting the highest performing products to patients while maintaining appropriate regulatory oversight of devices postmarket.

B. Challenges with Regulatory Pathways for Software as a Medical Device

The ability to monitor health conditions and deliver care anywhere has been amplified through the proliferation of digital health technologies, such as wearables, data analytics and predictive modeling tools, remote patient monitors, telemedicine platforms, and data trackers, among others.[45] These technologies have the potential to increase access to care, improve provider and patient engagement, and enhance the quality of health services and outcomes.[46] Expanded use of software in health care settings has clashed with FDA's current regulatory framework. For example, some software is hosted on a cloud platform, rather than on a particular physical device, to maximize functionality, minimize network costs, and safeguard collected data. FDA has historically struggled with reviewing cloud-hosted technologies, due to manufacturers' lack of exclusive control over cloud vendor decision-making.

Digital health technologies use software to either serve the purpose of a medical device or as a component in non-device products.[47] Software assists in a variety of health functions, such as clinical decision-making, tracking fitness and wellbeing, measuring drug adherence, and predicting fertility. It is constantly evolving, taking advantage of new and updated functionality and enhancing safety and security. For software used both as and in medical devices, FDA has struggled to develop a framework within current authorities with the appropriate flexibilities needed to regulate such dynamic and novel technologies. New software approaches often fit awkwardly, or do not fit at all, into FDA's traditional device frameworks.

The existing medical device framework involves the review of a static device within a specific risk classification and does not allow for much change without subsequent FDA review and authorization. As digital health technology advances and an increasing number of updates come before FDA for review, FDA's backlog may worsen, potentially overwhelming the agency. Congress should consider ways to change or supplement the existing medical device review pathways to properly evaluate software so these new products have an efficient and appropriate pathway to market.

In 2017, FDA piloted a precertification program for software similar to existing efforts in peer countries, such as the United Kingdom, Canada, and South Korea.[48] Through this program, FDA reviewed the processes by which developers would develop, validate, update, and secure their software in order to grant a certification to those developers as trusted entities. Pre-certified developers were given greater flexibility to launch software products without having to go through full product-specific FDA review. The pilot concluded in 2022 with mixed results. In its postmortem review, FDA pointed to a lack of statutory authority that disincentivized developer participation in the pilot, since the long-term viability of the program was not established.[49] FDA also acknowledged that the pilot highlighted unique challenges associated with software development and that the agency needed to improve review of software in the future.[50]

C. Unique Considerations for Medical Devices that Integrate AI

FDA has already taken important steps to consider the role of AI in health care. Its action plan to address AI and machine learning provided a first step in engaging with stakeholders to support development of these tools.[51] Yet as is the case with fast-evolving technology, the action plan is already outdated. The agency's principles focus almost exclusively on machine learning (static-model predictive AI) and do not yet address generative AI (where the same inputs will generate different outputs with each entry). While machine learning is an important component of AI, generative AI poses the greatest opportunity for leveraging technology to improve patient care. FDA will also need to evaluate how its current risk framework will approach AI applications to ensure safety and efficacy without deterring future discovery. The risk of AI tools may shift over time as algorithms are honed and tested in the real world, and FDA's framework must be nimble enough to facilitate moving these devices up or down risk classes.

Manufacturers must responsibly develop and apply AI tools to build trust. Building trust that a tool's output is accurate for its intended applications will require transparency. "Explainability" of how an algorithm is developed and implemented is important for patient and provider autonomy and decision-making. But manufacturers must also be mindful of not overloading patients and providers with more information than is meaningful or useful. There also needs to be balance between addressing bias concerns and sacrificing the quality of an AI dataset. No algorithm can entirely remove bias, but understanding bias is critically important for proper application in health care delivery and research.

FDA will need to work with other agencies within HHS, as well as government-wide, to ensure that standards and frameworks do not conflict. The National Institute of Standards and Technology has already published its own AI risk framework that should inform FDA's efforts in this area.[52] Manufacturers need consistency; Congress must ensure that they are not subject to redundant and duplicative regulation. Particularly as the White House's January 2025 Executive Order on AI directs federal agencies to remove barriers for the development and use of AI, Congress will need to affirm FDA's appropriate role and expertise in this field.[53]

D. FDA's Role in Regulating Clinical Decision Support Tools

Clinical decision support (CDS) tools are software programs, often embedded in electronic health records, intended to assist clinicians in providing clinical care to patients. They may provide administrative support;

provide recommendations to a provider about prevention, diagnosis, or treatment of a disease; suggest ways for patients to maintain or encourage a healthy lifestyle; transfer, store, and convert digital formats; display data and results; and perform other similar functions.[54] They typically integrate AI to analyze patient data and produce the most helpful alerts and suggestions. Providers themselves develop many of these tools internally using in-house data to produce notifications that alert other inhouse providers about potential diagnoses or prompt them with educational information to inform decision-making.[55] These tools provide immense value to the medical workforce and improve patient health outcomes.

Congress, in the 21st Century Cures Act, explicitly carved out many CDS tools from being defined as medical devices.[56] This rejected FDA's authority to categorize CDS tools as a medical device, except in limited circumstances. Yet FDA published guidance in 2022 exerting oversight over the use of much CDS software on the basis that such software is a medical device, conflicting with statutory definitions.[57] Stakeholders who develop and use CDS software have raised concerns with this guidance as they have historically had no regulatory interactions with FDA, including product review and required payment of user fees. Requiring FDA review of these tools will likely stifle and slow advancements in digital health. While FDA recently published revised guidance this year, it is important that FDA continue to exercise its authority within the bounds of what Congress directed in the 21st Century Cures Act.

V. Food Safety and Innovation

A. Review Over the New Human Foods Program

FDA has struggled to prevent and respond to food safety incidents, most recently in the 2022 infant formula shortage. For example, the HHS Office of Inspector General recently issued a report criticizing FDA's response to the infant formula shortage, citing a lack of an organizational structure to identify risks to infant formula and the appropriate response to maintain safety.[58]

In response to these challenges and based on recommendations from the Reagan-Udall Foundation, FDA announced a reorganization of its food safety responsibilities into a new Human Foods Program (HFP) that took effect on October 1, 2024.[59] This unified organization under a new Deputy Commissioner for Human Foods combines all of FDA's food safety functions into a single program to provide clear lines of sight into how these different parts function. Congress must ensure that this reorganization concretely advances the health of American families and protects American consumers from food safety crises, including clear goals and metrics for assessing the program's performance. This includes reviewing the Office of Critical Foods that Congress created in FDORA to prevent disruptions experienced during the 2022 infant formula shortage.

Moreover, Congress may wish to examine how the Food Safety Modernization Act (FSMA) is working. Congress passed FSMA in 2011 to improve FDA's tools to better address foodborne illness outbreaks. FSMA required FDA to issue a number of rules to prevent, detect, and respond to food safety problems. Now that FDA has largely implemented these rules, Congress needs to look at whether FSMA has actually *worked* to reduce foodborne illnesses.

In addition to FDA's role in protecting our food supply, Congress must also look at what the agency is doing to support consumer access to essential and nutritious foods that will help make America healthy again. As part of its reorganization, FDA established a new Nutrition Center of Excellence to serve as a central hub for its work to promote health and wellness. This includes managing FDA's work to promote transparency about ingredients in the foods we consume and coordinating scientific research on nutrition science. Congress should evaluate the work of this new center to ensure that it is taking meaningful steps to promote the availability of healthy food.

B. Review of Food Products and Ingredients

Nutrition has a direct and significant impact on Americans' health. The growing prevalence of obesity and other diet-related chronic diseases highlights an opportunity to improve health through better nutrition. Given FDA's role overseeing approximately 80% of the U.S. food supply, Congress and FDA should consider how the agency's processes to review food products and ingredients could be improved to better empower American families with more confidence and peace of mind.

FDA primarily reviews food ingredients two ways: approving petitions for food additives and color additives, and reviewing ingredients for compliance with Generally Recognized as Safe (GRAS) requirements. Manufacturers that submit a food or color additive petition must go through premarket review and demonstrate that ingredients are safe for human consumption. If a manufacturer determines that an ingredient is GRAS (as determined by qualified experts or through extensive real-world experience), it does not need to go through FDA review before marketing. While FDA has the authority to re-review GRAS determinations, it appears to seldom do so. Indeed, since 2010, FDA has determined that a food ingredient was not GRAS a mere 15 times.[60] Of those 15, FDA only made an official regulatory determination for one—FDA has taken ad hoc enforcement action or posted scientific memos for the others.[61] Many ingredients approved as food or color additives or found to be GRAS have not been reviewed for decades, resulting in a lack of updated scientific assessment about their safety. Moreover, FDA struggles with conducting timely reviews of new submissions. In FY 2022, for example, FDA completed review of only 57% of food and color additive petitions within the 360-day goal.[62] FDA should consider ways to ensure that GRAS determinations reflect the best available scientific evidence and work to better communicate these updates to consumers.

FDA also continues to face challenges in keeping pace with advances in food science that can provide American consumers with more healthy food options, like produce with more nutrients. The current statutory framework for regulating innovative foods, particularly those created using biotechnology, has struggled to adapt to rapid scientific advances. For example, genetically engineered (GE) foods are subject to the Coordinated Framework for the Regulation of Biotechnology. Created in 1986 and last updated in 2017, the framework outlines the roles and responsibilities of the three principal regulatory agencies with oversight over biotechnology— FDA, the U.S. Department of Agriculture (USDA), and the U.S. Environmental Protection Agency (EPA)—within the distinct statutory frameworks implemented by each agency.[63] In May 2024, the agencies issued a joint plan for regulatory reform within the coordinated framework.[64] This plan, implementing feedback from a 2022 request for information, aims to identify areas for update or streamlining, and other opportunities to address Framework gaps.

Although the plan is an encouraging sign that the agencies are working together to modernize the framework for cutting-edge products, stakeholders have well-founded concerns regarding how "coordinated" the Coordinated Framework will be in practice. Additionally, FDA's "voluntary" consultative process for GE foods from plants has become de facto mandatory, as developers face the risk of future FDA scrutiny and challenges accessing foreign markets without FDA review. This consultative process is slow, with developers reporting wait times of two years or more before FDA issues a response letter. Meanwhile, other developed countries complete their reviews in a matter of weeks, or even days. Congress should assess the extent to which the marketing pathways for these products are science-based and tailored to address relevant risks.

Conclusion

The Food and Drug Administration (FDA) is charged with regulating some of the most important products in our lives—the products that treat debilitating diseases, commonplace conditions, and that we use every day to keep our families healthy. Despite this broad mandate and FDA's regulatory complexities, the agency can be easily assessed through one question: is FDA fulfilling its responsibility of putting American patients and families first? This means ensuring safe and effective products come to market, while addressing barriers, decreasing opportunity costs, and unleashing new products that help Americans flourish. Drawing on feedback from a diverse group of stakeholders representing a wide range of perspectives, the HELP Committee has developed the following recommendations to advance FDA modernization:

- Congress and FDA should apply the "least burdensome" approach beyond medical devices to other product categories while maintaining patient safety and evidentiary standards.
- To reshore early-stage clinical research, FDA should launch a voluntary program in which FDA pilots a notification pathway for eligible Phase 1 clinical trials.
- As clinical trials continue to evolve from three-phase, sitebased studies towards more decentralized and innovative designs, FDA should continue supporting the use of digital health technologies, while ensuring that validation requirements for these tools are tailored to their relative risks.
- To ensure that AI standards and frameworks do not conflict, and that FDA grows its talent pipeline, FDA should further its partnerships across HHS agencies while expanding external fellowships.
- FDA should consider how to improve predictability in the drug review process, which should include more judicious use of clinical holds and greater transparency in its dialogue with sponsors.
- Congress should codify recent agency actions to tailor CMC requirements for therapies intended for small populations.
- To accelerate rare disease drug development, FDA should more consistently use tools like accelerated approval and better coordinate reviews across its divisions and offices.
- Congress should create a new streamlined intermediate pathway for biologics through which more innovative and affordable products can get to patients. One useful model for such a pathway is the existing 505(b)(2) pathway that allows small molecule drugs to use previous safety and efficacy findings to speed FDA review of new drugs.
- Congress should simplify the current requirements for new biologics, including simplifying the outdated interchangeability designation and streamlining the studies needed to obtain biosimilar approval.
- Congress should pass bills advanced by the Senate HELP Committee to address abuses in our health care system that permit FDA to reject frivolous citizen petitions aimed at delaying generic entry and tackling exclusivity "parking" to incentivize timely market entry of competitive generic products.
- Congress could require FDA to provide clearer guidance on the clinical data and evidence needed to support premarket submissions, especially for novel, complex health technologies.
- Congress should consider ways to change or supplement the existing medical device review pathways to properly evaluate software so these new products have an efficient and appropriate pathway to market.

- Congress should ensure that FDA implements guidance on CDS in the spirit of what it directed in the 21st Century Cures Act.
- Congress and FDA should consider how the agency's processes to review food products and ingredients could be improved to better empower American families with more confidence and peace of mind.
- FDA should consider ways to ensure that GRAS determinations reflect the best available scientific evidence and work to better communicate these updates to consumers.

The recommendations in this paper propose either implementation of new policies or prioritization of existing programs and authorities that have shown promise in facilitating medical product innovation. While FDA has made progress, there remains enormous potential for the agency to support better and more affordable products for patients. The HELP Committee looks forward to coordinating with FDA under its new leadership to promote patient access, accelerate U.S. competitiveness, and improve the health of American families.

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