A Blueprint for FDA: Recommendations to Improve Innovation and Access

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EXECUTIVE SUMMARY

New leadership at the United States Food and Drug Administration (FDA) are reevaluating policy at a time when scientific and technical advancements are rapidly accelerating development of innovative products that hold remarkable promise for patients. These tools and approaches—including innovative trial designs, sophisticated methods for developing evidence from real-world clinical practice, and systems powered by machine learning and artificial intelligence—are bringing medical products to market faster while meeting the same rigorous regulatory standards.

For the U.S. to fully realize the promise of these advancements, it is critical for FDA to update its regulatory frameworks to adapt to new technologies and methods, provide clear guidance about its regulatory expectations so that product sponsors can develop them with less uncertainty, eliminate unnecessary regulatory barriers, and ensure efficient and effective agency operations. This is an ambitious set of priorities under any circumstances, but executing them today is more complex in light of unprecedented challenges for the agency:

- The aftershocks of the COVID-19 pandemic continue to disrupt the agency, which faces a significant backlog in critical functions like inspecting manufacturing facilities[1] and a deficit in public trust.[2,3]

- Changes in the legal landscape for administrative agencies, including how courts evaluate agencies' interpretation of statutes,[4,5] mean that many FDA decisions will be subject to increased scrutiny, and the agency may need to reexamine existing rules.

- FDA as an organization has faced substantial cuts to its staff and programs, and a significant reorganization plan has been discussed.[6,7] The agency will need to find new ways to leverage its resources to accomplish core objectives without stalling medical product development through delayed feedback to product sponsors or creating unnecessary uncertainty regarding how reviews will be conducted.[8]

- Patients continue to face difficulties accessing many approved medicines, including challenges related to drug shortages and the time and cost associated with development and approval of new products.[9,10]

In the face of these challenges, agency leadership should pursue a proactive policy agenda that creates a regulatory environment responsive to both prongs of FDA's dual mission: to "protect the public health" by ensuring medical products are safe and effective, and "promote the public health" by acting "promptly," "efficiently," and in a "timely manner."[11] While maintaining rigorous standards, FDA should ensure that its programs do not create unnecessary barriers to development of medical products that benefit patients or patients' ability to access them.

Promoting innovation and access is a core part of FDA's mission, and should be a core part of the agency's medical product agenda. By defining and enforcing standards for bringing products to market, developing evidence requirements and ensuring post-market oversight, FDA fundamentally shapes medical product innovation.[12] FDA policies directly affect which products are developed, how quickly they become available, and how they satisfy patient demand for effectiveness, quality and safety. FDA should exercise these authorities not only to protect the public from unsafe or ineffective products, but also to promote the public health by enabling innovation to flourish.

FDA should also pursue policies that promote patient access. While FDA does not regulate prices of medical products, its policies have a significant impact on patients' ability to access and afford them—by affecting costs of developing and marketing products and by managing the supply of competing products in the market.[13] Policies that reduce time and cost of bringing novel products to market, while balancing innovation with competition, can deliver significant improvements to patient access and the health ecosystem.

We propose a set of recommended actions FDA should take to accelerate development of transformative medical technologies and enhance patient access. In six areas, we identify opportunities to build on existing FDA work and change course, as appropriate, as part of a proactive medical product policy agenda.

These recommendations are focused on medical product policy. The paper does not address issues in other areas of FDA's jurisdiction, and it generally does not focus on broader institutional issues, like FDA's structural organization, budget or headcount. While organizational factors affect implementation, our focus is upstream—defining policy priorities applicable in any political or budgetary environment.

SUMMARY OF RECOMMENDATIONS

1. Modernize Evidence Generation

1.1 Expand FDA's efforts to facilitate novel trial designs.
FDA should update its pilot programs to allow more programs to benefit, disseminate learnings more rapidly and better encourage the appropriate use of external control arms.

1.2 Encourage the use of patient preference information to "right-size" clinical trials.
FDA should expand its approach of encouraging patient perspectives in medical device applications to all medical products. This would improve trial design by informing endpoint selection and statistical considerations, allowing trials to better fit the needs of patients.

1.3 Develop a framework for addressing privacy considerations related to FDA's review of real-world data sources.
FDA should update its privacy framework to enable submissions with more reliance on data from real-world clinical sources.

1.4 Eliminate unnecessary burdens relating to data formatting.
FDA should eliminate the requirement to convert all real-world data into the same format as clinical trial data, which requires significant effort relative to benefit and discourages the use of relevant and reliable data.

2. Advance Innovation for Rare Disease

2.1 Provide greater specificity, consistency and predictability as to how FDA will assess the evidence for rare disease products.
FDA should standardize evidence assessment for rare disease products across all FDA centers and review divisions, potentially supporting legislation to clarify and improve consistency of regulatory approaches.

2.2 Modernize pathways for extremely rare and "n of 1" diseases.
FDA should take action to foster more scalable product development, including by leveraging its new authority to designate platform technologies.

2.3 Enable greater use of external controls in studying rare disease.
FDA should update its guidance on external controls to better facilitate their use in rare disease contexts, including in combination with other novel trial designs (such as trials involving master protocols).

3. Enhance Supply Chain Oversight

3.1 Use all available tools to clear the COVID-19 inspection backlog.
FDA should prioritize clearing the inspection backlog that developed from pausing in-person activities during the pandemic, and strategically use remote inspection tools to manage the workload.

3.2 Designate foreign manufacturing oversight a core leadership priority and evaluate options for third-party support.
FDA should prioritize foreign inspections at the leadership level and explore partnerships with nongovernmental third parties to supplement FDA's oversight capacity for long-standing foreign inspection challenges.

3.3 Develop a rating system to incentivize quality manufacturing maturity.
FDA should develop facility ratings based on advanced technology adoption beyond minimum requirements to reduce supply disruption risks, guide inspection priorities and inform payor decisions.

3.4 Incentivize and de-risk investment in advanced manufacturing technologies.
FDA should reduce the regulatory risk of using advanced manufacturing technologies (AMTs) by clarifying how existing frameworks that were designed for conventional manufacturing techniques apply to new technologies, and update its guidance on AMT designation to expand incentives for using this new statutory program.

4. Strengthen the Accelerated Approval Pathway

4.1 Facilitate more data from real-world clinical practice in confirmatory studies.
FDA's efforts to improve timely follow-through on post-market requirements should include efforts to facilitate more confirmatory studies that draw on data from real-world clinical practice.

4.2 Pursue reform strategies that address programmatic concerns while prioritizing early availability to patients.
FDA should continue reforming the accelerated approval program, including by regularizing its procedures and updating the processes for withdrawing approval and using advisory committees, while monitoring new policies to ensure they do not unnecessarily delay patient access.

4.3 FDA should minimize unnecessary duplication with other agencies.
FDA should enhance the transparency of its decisions to enable agencies such as the Centers for Medicare and Medicaid Services to minimize duplicative review and improve regulatory predictability.

5. Invest in FDA's Use and Oversight of Artificial Intelligence (AI) and Other Advanced Computing Technologies

5.1 Accelerate modernization of FDA technical infrastructure and procurement of advanced tools to improve FDA workflows. FDA should accelerate its technology modernization to improve internal operations and product reviews, shifting staff time from manual tasks to ensuring consistency with agency policy and precedent.

5.2 Build upon existing frameworks to facilitate innovative uses of AI in safe and effective medical products, including with respect to potential third-party reviews.
FDA should build upon existing frameworks for AI in medical products rather than creating entirely new regulatory approaches.

5.3 Update FDA's approach to clinical decision-support software.
FDA should revise its guidance on clinical decision support software to better reflect congressional intent and facilitate development of fit-for-purpose tools.

6. Advance Drug Competition

6.1 Continue the Drug Competition Action Plan and Biosimilars Action Plan, and update them to account for changes under the 2022 Inflation Reduction Act (IRA).
FDA should devote sufficient resources to continue activities with a successful track record and update its plans to account for IRA provisions that may reduce incentives for generic and biosimilar development.

6.2 Further streamline the pathway for interchangeable biological products.
FDA should update its policies to provide a clearer pathway for licensing interchangeable products without the need for switching studies.

RECOMMENDATION 1: MODERNIZE EVIDENCE GENERATION

Key takeaways:

- Innovative methods and technologies offer the opportunity to develop the evidence to meet FDA's rigorous standards more efficiently, and to answer questions that might not be possible using traditional methods.
- FDA has helped advance these innovations through early-stage interactions with developers and guidance that provides greater certainty regarding regulatory expectations.
- FDA should further prioritize early-stage interactions and expand opportunities to help developers de-risk their use of innovative tools.
- FDA should update its guidance to help developers better identify appropriate use cases for novel approaches.
- FDA should incorporate quantitative patient preferences to inform clinical trial design.
- FDA should develop a framework for addressing privacy considerations related to its review of real-world data sources.
- FDA should eliminate unnecessary burdens relating to data formatting.

Modern technologies and methods are revolutionizing how medical products are developed. By implementing innovative trial designs and making better use of data from real-world clinical practice, product developers can generate the evidence needed to demonstrate safety and effectiveness more efficiently while meeting the same rigorous standards, answer questions they previously could not, and accelerate patient access to beneficial treatments and cures.[14,15] FDA should expand its current efforts to facilitate adoption of these approaches.

Historically, the evidence needed to support approval of a drug or biologic has consisted of two "adequate and well-controlled clinical investigations,"[16] often taking the form of randomized controlled trials (RCTs). RCTs are considered the gold-standard approach to generating evidence due to randomization's ability to minimize bias, but they can be time consuming and costly and provide limited information about how products perform outside of a highly controlled setting.[17] In the current development ecosystem, it takes an average of nine years to develop a new drug from the start of the first phase of clinical studies to submission of an FDA marketing application,[18] and the cost of bringing a new drug to market averages $314 million to $2.8 billion, accounting for the costs of failed research.[19]

Supplementing traditional RCTs with advanced evidence-generation techniques can introduce much-needed efficiencies, including:

- Streamlining trial activities, including by using technology to reduce the burdens of conducting and participating in trials
- Making better use of the data that are already being created in our health system, which can reduce unnecessary costs and burdens to patients and the broader health care system
- Providing data and outcomes beyond what typically can be learned in the controlled setting of an RCT, including information about products' performance in real-world settings

But these techniques can also be challenging to implement: They are often methodologically complex, and identifying appropriate circumstances for using each tool is not always straightforward.[20–23] As a result, a developer interested in using an innovative approach may face considerable uncertainty regarding whether FDA will agree with how it navigated various complexities and how the product will fare before a reviewer who may never have encountered the approach before.

To help address these challenges and accelerate the potential benefits of modern techniques, Congress, as part of the 21st Century Cures Act in 2016, directed FDA to develop programs and guidance to advance the use of novel trial designs and evidence from real-world clinical practice.[24] Since that time, the agency has taken a number of responsive actions, including by issuing guidance documents to help developers address technical and methodological issues. For example, FDA has issued draft or final guidance documents to meet the requirements of the 21st Century Cures Act and otherwise advance modern evidence generation techniques:

One trial designs: Demonstrating substantial evidence of effectiveness with one adequate and well-controlled clinical investigation instead of two, plus confirmatory evidence (e.g., evidence from related products, evidence of disease progression absent treatment, evidence from real-world clinical practice)[25]

Master protocols: Using a single trial to study (1) multiple products for the same disease or condition, which can be done (a) concurrently (umbrella trials) or (b) with products entering or leaving on an ongoing basis (platform trials), or (2) multiple diseases or conditions that might be treated by a single product (basket trials)[26]

Adaptive trials: Using trial designs that can be modified based on accumulating data from the trial

Decentralized trials: Conducting trials in which at least some activities are conducted outside of traditional clinical trial sites, such as by using wearable technologies[29]

Real-world data and evidence: Using data from real-world clinical practice (such as electronic health records, medical claims data, and patient registries) to generate evidence about the safety or effectiveness of a medical product[30–32]

Externally controlled trials: Using data from outside a clinical trial (such as data from another trial or from real-world clinical practice) as the control arm, instead of randomizing patients into a placebo or other control group[33]

Trials integrating clinical practice: Designing randomized trials that can be integrated into routine clinical care (e.g., collecting additional data during routine patient visits)[34]

In addition, FDA has also been engaging directly with product developers through public workshops and programs to provide additional feedback and support.[35–38] Both the guidance and these feedback opportunities help de-risk the use of innovative approaches by reducing regulatory uncertainty regarding how FDA will review the evidence these approaches generate.

These efforts mark important progress, but there is still much work to be done. While an increasing number of studies are deploying innovative trial designs like master protocols and adaptive elements,[39–41] and FDA has approved several products that used real-world evidence (RWE) as the primary evidence of effectiveness,[42,43] implementation is still in its early days. For example, while the use of RWE in marketing applications has become increasingly common—85% of novel applications for new drugs or biologics use real-world data in some way—sponsors use this RWE mostly to bolster other evidence or provide therapeutic context (e.g., prevalence or incidence of a disease), not as the primary evidence of safety or effectiveness.[44] FDA can do more to expand its current efforts and provide the regulatory clarity and policy reform necessary to eliminate unnecessary barriers and facilitate more substantial use by sponsors of innovative approaches.

Prioritizing these actions has even greater significance in light of disincentives created under the 2022 Inflation Reduction Act (IRA). Under the IRA, the Centers for Medicare and Medicaid Services (CMS) imposes a substantially reduced rate for Medicare reimbursement—called a "maximum fair price"—as early as nine years after a drug is first approved (or 13 years for a biologic), regardless of whether the product is subsequently approved for additional uses (or populations, doses, etc.).[45] This means, for example, that if a drug is first approved in a relatively small population, and additional research results in that drug being approved for use in a larger population eight years later, a significantly lower reimbursement rate could take effect as soon as one year after the subsequent approval, leaving the sponsor with limited time to benefit from sales to the larger population at a higher reimbursement rate. The result is effectively a lower expected return on investment for research that leads to subsequent approvals, which could reduce incentives for conducting such research.[46] Approaches to evidence generation that lower the time or cost of development can make research supporting subsequent approvals more feasible at the margins in this environment.

Recommendation 1.1: Expand FDA's efforts to facilitate novel trial designs

FDA has made important progress in its efforts to facilitate greater use of novel trial designs, but the agency can do considerably more to help ensure that developers have appropriate guidance and clear and predictable regulatory frameworks for implementing innovative techniques in evidence generation.

First, FDA should expand its programs to provide meetings and individual guidance to developers who are using cutting-edge approaches to evidence generation. These programs provide product sponsors with important guidance as to how FDA will approach specific approaches while also providing the agency with deeper experience that it can use to mature its own thinking. For example:

- In 2018, FDA launched a pilot, the Complex Innovative Trial Design Meeting Program, to support facilitating and advancing use of complex adaptive, Bayesian and other novel clinical trial designs by offering selected product sponsors for increased interaction with FDA staff to discuss their proposed approaches. Based on the success of the pilot, the program has been continued on a more permanent basis.[37,47]
- In 2022, FDA launched the similar Advancing Real-World Evidence Program to support sponsors proposing to use of evidence from real-world data sources for regulatory purposes.[37]

These programs have been successful but are limited in their reach; only a small number of development programs are actually accepted for enhanced support. FDA should:

1. Accelerate its expansion of these programs to allow more products to benefit
2. Develop and implement strategies to disseminate learnings more rapidly so that they are consistently and predictably reflected in product reviews across the board
3. Prioritize other opportunities for early engagement outside the context of established pilot programs, such

as user-fee funded meetings that provide initial targeted engagement (such as INTERACT meetings),[48] to enable more meetings to be granted on a timely basis

4. Pursue dedicated funding streams, and explore innovative new user fee models, to facilitate more of the early engagement that can help de-risk and facilitate innovative approaches

FDA should also do more to encourage the appropriate use of external control arms (ECAs). Although randomizing patients into a control group is often the best method for eliminating bias in a study, ECAs can, when used properly and in suitable contexts, offer considerable benefits, such as by enabling research in situations where randomization may not be feasible or ethical (e.g., in very small patient populations), allowing more patients to benefit from the product being studied, and reducing the size and cost of trials.[49,50] Although external controls can be challenging to implement, many of these challenges can be abated with appropriate trial designs and analytic approaches.[21] Indeed, analysis of FDA approval decisions shows that the agency has long been able to approve a substantial number of products without a traditional randomized control: From 1999 to 2014, 60 different indications were approved without an RCT, and 80% of those approvals were in products for which an RCT was not conducted for *any* indication.[51]

FDA should help product developers better understand the benefits of using ECAs and identify appropriate use cases that can be supported by current best practices. The agency's current draft guidance instead focuses on the limitations and complexities of using ECAs, with little to no discussion of when and how ECAs can be beneficially deployed, or the benefits of using existing data when possible.[52] This is an unfortunate omission: While it is important for practitioners to be aware of potential pitfalls, addressing challenges without also providing examples and guidance may discourage ECA adoption. In addition, FDA should prioritize issuing guidance on topics critical to the use of ECAs that it has previously left out, such as using an external control to supplement a control arm in a traditional randomized trial[52] or using a master protocol to study multiple interventions using a single external control.[53]

Recommendation 1.2: Encourage the use of patient preference information to "right-size" clinical trials

FDA already encourages medical device companies to include patient perspectives throughout the medical device lifecycle, particularly in clinical trial design, to ensure that device clinical studies evaluate what matters most to patients.[54] By expanding this approach to all medical product evaluations (including drugs and biologics as recommended in statute[55]), patient preference information (PPI) that is appropriately collected in alignment with FDA guidance[56] can significantly impact the design of clinical trials, ensuring that trials focus on outcomes that matter most to patients, improve the patient experience, accelerate enrollment, increase retention and long-term follow-up, and improve data quality.[57] Clinical trial design is the stage of product development where PPI can be most impactful because it can help shape which data and what kind and quality of data are to be collected, which often informs downstream decisions (e.g., regulatory approval, health technology assessment, market access, payment and coverage decision-making, and provider prescription behavior).[58] By understanding what outcomes are most important to patients, researchers can design more patient-focused clinical trials that:

- Ensure all relevant outcomes that matter to patients are included in endpoint measurement
- Reduce the number of endpoints in a study to focus on those that matter most to patients
- Establish acceptable endpoint thresholds for evaluating the success/failure of a technology's ability to achieve an endpoint
- Inform the design of a composite endpoint within a clinical trial and how to appropriately weight each element within the composite
- Inform statistical considerations of clinical trial design, such as sample size, significance threshold and power[58]

Some patients—for example, those with a serious medical condition, rapid disease progression and/or lack of effective therapies—may be willing to accept more uncertainty about the benefits and risks of using a new medical product in exchange for having access to it sooner. In such cases, it may be preferable, from a patient and society perspective, to design a clinical trial with a smaller sample size so the study can be completed in a shorter timeframe or incorporate a higher level of statistical uncertainty. These preferences can be systematically incorporated into trial design through quantitative approaches. For example, researchers have developed a statistical framework that uses Bayesian decision analysis to transparently incorporate patient preferences when setting a statistical significance threshold in clinical trials.[59,60] FDA should explicitly incorporate this or similar approaches into its frameworks for evaluating drugs and biologics in addition to devices and provide this guidance to product sponsors.

Recommendation 1.3: Develop a framework for addressing privacy considerations related to FDA's review of real-world data sources

As medical product research increasingly makes use of real-world data sources, such as electronic health records and claims for payment, FDA will need to address data privacy in ways it has not previously. Although FDA does not regulate patient privacy, the review of data derived from real-world clinical practice raises privacy considerations that the agency will need to account for in its policies. Unlike traditional clinical trials, in which patient data are generally collected under protocol, many RWE studies involve secondary analysis of

data originally created for non-research purposes, such as care delivery and billing.[61] These studies commonly use data from which patients' identifying information has been removed to protect privacy and comply with laws such as the Health Insurance Portability and Accountability Act (HIPAA).[62] FDA, however, has not yet developed a framework for reviewing such studies while maintaining the built-in privacy protections.

FDA has advised product sponsors that they should ensure FDA has access to the identifiable patient source records underlying these studies.[63] This access is important for agency reviewers to assess the reliability of the data and is comparable to what FDA has historically expected when reviewing traditional clinical trials.[64] But in the context of a study using anonymized data from clinical practice, providing this access raises novel issues that FDA has not yet addressed.

For example, the researchers working with anonymized data may have obtained the data from a third-party organization and may not themselves have access rights to the underlying patient source records (for good reason, from a privacy perspective), and a sponsor trying to negotiate access rights for FDA from an upstream data provider could face a variety of challenges, including:

- The data provider may need assurances regarding FDA's ability to protect the data, particularly considering federal disclosure laws such as the Freedom of Information Act (FOIA).
- Foreign privacy laws may limit the sharing of data from foreign jurisdictions (such as in Europe) with a U.S. regulator.[65]
- If the data provider uses a mechanism to share information with the FDA that the researchers cannot themselves access,[63] it creates regulatory risk and uncertainty for sponsors who may worry that their applications could be negatively affected by information they do not have.

FDA should proactively address these concerns to remove potential barriers to the use of RWE in marketing applications. It can do this by first providing greater public transparency and assurances as to how it will protect patient-identifiable data, including in the context of FOIA requests, which would help sponsors negotiate agency access rights to the extent they are needed. FDA should also prioritize negotiating data access programs with foreign regulators so that FDA is able to review data from global development programs as readily as it can from domestic research.

In addition, FDA should pursue policies that reduce uncertainty regarding how it will assess a given data source, which could facilitate more FDA-facing research using anonymized data. FDA staff recently published a journal article describing the agency's general perspective on data inspections,[66] but a high-level discussion in a medical journal does not provide formal guidance to industry or staff. FDA should provide actionable guidance regarding when and how it will conduct inspections of data sources—a significant gap in its current suite of guidance—as well as measures to promote greater standardization in how underlying records from routine clinical care are curated and transformed into research-ready data sets. There is currently no industry-standard method for conducting these transformations,[67] which increases regulatory uncertainty by requiring bespoke assessments. If data sources could be certified as meeting a recognized standard, similar to certifications in other contexts, [68,69] it would reduce uncertainty regarding data quality and streamline regulatory reviews. FDA should facilitate adoption of such a standard by working to identify best practices, including through demonstration projects designed to identify data-processing techniques associated with a high degree of data quality, and incentivizing their use by clarifying how doing so would enable more efficient and predictable regulatory reviews. These incentives might include, for example, policies identifying circumstances in which the agency's review of patient-level data is unnecessary because the curation practices are validated and well-understood.

Recommendation 1.4: Eliminate unnecessary burdens relating to data formatting

In late 2023, FDA finalized guidance imposing a requirement that when data from real-world sources are submitted to the agency as study data in support of many types of product applications, that data must be formatted according to the same requirements that govern data from traditional clinical trials.[70] (Unlike FDA's guidance on most topics, which contain nonbinding recommendations, its guidance on formats for electronic submissions may contain binding specifications.[71] But these formatting requirements are a poor fit for many real-world data sources. Whereas a clinical trial can be designed so that data collected during the trial are recorded in the format FDA specifies, a study using data collected for other purposes cannot specify how the data were recorded, and the researchers would need to convert the data if FDA requires a different format. Unfortunately, that conversion process is labor intensive, time consuming, prone to human error that diminishes data quality, and can lead to the loss of detail in both the data fields themselves and in the metadata that can help contextualize the information and support reviewers to assess the data's relevance and reliability (e.g., information about where and how the data were generated).[70,72,73]

These burdens may be necessary in some circumstances—such as when data from real-world sources are being used alongside clinical trial data collected in a regulator-specified format, to facilitate apples-to-apples analysis—but the benefits are far less apparent in studies involving only data from real-world sources, where comparison to data in other formats is not needed, and the labor-intensive data conversion process can introduce human error and other issues that diminish data quality. FDA should revise the guidance and provide additional flexibilities to eliminate this burden (and additional risks to data quality) when it is not necessary to facilitate the study.

RECOMMENDATION 2: ADVANCE INNOVATION FOR RARE DISEASE

Key takeaways:

- Rare diseases affect an estimated 30 million Americans and impose substantial burdens, but only about 5% of those diseases have FDA-approved treatments.
- Developing rare disease therapies is uniquely challenging due to factors such as the small patient populations and often limited understanding of the diseases.
- Products for rare diseases must meet the same approval standards as other products, but FDA has taken a pragmatic approach to determining what evidence is needed. While this more flexible approach has enabled innovative approaches, developers lack predictability as to how FDA will apply its requirements.
- FDA should provide greater specificity, consistency and predictability by finalizing draft guidance, promoting greater coordination through the Rare Disease Innovation Hub and working with Congress to codify certain approaches.
- FDA should support scalable approaches to developing products for extremely rare and "n of 1" diseases, including by expanding the Platform Technology Designation Program for Drug Development to specifically address rare diseases.
- FDA should enable greater use of external controls in studying rare diseases.
- FDA should address the impact of the IRA on rare disease therapy development.

As FDA works to facilitate modern approaches to evidence generation, it should give particular focus to advancing the frameworks for developing treatments and cures for rare diseases. There are as many as 10,000 identified rare diseases (defined as any disease or condition that affects fewer than 200,000 people in the United States) that affect an estimated 30 million Americans, but only about 5% of those diseases have FDA-approved treatments.[74] Many of these diseases involve severe or life-threatening conditions that worsen over time and impose substantial and tragic burdens on American families, including many progressive conditions that impair children's development and cut short their lives.[74,75] Rare diseases also impose substantial economic burdens: One recent study found that the 2019 U.S. costs associated with 379 rare diseases were $997 billion.[76]

Unfortunately, developing drugs and biologics for rare diseases involves distinctive scientific, clinical, and ethical challenges. Small and often heterogenous patient populations can make traditional, randomized clinical trials infeasible, and the severity of many rare diseases can make the ethics of placebos especially challenging. In addition, there is often limited information on what course the disease takes absent treatment (often referred to as its "natural history"), which can make it difficult to generalize from anecdotal reports or know what outcomes to measure when studying a treatment. And many rare diseases progress slowly, meaning that it can take years to tell what effect, if any, an investigational treatment may have. For a patient who is not receiving that treatment as part of a study, waiting years for a trial to be completed could have severe or fatal consequences.[74,77,78]

FDA has launched a variety of programs to help address these challenges, including programs to advance scientific knowledge and provide early support for rare disease development programs.[79–81] In late 2024, it established a Rare Disease Innovation Hub to coordinate activities across the agency's drugs and biologics centers.[82] In addition, while products for rare disease must meet the same approval standards as other products, FDA has taken a pragmatic approach to determining what evidence is needed to meet these standards. This approach has included flexibility on the design, size and number of clinical trials needed to demonstrate substantial evidence of effectiveness; using surrogate endpoints (early markers of a product's effect that are predictive of its eventual clinical benefit) when possible to reduce the time needed to study a product before approval; using the accelerated approval pathway to enable more timely patient access based on a likelihood of clinical benefit; and accepting greater uncertainty about a product's effectiveness when it would address a significant unmet need and developing more robust evidence is not feasible.[83]

These steps mark important progress in addressing the regulatory challenges of developing rare disease products, but much more can and should be done. FDA should prioritize actions to further advance innovative product development to address the serious unmet needs in this space.

Recommendation 2.1: FDA should provide greater specificity, consistency and predictability as to how it will assess the evidence for rare disease products

As FDA continues to develop and refine its policies for regulatory pragmatism in rare disease product development, it should prioritize actions to ensure that its policies and approaches are consistently and predictably applied across centers and review divisions. Reducing regulatory uncertainty is important in any context, but particularly so when addressing rare disease, because (1) the challenges of development using conventional methods often leads developers to rely on innovative methods for which there may be limited precedent; (2) small patient populations may limit opportunities for financial return on investment, thereby making regulatory

certainty all the more important; and (3) developers targeting a particular rare disease area may have product candidates that fall into multiple product classifications (e.g., drugs, biologics and medical devices), such that consistency in regulatory feedback is critical.

A recent report by the U.S. Government Accountability Office found that product sponsors are concerned about the consistency with which FDA applies its review standards to rare disease development programs. In one example, a sponsor reported an experience in which one FDA product center was reluctant to accept a surrogate endpoint for a disease even though another center had already accepted the same endpoint for the same disease.[83] When regulatory standards are applied inconsistently, it creates uncertainty as to what approaches are likely to pass muster. By applying its authorities more predictably, FDA can reduce this uncertainty and facilitate more product development that is likely to align with regulatory expectations.

FDA can take several concrete steps to advance this goal:

First, it should prioritize revising and finalizing the draft guidance documents it has already issued. In 2021, an FDA-commissioned analysis of decision-making on "borderline" applications found that the agency "has no mechanism to find or tradition to cite similar cases when weighing evidence for approval, resulting in stand-alone, bespoke decisions."[84] Even if agency staff are willing to think flexibly about what evidence of effectiveness is required for each rare disease, it is difficult for product sponsors to invest in development programs when it is unclear how reviewers will apply the agency's evidentiary requirements in any given case. Written guidance documents can help.

Although FDA guidance documents generally are not legally binding, they represent the agency's "current thinking," and FDA staff cannot depart from them without "appropriate justification and supervisory concurrence."[85] They provide a common touchpoint for reviewers and product sponsors alike and, as such, can introduce additional predictability and stability into the process. FDA can improve its guidance on rare disease in two key respects:

- *Provide more specific examples:* FDA should update its guidance to provide more case studies, hypothetical or real, that can guide reviewers and help align individual product decisions toward a more consistent agency policy.
- *Finalize draft guidance:* Unlike final guidance, draft guidance documents are issued for comment purposes only and are not meant for agency-wide implementation.[85] Although FDA has finalized some of its guidance on developing treatments for rare diseases,[86] much of the guidance describing approaches in this area is still in draft form, including guidance on early drug development,[87] natural history studies[88] and demonstrating substantial evidence of effectiveness.[83] Finalizing this guidance would enable the agency to formally implement the policies and better educate its reviewers to ensure consistent practices.

Second, FDA should empower the new Rare Disease Innovation Hub to promote consistent practices. The Hub was established with the explicit goal of "enhanc[ing] intercenter collaboration," including by addressing "cross-disciplinary approaches related to product review" and promoting "consistency across offices and Centers."[82] FDA should ensure that the Hub has the delegated authority and resources necessary to effectively meet these goals and practice, and that it does not simply become an added layer of bureaucracy.[89] To this end, the agency should report regularly on the specific work the Hub is doing to advance these goals, including its progress on efforts described in its strategic agenda,[90] the authorities and resources it is being given to do so, and the progress it is making to build a library of precedents that will enhance predictability for drug developers. If the Hub is successful, it would not only benefit the rare disease community, but it could serve as a model for other non-rare disease products to promote regulatory alignment across therapeutic areas regardless of the product modality.

Third, FDA should work with Congress to develop legislation that codifies many of the pragmatic approaches already being utilized. Such legislation would promote clarity and predictability by providing reviewers and developers alike with direct statutory language. This legislation should include specific direction on the use of quantitative patient preference information to guide FDA on the acceptability of varying uncertainty levels in its regulatory decisions, including with respect to clinical trial design and the ultimate benefit/risk approval assessment.[56,91]

To be clear, the approaches FDA has been using are fully consistent with existing statutory authorities; although the same approval standards apply to all drugs and biologics without regard to the prevalence of the underlying disease or condition,[92,93] FDA has considerable flexibility in how it applies those standards to weigh the benefits and risks presented by individual products.[94] However, the lack of statutory language addressing certain concepts—such as FDA's ability to accept a higher degree of uncertainty in appropriate contexts—can make it more challenging to ensure that those concepts are utilized appropriately across the board.

In advancing such legislation, it will be important not to inadvertently diminish existing authorities or approaches already being used in the rare disease context or otherwise. For this reason, any legislation should include language clarifying that (1) codifying the availability of particular approaches does not imply that the flexibility of using that approach is not available in other circumstances, and (2) FDA retains the flexibility to use approaches that are not specifically identified in the legislation.

Recommendation 2.2: Modernize pathways for extremely rare and "n of 1" diseases

The challenges associated with rare disease product development are particularly acute for extremely rare and "n of 1" diseases, in which the population (n) of people with the disease may be as small as just one or a few individuals.

Developing drugs and biologics in this context uniquely challenges the traditional frameworks for clinical research. For example, when the population is this small and there is limited information about how the disease might progress untreated, it can be difficult to know what effects—positive or negative—should be attributed to the treatment, or what dose and treatment regimen are most appropriate.[95] In addition, when the entire known universe of people suffering from the disease may be already receiving the product as part of a study, practical considerations may lead many researchers to maintain the product in perpetual study rather than pursue a regulatory approval for which there is no clear pathway. Given this reality, it is unsurprising that FDA's guidance on extremely rare and "n of 1" drug development is focused on helping academic researchers navigate the regulatory requirements of FDA's framework for studying investigational new drugs (INDs), not with submitting an application for product approval.[96]

Against this regulatory backdrop, the path to scalable commercial development for these products is highly uncertain. Much of the research is being conducted by academic investigators who do not have the experience or infrastructure to support large-scale development.[97] Nor is such development feasible while the products remain in investigational status under FDA's IND framework, which imposes strict limits on how drugs can be promoted, commercialized or compensated before they receive FDA approval.[98,99] Although there is precedent for some products to remain in investigational status for decades, supported by nonprofit organizations or the government,[95] that model is not designed to facilitate innovation at scale. FDA can be doing more to facilitate such innovation.

First, FDA should support scalable efforts to study products for multiple "n of 1" diseases as subgroups of broader diseases or conditions. As we gain greater understanding of the pathophysiology of various diseases, opportunities increase to categorize many diseases into subgroups, each responding differently to a given treatment, that can be researched in precise ways while leveraging shared infrastructure.[100] FDA should support efforts to research "n of 1" diseases under this model, such as through multiple smaller trials under a single umbrella (or in a single basket) that share common data standards and endpoints. To this end, the Rare Disease Innovation Hub should specifically include such efforts as part of its work to advance methods development including novel endpoints, biomarker development and assays, innovative trial design, real world evidence and statistical methods.[101] It should also look to learnings from efforts and pilot projects in other jurisdictions, such as the Rare Therapies Launchpad in the United Kingdom.[102]

Second, FDA should do more to facilitate greater use of section 506K of the Federal Food, Drug, and Cosmetic Act in the context of extremely rare disease. This provision, which Congress added in late 2023, authorizes FDA to designate certain technologies that can be used across multiple drugs or biologics (e.g., a nucleic acid sequence, molecular structure or vector) as "platform technologies," and then facilitate more streamlined development for products that incorporate these designated technologies.[103] This new authority has the potential to revolutionize development for extremely rare and "n of 1" diseases by enabling multiple products that share a common chemical backbone or other feature to achieve scalable efficiencies.

Unfortunately, FDA's recent draft guidance on the 506K designation program does not mention rare diseases at all.[104] This is a missed opportunity. FDA should revise the guidance to provide clear direction on how programs seeking to develop products for multiple extremely rare or "n of 1" diseases can use 506K designation to achieve efficiencies and scale not possible when developing each extremely rare product on a wholly distinct basis. FDA should also provide further guidance as to how such development programs can navigate the regulatory restrictions on commercializing investigational products[98,99] when building a commercial program around a designated platform technology. These guidance updates should be a priority regardless of whether FDA expects a critical mass of readily deployable platform technologies soon, since greater regulatory certainty can help provide a foothold for novel commercial arrangements.

Recommendation 2.3: Enable greater use of external controls in studying rare disease

Rare disease studies are often the clearest cases that would benefit from using ECAs, given that the patient populations are often too small to support traditional controls, and it can be ethically fraught to withhold potentially effective treatments from patients who have no other treatment options.[50,105,106]

Unfortunately, as discussed under Recommendation 1.1, FDA's existing guidance on ECAs could be read as overly discouraging, given its emphasis on challenges to the exclusion of helping developers identify appropriate use cases. As FDA updates this and other guidance to present examples and considerations for beneficial use cases, it should ensure that it addresses the unique challenges and opportunities associated with using ECAs for rare disease development. In its current form, FDA's draft guidance on ECAs does not address rare disease as distinct from other disease areas.[33] The guidance should be revised to provide specific considerations for rare disease.[107] In doing so, FDA should cross-reference and expand upon its draft guidance on natural history studies for rare disease, which contains a short discussion of using natural history studies as ECAs.[108]

FDA should also facilitate design approaches in which ECAs are used in connection with master protocols. For example, master protocols can be used to collect information for use as an external control in a subsequent trial,[109] or to enable the use of a single ECA to study multiple candidate treatments. However, external controls are carved out of the scope of FDA's draft guidance on master protocols.[53] FDA should update the guidance to include these topics and help guide innovative approaches.

RECOMMENDATION 3: ENHANCE SUPPLY CHAIN OVERSIGHT

Key takeaways:

- Medical product shortages jeopardize patient care and impose significant costs on the healthcare system, including over $600 million per year for American hospitals.
- Most drug shortages are caused by manufacturing disruptions, most frequently with older, low-profit medicines.
- FDA continues to struggle with overseeing foreign drug manufacturing with the same rigor that it applies to domestic facilities.
- FDA should leverage remote inspection authorities as supplemental tools to end the COVID-19 inspection backlog.
- FDA should designate foreign manufacturing oversight as a core leadership priority and evaluate options for third-party support.
- FDA should develop and implement a rating system to incentivize quality manufacturing maturity.
- FDA should incentivize and de-risk investment in advanced manufacturing technologies to help reduce supply disruptions and address national security risks.
- FDA should address the impact of the IRA on rare disease therapy development.

As FDA works to advance the availability of critical medical products to patients, it should prioritize efforts to address drug shortages and other supply chain disruptions.

When medical products go into shortage—meaning that the supply in the United States is not sufficient to meet demand—there can be significant impacts for patients and the broader healthcare system. Patients may face delays or disruptions in their treatment, which can lead to negative health outcomes and higher costs of care, and care providers may incur substantial costs managing the impacts, which can total over $600 million per year for American hospitals.[110,111] To reduce these burdens, a more resilient supply chain is needed.

FDA has made progress on combating drug shortages, but there is still considerable work to be done. While the number of drug shortages has declined significantly from its peak of 251 new shortages in 2011, the number worsened during the COVID-19 pandemic: FDA recorded between 40 and 55 new shortages per year from 2021 to 2023.[112] In addition, drug shortages have been lasting longer—in some cases eight years or more—so the number of ongoing shortages is also increasing.[110,112] Moreover, many drugs in shortage are essential medicines,[113,114] including common chemotherapeutic agents whose shortages could create significant challenges for cancer patients and their providers.[115,116]

While some shortages are driven by spikes in demand, most are precipitated by disruptions in production due to manufacturing problems.[111] These disruptions occur most frequently among drugs that share a certain profile: They tend to be older, off-patent drugs with low profit margins.[110] They also tend to be among the more difficult drugs to manufacture properly—most are injectable drugs, which must be produced in sterile environments.[110] Drugs with this profile tend to go into shortage more frequently because they face several fundamental economic challenges. Low profit margins—particularly for drugs that are more complicated to make—limit economic incentives for additional manufacturers to enter the market, or for existing ones to invest in cutting-edge manufacturing technologies (above and beyond minimum regulatory requirements) that might reduce the risk of disruption. Even after a product goes into shortage, high startup costs (including the regulatory approval process) can make it challenging for new entrants to step in to help meet demand in a timely manner.[110]

One way for FDA to mitigate the risk of shortages is by conducting timely facility inspections, through which it can identify emerging problems in manufacturing quality and work with the manufacturer to address them before they reach the point of disrupting production, or before unsafe or ineffective products make their way to patients. Unfortunately, two major barriers are impeding this early detection capability.

First, FDA limited in-person inspections during the COVID-19 pandemic, which created a substantial backlog that continues to persist.[117] As of September 2024, 42% of registered drug manufacturing facilities had not been inspected in over five years.[117] When problems with manufacturing quality go undetected, they endanger patient safety and increase the risk of supply disruptions that could lead to shortages.

Second, a substantial portion of the drugs produced for the U.S. market—both active ingredients and finished products—are now produced in foreign facilities where FDA historically has struggled to provide adequate oversight. As of January 2024, 58% of all pharmaceutical manufacturing sites subject to FDA inspection were located outside the United States, with nearly 40% of foreign facilities concentrated in India and China.[118] FDA issues a disproportionate share of warning letters to manufacturers in these two jurisdictions, including for serious violations like the presence of carcinogens in medicine, destroying or falsifying data, and not following sterile manufacturing processes when required.[119] Even though all drugs produced for the U.S. market are legally subject to the same manufacturing and quality requirements, the practical challenges associated with conducting inspections in certain foreign jurisdictions have made it harder for FDA to ensure the applicable rules are being followed across the board.[118]

The agency conducts many more foreign inspections than it used to;[118,120] however, significant challenges remain—even after decades of effort. For example, the agency has continued to struggle with critical issues such as hiring and retaining qualified staff to conduct inspections in foreign facilities, obtaining timely visas and other forms of clearance from foreign governments, securing reliable interpreters and conducting inspections on an unannounced basis (to minimize opportunities for manufacturers to conceal problems) similar to what FDA has historically done for domestic facilities.[118,120]

The upshot of these persistent logistical challenges is that, in key respects, foreign manufacturing facilities may still be able to avoid the same level of regulatory scrutiny as their domestic counterparts. From a policy perspective, this is exactly backward. Given the geopolitical risks associated with the United States relying on foreign countries like China and India for critical medicines and their active ingredients,[121] the United States should be encouraging more domestic manufacturing—or, at the very least, reducing unintentional disadvantages.

Recent actions by the White House and FDA will help the agency advance this goal. In May 2025, President Donald Trump issued an executive order directing FDA to enhance its inspection of foreign manufacturing facilities and promote domestic production of critical medicines,[122] and FDA announced that it will expand the use of unannounced inspections at foreign facilities.[123] As FDA continues to carry out the executive order and take additional steps consistent with that policy, it should prioritize concrete actions that will help to build a more secure and resilient supply chain.

Recommendation 3.1: FDA should use all available tools to clear the COVID-19 inspection backlog

FDA's immediate priority should be ending the COVID-19 inspection backlog. In doing so, FDA should fully deploy its remote inspection tools, as appropriate, to use its resources most effectively.

During the COVID-19 pandemic, FDA implemented various tools that allowed it to continue monitoring facilities remotely, including remote records reviews and interactive evaluations using livestream video and other technologies.[124] These tools enabled FDA to provide oversight when travel was limited, but they do not allow for as complete an assessment as can be done in person and cannot be used in many foreign facilities due to technical and logistical issues.[118]

Now that FDA is catching up on inspections, it should use its remote tools in additional ways to supplement its in-person work and accelerate the in-person work that is necessary to eliminate the backlog. FDA has indicated that remote tools can be used on a targeted basis to mitigate staffing challenges, but it is still assessing how best to deploy them.[118,125,126] The agency should prioritize its efforts to use these tools to improve the efficiency of its in-person work. If more of the work that is amenable to remote observation can be done without an inspector onsite, it could enable inspectors to visit more facilities in a given time period, or on a single trip.

Recommendation 3.2: Designate foreign manufacturing oversight as a core leadership priority and evaluate options for third-party support

With respect to FDA's oversight of foreign manufacturing facilities, new approaches are needed to address the practical challenges that have persisted for decades. FDA leadership should take concrete actions to ensure that the agency's oversight of foreign facilities is at least as effective as its oversight of domestic ones.

First, FDA should designate this goal as a core priority of the Commissioner's office. This designation would bring focused attention and capacity and help ensure that FDA successfully follows through on key recommendations from the Government Accountability Office, such as developing and implementing an action plan for hiring and retaining qualified inspectors for foreign facilities.[118] High-level focus will help the agency appropriately prioritize this in the context of the recent major reorganization in FDA's inspectorate,[127,128] including by focusing on important organizational questions, such as whether the agency should revisit the geographic distribution of its inspectorate and renew efforts to increase its in-country presence in key jurisdictions.

Second, FDA should be maximally transparent about how effective various strategies will be at addressing the issues that persist, and where new approaches may be needed. For example, FDA has had recent success in negotiating mutual recognition agreements with regulators in Europe, which have enabled it to rely on the results of inspections conducted by these trusted partners, effectively expanding the agency's capacity and limiting duplicative work. But, to date, this reliance has been most effective for facilities in the European regulators' home countries; success has been more limited for facilities in India and China because (1) European regulators conduct relatively fewer inspections in those countries and (2) the drugs manufactured for the U.S. market are often produced in separate areas that non-U.S. regulators do not inspect.[128] In addition, relevant laws—including those governing confidential and trade-secret information—may place practical limits on information sharing between regulators. As FDA continues to build on this and other programs, it should ensure their limits are well understood—and, ideally, quantified—so that policymakers can assess the need for other approaches.

Third, FDA should embrace technological solutions that improve the efficiency or effectiveness of its inspection operations. For example, FDA recently developed a data dashboard to plan surveillance inspections more efficiently.[129] FDA should review its operations and identify other opportunities to deploy technology to improve operations and maximize the time that inspectors are able to spend conducting inspections.

Fourth, FDA should consider novel approaches to supplement its inspection resources. These approaches could include:

- *Collaborative hybrid inspections:* FDA recently participated in a pilot program by the International Coalition of Medicines Regulatory Authorities to assess the feasibility of hybrid inspections in which multiple regulators conduct an inspection through a combination of remote and in-person inspectors.[130] This model could enable FDA to expand its reach without having to put as many boots on the ground, but it also would require additional coordination, and could face many of the same practical issues that have limited the effectiveness of mutual recognition. FDA should assess carefully.

- *Assessments by nongovernmental third parties:* The agency already has experience with relying on accredited third parties to conduct inspections for certain types of devices,[131] and it could work with Congress to design a similar program to expand the reach of its foreign overnight. Although there would be legal and practical limits on how FDA could use the results of such assessments, they could be a useful tool to enable FDA to identify potential quality problems earlier than might otherwise be possible.

Recommendation 3.3: Develop a rating system to incentivize quality manufacturing maturity

In addition to improving inspectional oversight, FDA should be doing more to incentivize manufacturers to invest in mature quality management systems. While FDA's Current Good Manufacturing Practice (CGMP) requirements set a regulatory minimum that applies to all drugmakers, some have begun investing in enhanced systems that apply technology and mature management principles to go beyond the minimum legal requirements and make disruptions from quality failures easier to detect and less likely to occur.[110,132] Unfortunately, the market does not directly reward investment in such systems. Drug purchasers typically lack information about which products are made in facilities that use these mature practices (and are therefore less likely to experience disruptions), and many manufacturers—particularly those of low-cost, low-margin drugs—may find it infeasible to invest in mature systems without the opportunity for short-term returns on investment.[110]

FDA can begin to address this dynamic by developing a public system for measuring and rating the maturity of the quality management system for the facility where each drug is produced.[133] Internally, this rating system would help FDA better predict which products are at risk of going into shortage, and take those risks into account when prioritizing surveillance and enforcement activity. Outside the agency, purchasers (both public and private) and group purchasing organizations could use public ratings to inform their contracting and reimbursement decisions (e.g., by taking ratings into account when evaluating options for multisource drugs). This would enable manufacturers to compete on quality in addition to price and realize more immediate returns on investments—as opposed to longer-term benefits, such as reducing the cost of manufacturing disruptions over time.

FDA and the U.S. Department of Health and Human Services (HHS) have proposed versions of this idea under both Republican and Democratic administrations,[110,111] and FDA should prioritize its implementation. FDA has the existing authority to evaluate and rate the maturity of facilities' quality management systems to prioritize its inspections,[134] and it can begin evaluating the extent to which it has authority to share information about those ratings with manufacturers and/or the broader public. To the extent that additional legislative authority is needed to collect information for accurate ratings, FDA should identify the gaps and communicate them to Congress.

Recommendation 3.4: Incentivize and de-risk investment in advanced manufacturing technologies

Over the longer run, one of the most impactful ways to reduce the risk of supply disruptions is to make it more feasible for medical product manufacturers to invest in advanced manufacturing technologies (AMTs) that improve the reliability, quality and efficiency of production. AMTs go beyond upgrades to system maturity (as discussed above) and include technologies such as:

- *Continuous manufacturing:* Products are produced in a continuous stream, as opposed to traditional batch manufacturing in which products are produced in a set of discrete steps with pauses in between. Continuous manufacturing methods can increase manufacturing speed, make it easier to bring new production online in response to a shortage, and make it easier for manufacturers to identify potential quality issues before they arise.[135–137]

- *Additive manufacturing (3D printing):* Products produced using 3D printing technology can enable greater customization (e.g., modifications to pill sizes) as well as distributed manufacturing models in which the product is printed closer to the point of care.[136]

- *Artificial Intelligence (AI) and machine learning (ML):* AI and ML technologies can be deployed to improve manufacturing processes, such as by identifying optimal parameters to improve efficiency, controlling and monitoring processes, and detecting potential problems.[138]

FDA has encouraged the adoption of AMTs, most notably by providing manufacturers with early engagement and technical assistance through the agency's Emerging Technology Program.[136] Unfortunately, the success of these efforts has been limited. As of October 2022, FDA had approved only 16 applications for drugs using AMTs—a drop in the bucket compared to the thousands of new and supplemental drug applications that FDA approves each year.[136] The primary barriers have less to do with technological feasibility and more to do with the uncertain business case for investing in technology that is not only more expensive but carries significant regulatory uncertainty given that the existing regulatory framework was designed for conventional manufacturing.[136]

Improving the feasibility of adopting AMTs would not only help reduce supply disruptions but would also, to the extent that technologies are adopted by domestic firms, help address national security risks posed by having the production of critical medicines concentrated in certain foreign countries. FDA should take steps to reduce the barriers to AMT adoption, including:

- *Updating the regulatory framework to support AMTs:* FDA should reduce the regulatory uncertainty that makes adopting AMTs riskier than it needs to be. The agency has already started this process by issuing guidance on technical and regulatory considerations for using continuous manufacturing technologies,[137] but significant challenges remain in applying FDA's regulations, particularly for other types of AMTs such as using AI and ML in the manufacturing process.[138] FDA should prioritize a comprehensive effort to update its regulations as needed, issue guidance on how existing regulations apply to new technologies, and ensure that staff are appropriately trained when they encounter new approaches. As a first step, FDA could issue a request for information (RFI) to begin assessing ways in which current regulations are outdated or pose challenges for deploying AMTs.

- *Expand the benefits of using AMTs:* In 2022, Congress authorized a new AMT designation program, under which FDA can review and designate certain AMTs outside the context of a product application, then provide early assistance and expedited review for product developers who use designated AMTs.[139] This program has the potential to make it more attractive for developers to adopt AMTs, as FDA recognized in its implementing guidance.[135] As FDA continues to implement the program, it should look for opportunities to expand the benefits of AMT designation, such as clarifying how the use of designated AMTs can simplify or streamline compliance with post-market requirements. In addition, FDA should further incentivize AMT adoption through other programs; for example, as FDA develops a quality maturity rating program, it could implement a policy that using AMTs will increase a facility's rating.

RECOMMENDATION 4: ENHANCE THE ACCELERATED APPROVAL PATHWAY

Key takeaways:

- FDA's accelerated approval program has led to early patient access to over 300 products.
- Despite this success, the program has proved controversial politically and publicly.
- FDA can improve the program through procedural reforms and enhancements to the advisory committee process. These efforts should be implemented in ways that maintain the program's success in accelerating availability to patients.
- Data from real-world clinical practice should play a larger role in efforts to ensure confirmatory studies are completed on a timely basis.
- FDA should leverage transparency to minimize unnecessary duplication with other agencies and improve regulatory predictability.

FDA's accelerated approval program, which enables medicines for some of the most serious diseases and conditions to be made available to patients sooner, has been the subject of recent controversy and reform efforts. New agency leadership has inherited a set of ongoing reforms and should work to ensure that they succeed in putting the program on a stronger footing and enhance the core goal of accelerating availability to patients.

The accelerated approval program, first instituted in 1992, grew out of activism by patients during the HIV/AIDS epidemic who lacked treatment options and argued that they not should suffer or die while waiting for multiyear studies to definitively verify the clinical benefit of promising medicines.[140,141] Earlier access can be critical for patients in many circumstances, especially when timely treatment is important but the course of the disease is lengthy or variable enough that it may take many years before a drug's intended clinical benefit can be fully evaluated—a common fact pattern for many oncology and rare disease indications.

Under the accelerated approval pathway, a drug or biologic for a serious or life-threatening disease or condition may be approved based on evidence demonstrating that it has an effect on a surrogate or intermediate endpoint that is "reasonably likely to predict" clinical benefit, rather than waiting an extended period of time for completion of studies to fully measure clinical benefit.[142] Although the evidentiary standard is the same as for traditional approval, the outcome being measured is different. Instead of providing evidence of a beneficial clinical outcome, the sponsor can instead provide evidence that the product has an effect on a biomarker (e.g., a laboratory measurement) or intermediate clinical measurement that is not itself beneficial enough to support approval but is thought to be predictive of actual clinical benefit.[142,143]

By using these alternative endpoints, patients can access products that provide meaningful advantages over available therapies years earlier than would be possible through the traditional approval process. But because the approval is based on a prediction of clinical benefit rather than a demonstration of benefit itself, FDA typically requires the sponsor to conduct post-approval studies to confirm benefit, and can withdraw approval if, among other things, the studies are not completed or the product fails to show benefit.[142,144]

The program has been incredibly successful at accelerating the availability to patients of safe and effective products. Since its inception in 1992, FDA has granted accelerated approval to more than 300 products (over 100 of which are for rare disease) and, as of December 2021, has converted 50% of accelerated approvals into traditional approvals based on a demonstration of clinical benefit.[145–147] For these converted drugs, the median time from accelerated approval to conversion was 3.2 years—meaning a median of 3.2 years of earlier availability to patients relative to traditional approval.[147] The accelerated approval has transformed cancer care,[148] turned HIV/AIDS into a controllable disease, and offers promise for rare disease.[149]

Despite these successes, the program has proved controversial. FDA has faced well-founded criticism over whether it is doing enough to ensure that confirmatory studies are completed on a timely basis and that products are withdrawn as appropriate.[146,150,151] (As of December 2021, 12% of accelerated approvals had been withdrawn.)[147] In addition, individual approval decisions have proven contentious due to disagreement over which endpoints are "reasonably likely to predict" benefit, or when accelerated approval should be used for products that initially came to the agency seeking traditional approval.[150,152] These controversies can diminish public confidence in products approved through the accelerated approval pathway and have led payors including CMS to restrict coverage in some circumstances.[153,153–155]

In December 2022, Congress passed a set of reforms to address some controversial elements of the program. These reforms included, among other things, expedited procedures for withdrawing approval and provisions to improve the completion rate for confirmatory studies, including the requirement for FDA to set study conditions before approval and authorizing the agency to require the studies be underway before accelerated approval.[156]

FDA is now implementing these reforms. For example, it has published draft guidance on new statutory processes and established an intra-agency accelerated approval council to coordinate activities and promote consistent use of the pathway.[143,157,158] As new leadership assumes responsibility for these works in progress, there are significant opportunities to enhance the program and ensure a well-functioning pathway for accelerating the availability of critical medicines.

Recommendation 4.1: FDA should facilitate more data from real-world clinical practice in confirmatory studies

Recent reforms have tried to address the completion rate for confirmatory studies by regulating how far along the study should be at the time of approval, but perhaps the most important tool FDA has to improve completion is in the design of the studies themselves. FDA has been working to facilitate studies that are designed to maximize the chance of success and avoid common pitfalls. Data from real-world clinical practice should play a larger role in these efforts.

One of the biggest challenges for confirmatory studies is that once a drug is approved and can be accessed on the market outside of the research setting, it becomes more difficult to recruit patients and conduct ongoing trials.[157] In addition, many studies require years of treatment and follow-up, making retention an issue.[143] FDA has been encouraging various innovative trial designs that can help overcome these challenges,[143] but it has provided little to no guidance on using data from real-world clinical practice for this purpose. The gap is surprising because RWE studies are a powerful tool for understanding how patients in real clinical settings may or may not be benefiting from a product, without having to ask patients to risk changing their care.[159]

While it would be challenging to fully replace existing confirmatory requirements with RWE studies,[160] RWE can nonetheless be an important element of a confirmatory study plan—and, indeed, there are multiple examples in which FDA has agreed to confirmatory evidence that included real-world data elements such as registries, chart reviews, medical and claims records, and prospective data collection.[161] FDA should update its guidance to highlight the important role that such evidence can play and help product sponsors identify appropriate use cases.

Recommendation 4.2: Pursue reform strategies that address programmatic concerns while prioritizing early availability to patients

As FDA continues to implement reforms to strengthen the accelerated approval program and address concerns with its operation, it is important that the agency do so in a way that respects and builds upon the pathway's considerable historical success in accelerating the availability of drugs to patients.

Process concerns with the accelerated approval pathway are generally limited to a narrow subset of total actions—a point underscored by a recent report from the HHS Office of Inspector General that identified concerns with FDA's actions in only a small percentage of total approvals, all of which related to FDA procedural decisions regarding the handling of scientific disagreement, documentation of meetings, and the use of analyses not included in sponsors' original analysis plans.[152]

The challenge for FDA is to implement reforms that address high-profile concerns without disrupting a pathway that works well in the overwhelming number of cases. The agency can accomplish this through targeted reforms to the accelerated approval program in combination with broader reforms to the agency's advisory committee process.

Concrete steps the agency can take include:

- *Establishing regularized and flexible procedures:* FDA should work through the Accelerated Approval Council to develop and publicize updated procedures for evaluating endpoints and determining whether the accelerated approval standard has been met, including procedures on how to manage scientific disagreements. The procedures need not establish a formal role for the council, which could complicate intra-agency appeals,[152] and should be flexible enough to allow for product-specific judgments and maintain a clear process for leadership to manage disagreement. The goal of these reforms should not be to make any substantive outcome more or less likely, but to establish a regularized, principled, and well-documented process that provides transparency and instills greater public confidence in the agency's scientific decision-making.
- *Updating guidance on withdrawal after a failed confirmatory trial:* FDA recently provided new guidance on the procedures for withdrawing accelerated approval, but the guidance is focused on process rather than explaining how FDA will apply the substantive standard for determining when withdrawal is appropriate.[143] The guidance should be updated to discuss when the failure of a confirmatory study to establish benefit will—and, importantly, will not—warrant withdrawal of approval. As senior FDA leaders recently explained, there are many reasons why a study might fail to show benefit, and it is important to understand to what extent the failure is attributable to problems with the study (e.g., methodology or dosage) as opposed to problems with the drug.[162] Guidance on how FDA intends to apply this principle would provide needed clarity for product sponsors and the public alike.
- *Ensuring that new policies do not meaningfully delay patient access:* In recent draft guidance implementing the 2022 legislative reforms, FDA announced a new policy that "FDA generally intends to require that the confirmatory trial(s) be underway prior to the accelerated approval

action."[162] This policy is expected to facilitate more timely completion of confirmatory requirements, but depending on how it is implemented, it also carries the potential risk of delaying accelerated approvals by shifting activities from post-market to pre-market. FDA should carefully analyze this risk and closely track the timing of accelerated approval actions relative to the start of clinical studies so that the agency can understand and address any impact.

FDA can also strengthen the accelerated approval pathway by improving its use of advisory committees. FDA's advisory committees are panels of outside scientific experts and community members (including industry, consumer, and patient representatives) who provide advice and recommendations to inform agency decisions. They provide this advice through both public discussion and nonbinding votes, which can not only improve the quality of FDA's decisions by expanding the expertise and viewpoints that the agency considers, but also help build public confidence in those decisions by providing transparency into the deliberative process.[163,164] However, FDA has been criticized as falling short of this ideal, including with respect to its recruitment of committee members and the procedures by which it conducts meetings and considers the committee's advice.[165,166]

As FDA evaluates potential reforms to its use of advisory committees—a process it has already initiated[164]—it should include measures that would help address concerns with the accelerated approval program in particular. These include:

- *Requiring a written public statement explaining any decision to approve a product after an advisory committee voted against approval:* Whereas FDA almost always follows committee recommendations to approve a drug, it departs more frequently when the committee votes against approval (97% versus 67%).[167] A requirement to explain these departures would not change the bar for approval, but it would allow the public to better understand the agency's rationale. In many cases, the explanation may reveal that the agency did not ignore the committee's recommendation, but rather that the committee process revealed problems with an application that the sponsor was able to address.[168]
- *Establishing clear rules for when to reconvene committees:* When an advisory committee votes against approval and the sponsor subsequently addresses issues with its application, or the agency decides to consider the application under a different approval pathway (e.g., accelerated rather than traditional approval), it should trigger a process for deciding whether to reconvene the advisory committee to consider the new information. While the agency should maintain flexibility with respect to its substantive decisions, clear rules about what types of changes warrant reconvening could help foster confidence in the ultimate decision.
- *Updating committee procedures to provide fair scientific consideration:* For advisory committee meetings to serve their purpose, they must be organized around the principle of genuine scientific inquiry and not designed to achieve a preordained result. FDA has been criticized in this regard for, among other things, not providing enough time for the public to review meeting materials (which may be distributed as little as 48 hours before the meeting),[165,169] or posing "leading" questions to the committee that appear weighted toward a particular outcome.[170] FDA should adopt standardized procedures that revise these practices and strengthen the advisory committees as a tool for appropriately managing divergent scientific views, such as those that may arise when evaluating whether an endpoint is predictive of clinical benefit.

Recommendation 4.3: FDA should minimize unnecessary duplication with other agencies

Although policies for the payment and reimbursement of accelerated approval drugs fall outside of FDA's purview, these policies can have a significant impact on patient access. FDA can help CMS minimize duplicative scientific reviews and facilitate patient access by improving how it explains its accelerated approval decisions.

Once FDA approves a drug, coverage under Medicare is determined based on whether the product is "reasonable and necessary for the diagnosis or treatment of illness or injury."[171] Although historically CMS has applied this standard to cover drugs approved through the accelerated approval pathway in the same fashion as other drugs, more recently it has taken a different approach. In the context of a 2022 National Coverage Determination, CMS announced that Medicare coverage for accelerated approval drugs will depend on whether "there is scientific evidence that the surrogates are directly affect [sic] the clinical outcomes," and applied this standard to restrict coverage for a class of drugs based on CMS's evaluation of the scientific evidence.[153] In 2023, CMS announced that it was working in consultation with FDA to develop a new payment model that would reduce Medicare Part B payments for accelerated approval drugs until they have generated confirmatory evidence.[172,173]

These coverage policies may reduce federal spending and strengthen financial incentives for completing confirmatory studies,[46] but they also risk limiting access to treatments for serious diseases and conditions under circumstances where FDA has already reviewed the scientific evidence and determined that the product should be made available to address unmet need.[174] Over time, they may also depress developer interest in utilizing the accelerated approval pathway. While FDA does not have purview over how CMS applies the "reasonable and necessary" standard, and it should not modify its own review to account for considerations that CMS may bring to bear, FDA should update how it presents the information from the reviews it is already conducting to minimize the risk that coverage decisions will create duplicative work or undermine the broader access goals of the accelerated approval program.

Goals for this effort should include:

- *Minimizing duplication of effort:* Although accelerated approval and Medicare coverage are governed by different statutes, the underlying science for a given drug does not change between the two contexts. To the extent FDA has already analyzed a scientific question in the context of an approval decision, it is unnecessary and wasteful for CMS to relitigate the same scientific question when evaluating coverage. FDA should work with CMS to ensure that its scientific assessments are presented in a manner that improves CMS's ability to rely on them rather than relitigate the same question.
- *Focusing on what matters most to patients:* FDA should ensure that when patient preference information (PPI) is available as part of an approval package, it highlights that information to help inform CMS coverage decisions. Patient preferences are particularly important in the context of accelerated approval: When FDA evaluates whether an endpoint is reasonably likely to predict clinical benefit, the agency must determine—implicitly or explicitly—how much uncertainty is appropriate in a particular therapeutic context. Using quantitative PPI at the early stage of regulatory submissions (e.g., when applying for accelerated approval or in early trial phases) to identify patient priorities and tolerance for uncertainty would improve the transparency of FDA's decisions and facilitate CMS reliance. Likewise, by providing CMS with this information, FDA can help CMS focus its own evidentiary requirements on questions that are relevant and fit for purpose.
- *Maximizing predictability:* To the extent that FDA and CMS standards do not overlap, product sponsors should have clarity and predictability as to what the differences are and how they will be applied. The current approach does not meet this goal; under CMS's recently articulated position, it may restrict coverage even after FDA determines that the scientific evidence is strong enough to support accelerated approval, as long as the internal Medicare coverage group determines that the evidence is not sufficiently robust or "direct"—a standard that CMS has yet to define.[153] While it would be inappropriate for FDA to modify its own evidentiary requirements to require development of information to satisfy the "reasonable and necessary" standard, FDA should work with CMS to ensure that any differences between the approval and coverage standards are clearly identified and explained so that product sponsors can organize their development programs accordingly. Enabling sponsors to generate data with both agencies' review processes in mind would improve efficiency and potentially reduce the time and inconsistency between regulatory approval and coverage.
- *Maintaining appropriate incentives:* FDA should also provide input on how any novel payment models for accelerated approval drugs might affect drug developers' use of the pathway. If CMS uses a new payment model to reduce reimbursement for accelerated approval drugs until the sponsor generates confirmatory evidence, it could potentially disadvantage use of the pathway when considered in combination with other laws. Price restrictions enacted under the IRA can take effect as early as nine or 13 years after a drug or biologic is first approved, regardless of whether the approval was under the traditional or accelerated approval pathway.[45] If a new payment model reduces reimbursement on the front end until there is confirmatory evidence, and the IRA reduces payment again on the back end, it could leave developers with a narrower opportunity for financial returns on accelerated approval drugs relative to other products. In some cases, it may also lead developers to forgo the accelerated approval pathway altogether in favor of traditional approval, which would carry fewer reimbursement risks. Given where FDA sits in the regulatory ecosystem compared with CMS, the agency can play an important role in monitoring development activity for signs of potential impacts, and make that information available on an aggregated basis to CMS and the public.

RECOMMENDATION 5: INVEST IN FDA'S USE AND OVERSIGHT OF ARTIFICIAL INTELLIGENCE AND OTHER ADVANCED COMPUTING TECHNOLOGIES

Key takeaways:

- Artificial intelligence (AI), machine learning (ML) and other advanced computing technologies are revolutionizing medical products—as development tools, as features in the products themselves, and as tools to make FDA more effective and efficient.
- FDA should accelerate modernization of its technical infrastructure and procurement of advanced tools to improve its workflows and make product reviews more efficient and predictable.
- FDA should leverage existing frameworks to facilitate innovative uses of AI in safe and effective medical products, including with respect to potential third-party reviews.
- FDA should update its approach to clinical decision-support software.

Recent advancements in AI, ML, and other advanced computing technologies offer unprecedented opportunities, not only in healthcare, but across the United States economy and government.[175] In January 2025, President Trump declared it the policy of the United States to "sustain and enhance America's global AI dominance in order to promote human flourishing, economic competitiveness and national security," and ordered development of an action plan to advance this policy.[176] FDA has a critical role to play in these efforts, and agency leadership should make its advancement of AI and other advanced computing technologies a core priority.

The agency sits at the intersection of many transformational use cases:

- *FDA as user:* AI, ML and other advanced technologies can help FDA improve its capabilities and the efficiency of its operations across domains such as product reviews, post-market surveillance, inspections and import operations.[177,178]
- *Algorithmic and AI-enabled products:* AI and ML technologies are powering innovative medical products, with applications such as improving detection and diagnosis of disease, personalizing therapies and diagnostics, and improving the functions and user interfaces of a wide range of medical devices.[179]
- *Product development tools:* AI, ML and other advanced tools are being deployed for uses across the product lifecycle that include, for example, accelerating drug discovery by helping identify and research promising drug candidates, improving recruitment and selection of clinical trial participants, optimizing clinical trial sites, managing and analyzing data, improving the manufacturing process, and analyzing post-market surveillance data.[180]

FDA leadership should accelerate and update existing efforts to further the responsible advancement of these use cases and unlock the potential of advanced technologies to improve patient access to safe and effective treatments and diagnostics.

Recommendation 5.1: Accelerate modernization of FDA technical infrastructure and procurement of advanced tools to improve FDA workflows

In 2019, under the first Trump administration, FDA launched an initiative to modernize the agency's technical infrastructure and enhance its ability to deploy technology to support its mission. This effort, called the Technology Modernization Action Plan,[177] was expanded in 2022 through further efforts to modernize the agency's stewardship and use of data,[181] move the agency away from historically siloed approaches to information technology (IT) and toward enterprise-level IT management across programmatic areas,[182] and strengthen the agency's approach to cybersecurity.[183]

Agency leadership should make it a high priority to continue and build upon the work under these initiatives, with a focus on (1) developing the infrastructure to efficiently work with large volumes of data and deploy cutting-edge tools, (2) procuring solutions (both bespoke and commercially available) to use AI, ML and other advanced technologies to improve FDA workflows, and (3) implementing centralized IT solutions that enable the efficient migration toward more advanced systems.

FDA leadership has already indicated that the agency will work toward consolidating duplicative IT infrastructure[184] and implementing generative AI tools in product reviews.[185]

These initiatives have the potential to be transformative for the agency by improving operations, promoting efficiency, and improving agency-wide governance. As the agency continues to implement these and other initiatives, it should adhere to the following principles:

- *Efforts to better utilize advanced tools should not be limited to product reviews:* In recent years, FDA successfully employed advanced technology in other domains, such as by deploying tools to improve the efficiency of surveillance inspections[129] and more effectively screen certain food imports.[186] FDA should apply the learnings from these and similar experiences and use technology to improve

operations across more domains throughout the agency, including expanded uses in post-market surveillance and enforcement activities.

- *FDA should maintain strong governance principles, especially when deploying AI to support regulatory decision-making.* These principles should include rules (1) to ensure that "algorithmic-informed" decisions are made ultimately by humans who understand the risks and limitations of AI systems, (2) to minimize unnecessary duplication of systems across FDA's centers and programs, and (3) to provide appropriate transparency to users and the public into how results are generated.[175,182]
- *FDA should articulate clear objectives and use cases for deploying AI and other advanced tools in product reviews:* The most impactful opportunities go beyond merely summarizing data and may include, for example, using analytical platforms and other tools to improve the agency's ability to receive, manage and analyze the increasingly large datasets that are submitted in support of product applications.[177] Such tools could, among other things, enable reviewers to detect falsified data and other data quality issues more effectively and in a fraction of the time, or run analyses that otherwise might require substantial line coding by a statistician or computer engineer. Clearly articulating the anticipated use cases will enable stakeholders to understand how AI is being used in reviews and what controls are being used to mitigate risks.
- *FDA should articulate a clear plan for how it will use the efficiencies it generates to improve product reviews:* Among other things, more efficient reviews would help the agency keep up with the ever-increasing volume of applications, which is expected to rise substantially as developers continue to build AI and ML tools into their own processes.[177] In addition, increased efficiency would enable FDA reviewers to devote less time and attention to rote tasks and instead focus more on human-centric activities like ensuring that product reviews are consistent with agency policy and prior precedent—an area where the agency has historically struggled.[187,188]

Funding the infrastructure and procurement to drive these improvements should be a budgetary priority—internally within the agency, as part of the annual budget request to Congress and as part of the agency's requests for industry funding in negotiations for upcoming renewals to relevant user fee programs.

Recommendation 5.2: Build upon existing frameworks to facilitate innovative uses of AI in safe and effective medical products, including with respect to potential third-party reviews

Innovative uses of AI and ML in medical products—both to enable the products themselves and as tools to improve the development process and other activities throughout the product life cycle—present extraordinary new opportunities to advance patient health. At the same time, they present novel challenges for FDA as the regulator tasked with ensuring that the products are safe and effective, such as (to the extent relevant and consistent with FDA's authority) ensuring that the tools are trained on appropriate data, applying validation models to software that may rely on decision-making processes that are not readily understandable, and addressing adaptive technologies that continue to learn and evolve over time.[180,189–191]

As FDA continues the work to address these challenges and advance innovation, it should aim to maximize its use of existing tools and frameworks where possible in order to minimize the disruption and uncertainty associated with developing wholly new frameworks. While new approaches may be needed to address certain novel issues, FDA's existing tools and authorities provide a solid foundation for future efforts. For example:

- FDA has already used its existing authorities to support a significant volume of product development. The agency has authorized more than 1,000 AI- and ML-enabled medical devices, a body of precedent that includes health-tracking features on wearable devices such as smartwatches, sleep-monitoring software, complex radiological devices, and many other products.[192]
- FDA has also advanced significant policy development regarding how its tools and authorities can be applied to address novel questions in this space, and has published draft or final guidance on topics such as submitting marketing applications for devices with AI- and ML-enabled software functions,[193] how marketing submissions for AI- and ML-enabled devices should address anticipated changes over time (including through continuous learning),[179] and using AI to produce information or data to support FDA decisions about drugs and biological products.[194] A considerable portion of this guidance was still out for public comment in draft form at the change in presidential administrations, which means that the agency will have the opportunity to consider public feedback in the context of new administration priorities and executive actions, including with respect to emerging issues related to generative AI.

As FDA builds upon this foundation, it should pay particular attention to the potential use of third-party resources. Agency leaders have expressed concern about whether FDA has sufficient in-house expertise and bandwidth to effectively assess the various technologies that will come before it for review[195] and have begun exploring the concept of using a network of AI "assurance laboratories," possibly based in academic medical centers, to support validation and other vetting activities.[196,197] This model could significantly expand FDA's capacity, but the concept has proved controversial. Critics have argued, among other things, that the large institutions needed to support this effort would be too prone to conflicts of interest, are ill-equipped to operate across geographically diverse (and locally regulated) healthcare settings, and could impede innovation.[198,199]

FDA will need to navigate this ongoing debate in the context

of evolving national strategies on advancing AI. In doing so, the agency should look to existing frameworks, including the core principles of other third-party review programs that FDA has previously implemented. For example, the 510(k) Third Party Review Program allows device manufacturers—on a voluntary basis—to have certain marketing applications reviewed by accredited Third Party Review Organizations before FDA makes a final determination, which can streamline the review process and conserve agency bandwidth.[200] While the 510(k) Third Party Review Program has struggled to provide consistent and high-quality reviews or reduce workload relative to regular submissions,[201] FDA should consider whether some variation on its voluntary framework could provide a useful model for third-party assessments of AI technologies — for example, by establishing a system in which using outside assessors is an available option alongside other, equally viable pathways. The agency should also consider, a designation program for validation methods akin to the program for designating platform technologies,[45] in which an approach intended to be used across multiple products could be evaluated and authorized by the agency to facilitate streamlined development of products deploying that approach.

Recommendation 5.3: Update FDA's approach to clinical decision-support software

As FDA updates its AI policies, one immediate priority should be to revise the guidance it finalized in 2022 on clinical decision support (CDS) software.[202] That guidance—which deviates sharply from the approach the agency proposed in 2019 during the first Trump administration—has been highly controversial. Stakeholders have expressed concern that the agency is subjecting beneficial software functions to regulatory burdens that Congress did not intend and, as a result, causing developers to make their software less useful to healthcare providers (HCPs), and limit innovations that would benefit patients in order to avoid triggering FDA pre-market review.[203–205] FDA should revise its approach to avoid this outcome and better align its policies with congressional intent.

CDS software can encompass a wide range of functions that support HCPs' decision-making in the course of delivering clinical care, such as tools that analyze information about a patient to help an HCP make a diagnosis, identify potential drug-drug interactions and match patient-specific information to relevant treatment guidelines. These tools have enormous potential to improve patient health outcomes by reducing errors and driving better treatments decisions.[206] One recent study found that a commercial large language model (LLM) AI chatbot was able to significantly outperform doctors using conventional tools when making a diagnosis,[207] which shows significant potential for these and other tools to support HCP decision-making when properly deployed.

Many of these CDS software functions are, by statute, exempt from FDA regulation as a medical device. In the 21st Century Cures Act of 2016, Congress created a safe harbor that exempted CDS software functions from FDA medical device regulation as long as they met certain criteria.[208] To qualify, a software function must:

- Display, analyze, or print medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);
- Support or provide recommendations to an HCP about prevention, diagnosis, or treatment of a disease or condition;
- Enable the HCP to independently review the basis for the recommendations so that it is not intended for the HCP to rely primarily on any of the recommendations to make a clinical diagnosis or treatment decision regarding an individual patient; and
- Not be intended to acquire, process, or analyze medical images or signals from an in vitro diagnostic device or a pattern or signal from a signal acquisition system.[209]

Exempt software functions are still potentially subject to regulation under other authorities, such as state-level regulation of the practice of medicine, but they do not need to meet FDA's requirements for medical devices.

FDA's 2022 final guidance significantly narrowed the safe harbor.[202] For example, the guidance:

- States that, in order to limit the risk of "automation bias" (i.e., the tendency for humans to over-rely on suggestions from automated systems), FDA is applying the safe harbor only if the software recommends multiple options, as opposed to a single, specific recommendation. This distinction does not appear in statute.
- Imposes restrictions on the type of information that exempt software can analyze. According to the guidance, the safe harbor applies only if the software analyzes information about a patient of a type that would normally be communicated in a conversation between HCPs, or between patients and HCPs—an ambiguous restriction that does not exist in statute—or other medical information that is "independently verified and validated," a limitation that does not appear in the statute and might potentially exclude information from reliable real-world data sources, such as patient registries.

This approach would benefit from reassessment. First, by introducing limits on the safe harbor that do not appear in statute, the approach in the guidance may be legally vulnerable. In addition, the guidance could have the unintended impact of leading HCPs to use less fit-for-purpose AI tools to support their decision-making. As commercial AI tools proliferate, an increasing number of clinicians are using general-purpose tools to support their decisions; in one recent survey, a majority of physicians reported using general-purpose LLMs in clinical decision-making, including for uses like diagnosis support and checking drug interactions.[210] If developers decide to forgo releasing beneficial software functions due to the risk of regulation, HCPs may turn instead to tools not designed or optimized specifically for CDS use.

RECOMMENDATION 6: ADVANCE DRUG COMPETITION

Key takeaways:

- FDA has taken significant steps to advance drug competition under action plans that launched under the first Trump Administration and continued under President Joseph Biden.
- FDA should prioritize continued efforts under these plans and update them to account for changes under the IRA.
- FDA should further streamline the pathway for interchangeable biological products.

Although FDA does not regulate the price of drugs, its policies can nonetheless have a significant impact on prices—both by setting regulatory requirements that affect the cost of developing and marketing drugs, such as those discussed in other sections of this paper, and by encouraging competition between drug products. Such competition can take the form of follow-on products that are identical or similar enough to the original version that they can be used as substitutes and compete directly on price (e.g., generic drugs and biosimilars), or in the form of products in the same therapeutic class that may not only potentially compete on price but also provide important clinical differentiation for patients who may respond better to one drug than another.[211]

FDA has taken significant steps to advance drug competition under the Drug Competition Action Plan (DCAP) and Biosimilars Action Plan (BAP), which were launched under the first Trump Administration and continued under President Biden.[212,213] Going forward, the agency should (1) continue and expand upon the successes of DCAP and BAP, including by addressing changes to the competitive landscape introduced under the IRA and (2) further modernize the framework for developing versions of biological products that can be substituted at the pharmacy.

Recommendation 6.1: Continue the Drug Competition Action Plan and Biosimilars Action Plan, and update them to account for changes under the IRA

Under the DCAP and BAP, FDA has been advancing policies and programmatic reforms to encourage increased competition within the frameworks established by Congress. These frameworks, established under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act)[214] and the Biologics Price Competition and Innovation Act of 2009 (BPCIA),[215] balance the goals of incentivizing innovation and facilitating competition by combining periods of statutory exclusivity for novel products with efficient processes for identical or highly similar follow-on products (called generics for drugs and biosimilars for biologics) to obtain approval and resolve patent disputes.

Under these frameworks, a generic or biosimilar developer can avoid the time and expense of duplicating the studies that supported FDA's findings of safety and effectiveness for the brand-name product, and instead focus on demonstrating that its product is the same as, or similar enough to, the brand-name version and can therefore rely on FDA's earlier findings that the product is safe and effective.[216,217] The relevant showings are:

- A generic drug must show that it is "bioequivalent" to the brand-name version, meaning that it works in the same way and provides the same clinical benefit.[216,218]
- A biosimilar must show that it is highly similar to the brand-name biologic with no clinically meaningful differences.[219]

The different standards reflect that biological products are typically complex molecules for which inherent variation can be a natural part of the manufacturing process, as long as it is not clinically meaningful.[220]

This system has been remarkably successful in expanding patient access to safe and effective medicines at lower cost. Today, generics and biosimilars account for more than 90% of prescriptions dispensed in the United States, but only 13% of prescription drug spending.[221] In 2023, the average out-of-pocket cost to fill a generic prescription was $7.05, nearly four times less than the cost of a branded drug,[222] and savings increase further when there are multiple generic versions of the same product.[223]

As for biosimilars, while they are a newer product category that has not yet reached the same level of penetration—the first biosimilar license in the United States was not granted until 2015—they still have a significant impact on patient access. Among molecules subject to biosimilar competition, biosimilars accounted for 24% of the market in 2021, and the costs for those molecules (including both originator and biosimilar products) were down between 18% and 50% per unit.[222,224]

DCAP and BAP encompass a variety of policy initiatives and programmatic reforms intended to increase the number of approved generics and biosimilars and facilitate faster market entry for these follow-on products. The actions advanced under these initiatives have included:

- Issuing guidance documents to provide increased regulatory clarity for generic and biosimilar product developers, including through hundreds of product-specific guidance documents to help developers identify appropriate methodologies and generate the evidence to support their applications[225,226]

- Improving FDA's application review processes to reduce both the time that applications spend in agency review and the number of times an application must be returned to a sponsor to address deficiencies[227]
- Publicizing a list of drugs that are off-patent and off-exclusivity without any approved generics to encourage generic development for those products[228]
- Expediting review of generic applications for drugs with limited competition (e.g., three or fewer approved drug products)[228,229]
- Educating clinicians, patients and payors—who may have questions about the biosimilar product category given how recently it first became available in the United States—to reduce underutilization due to limited awareness or misconceptions[213]

FDA should continue to prioritize these efforts to help generic and biosimilar developers bring safe and effective products to the market as efficiently as possible. This means, for example, ensuring that the agency continues to make available the resources necessary to publish new product-specific guidance documents and update other public resources, such as the list of off-patent, off-exclusivity drugs. These are not static resources; the universe of products eligible for generic or biosimilar competition continually evolves as patents and exclusivities expire. Likewise, market dynamics are not static, and new barriers to competition can emerge over time and require updated policy responses. FDA leadership should ensure that the agency is equipped to carry this important work forward.

In addition to continuing with existing efforts under DCAP and BAP, FDA should update these plans to include specific actions to address the impacts of the IRA on competition. Although CMS, not FDA, is responsible for setting the "maximum fair prices" that Medicare will pay for prescription drugs and biologics under the IRA,[45] that price-setting process will affect how manufacturers approach competition under the Hatch-Waxman Act and the BPCIA. FDA's work under DCAP and BAP should include monitoring how the IRA is affecting the programs it administers and taking appropriate responsive action.

The potential impacts are significant. For one thing, the IRA could reduce generic competition by reducing incentives for generic and biosimilar manufacturers to enter the market. The Hatch-Waxman Act creates a powerful incentive for generic manufacturers to enter the market as soon as legally permitted by awarding the first generic drug manufacturer that successfully challenges the originator's patent 180 days of exclusivity as the sole generic.[230] The BPCIA likewise creates incentives for the first biosimilar that is interchangeable with its reference product.[217] However, the lower maximum prices for branded drugs and biologics under the IRA could reduce the prices that generic and biosimilar manufacturers can charge, reducing the value of their statutory exclusivities and lowering incentives for generic and biosimilar entry.[46]

Theoretically, the IRA also creates a counter-incentive by excluding products with generic or biosimilar competition from the CMS price-setting process, meaning that if generic or biosimilar entry occurs early enough, a product may never be subject to a maximum fair price. This structure creates a potentially significant incentive for brand manufacturers to encourage competition, but CMS has diminished the value of that incentive through guidance. Specifically, CMS has taken the position that a generic or biosimilar "is marketed" for purposes of the IRA only if CMS determines, based on the "totality of the circumstances," that the competitor is engaged in "bona fide marketing."[231] This vague standard, which does not appear in statute, could limit the IRA's incentive for competition by creating substantial uncertainty as to when competition will be considered sufficient to exclude a product from being subject to a maximum fair price.

In addition, the IRA could limit the potential for competition between branded products within the same therapeutic class—both on price and through clinical differentiation. Although the maximum fair price applies only to the drug or biologic for which it is set, it could apply market pressure to other drugs in the same therapeutic class. For example, if a developer is considering investing in a branded competitor to a product that has already been marketed for several years, it may face a limited period of time—as little as nine years from the time the *first* product in the class began marketing[45]—before the market effects of IRA price setting begin limiting its own return on investment. The impact on follow-on branded products could have significant public health implications because of the important role these products play in the therapeutic ecosystem, such as by providing improved benefit-risk profiles and additional options for patients, in addition to potentially driving competitive pricing.[232]

Given these potential impacts, FDA should update DCAP and BAP to include efforts such as (1) closely monitoring drug and biologic development activity for signals of how firms may be responding to changes in the incentive structure, (2) coordinating with CMS so that IRA implementation is well-informed about potential impacts to programs that FDA administers and agency leaders can work through competing considerations, and (3) developing FDA policies to help restore incentives that might be unintentionally diminished under the IRA, such as additional policies for expediting review in appropriate cases.

Recommendation 6.2: Further streamline the pathway for interchangeable biological products

FDA should also move beyond DCAP and BAP to facilitate increased competition in the biologics market. One significant opportunity is reforming the process for establishing that a follow-on biological product is "interchangeable" with its brand-name counterpart—meaning that a pharmacist can substitute it for the corresponding brand version unless the prescription specifies otherwise. The process as it currently stands poses unnecessary regulatory barriers to the utilization

of biosimilars, and while FDA has adopted several meaningful reforms, much more can be done.

There is a pressing need for reform. The market for biologics has been growing considerably faster than the market for small-molecule drugs and now comprises nearly half of all pharmaceutical spending.[224] However, even while the overall biologics market grows, the rate of biosimilar competition is far lower than it could be. Although the rate is increasing, it has been doing so more slowly than many anticipated, and there is still no biosimilar under development for 86% of eligible brand-name biologics.[221]

The current framework for establishing interchangeability has been one of the significant barriers to greater utilization. Whereas all generic drugs that meet the statutory standard of bioequivalence can be substituted at the pharmacy,[216,218] unlocking substitutability for a biologic requires additional work. Unlike a generic drug, a follow-on biologic that is licensed as a "biosimilar" is not pharmacy substitutable and can be dispensed only if it was affirmatively allowed by the prescribing physician. To be substitutable akin to a generic, the product must make the additional, heightened showing that it is "interchangeable" with the brand-name version—a statutory requirement under which it must demonstrate that it can be expected to produce the same clinical result as the brand-name version in "any given patient," and that switching or alternating between the two versions of the product does not create additional risks for patients.[219] Historically, FDA has required developers making this showing to conduct comparative clinical studies to assess the risk of switching or alternating between the biosimilar and brand-name versions of a product (e.g., "switching studies").[233]

This two-tiered approach was designed to protect patients against potential adverse effects of switching between versions of a product, such as harmful immune responses. However, it has also limited patient utilization by requiring a version-specific prescription unless the product can meet the heightened bar of interchangeability. It also differs from frameworks in other countries; the European Union, for example, approves a single type of biosimilar without restrictions on interchangeability.[234,235]

In recent years, FDA has begun rethinking its implementation of the interchangeability requirement. As the agency has gained more experience with biosimilars, and has had the benefit of observing a different regulatory approach in Europe, it has taken several actions to simplify the process for establishing interchangeability while maintaining appropriate safeguards for patients:

- *Insulin guidance:* In 2019, FDA issued a policy stating that, given the substantial history of patients safely switching between insulin products, comparative analyses like switching studies would not be necessary for biosimilar insulin to be licensed as interchangeable.[236] This policy change paved the way for FDA to begin licensing interchangeable insulin biosimilars, including the first-ever interchangeable biologic in 2021.[237]
- *"Intent to revise" guidance:* In 2024, FDA issued a "draft update" to its guidance on demonstrating interchangeability in which it stated that it intended to revise the guidance to simplify the interchangeability process for all biosimilar products. The document explained that, based on FDA's further experience with biosimilars and advancements in analytical technologies, comparative analyses like switching studies would no longer be necessary for any biosimilar to establish interchangeability. However, an applicant who chooses to forgo comparative analyses would still have to submit an "assessment" describing how other data in the application satisfy the statutory interchangeability standard.[238,239]

The 2024 "intent to revise" guidance represents a marked shift in the agency's approach to interchangeability, which could facilitate a substantial increase in the amount of interchangeable competition. But the draft is short on practical details. Going forward, FDA should prioritize issuing the actual revised guidance and filling the relevant gaps, including with details such as what data or other information can satisfy the interchangeability standard without comparative analyses like switching studies; under what circumstances the agency intends to require comparative analyses; and how the agency intends to adjudicate disputes about whether comparative analyses are needed in a given case.

FDA should also continue to advocate for a legislative update to the interchangeability requirement. In past years, the agency has proposed legislation to eliminate the statutory distinction between biosimilar and interchangeable products altogether, and to deem all approved biosimilars as interchangeable. Legislation along these lines would further simplify the path to pharmacy substitution beyond what FDA can do under current law, but it also carries risks of unintended consequences and, to the extent that legislation moves forward, FDA should work with Congress to address them. For example:

- If the statute is updated to deem all biosimilars interchangeable, it should be clear that FDA retains the ability to require comparative analyses like switching studies if it finds them necessary in individual cases. Otherwise, the legislation could unintentionally reduce competition in some cases by putting the agency in the position of potentially having to deny a biosimilar application because it could not resolve whether the product can be switched with the brand version without patient risk.
- For similar reasons, any legislation should also clarify that FDA retains the ability to approve biosimilars as non-interchangeable if concerns remain regarding the risk of switching. This could be accomplished by clarifying that FDA may license a biosimilar with restrictions on its distribution—which could be implemented as part of a Risk Evaluation and Mitigation Strategy (REMS)[92]—to preclude pharmacy substitution. Such a provision would avoid a situation in which a biosimilar that is found to present a risk to patients when switching, but that otherwise satisfies the standard for biosimilars, might be denied licensure as a biosimilar to avoid this risk.

CONCLUSION

The recommendations in this paper offer a set of actions, across multiple domains, that FDA can take to facilitate medical product innovation, expand products' availability to patients, and foster improved access. In some cases, the recommended action involves a new policy or a change in direction; in others, the recommendation is to continue with (or expand upon) a policy or program that has been successful. Particularly in the face of current uncertainty regarding FDA's resources and structure, identifying both types of priorities—and ensuring that the agency has what it needs to deliver on them—is important.

Identifying both types of priorities is also important because it provides medical product developers with greater clarity and predictability regarding FDA's future regulatory expectations. Uncertainty regarding what policies the agency will pursue, or the extent to which it will continue with existing initiatives, adds unnecessary risk to development programs. A proactive policy agenda, pursued energetically and communicated clearly, promotes the public health not only through the policies themselves, but by fostering a predictable regulatory environment in which developers are better able to make the big bets that fuel innovation.

POLICY IMPLEMENTATION PRIORITIES

Effective implementation of the recommendations in this white paper requires a strategic, phased approach that balances impact with feasibility. The prioritization framework presented below considers four key factors: ease of implementation, speed of potential execution, resource requirements, and expected impact on public health and FDA's mission. Given recent resource constraints and organizational changes, particular attention has been paid to identifying recommendations that can deliver meaningful results without requiring significant additional staffing or funding. The recommendations have been organized into three tiers to guide implementation planning and resource allocation.

Tier 1: Quick Wins (Months 1–6)

These recommendations can be implemented relatively quickly with existing resources while delivering significant benefits to FDA stakeholders. They represent opportunities for early momentum and visible progress.

Recommendation 1.4: Eliminate unnecessary burdens relating to data formatting
FDA should eliminate the requirement to convert all real-world data into the same format as clinical trial data, which requires significant effort relative to benefit and discourages the use of relevant and reliable data.

Recommendation 3.1: Use all available tools to clear the COVID-19 inspection backlog
FDA should prioritize clearing the inspection backlog that developed from pausing in-person activities during the pandemic and strategically use remote inspection tools to manage the workload.

Recommendation 4.1: Facilitate more data from real-world clinical practice in confirmatory studies
FDA's efforts to improve timely follow-through on post-market requirements should include efforts to facilitate more confirmatory studies that draw on data from real-world clinical practice.

Recommendation 5.3: Update FDA's approach to clinical decision-support software
FDA should revise its guidance on clinical decision support software to better reflect congressional intent and facilitate development of fit-for-purpose tools.

Recommendation 6.1: Continue the Drug Competition Action Plan and Biosimilars Action Plan, and update them to account for changes under the 2022 IRA
FDA should devote sufficient resources to continue activities with a successful track record and update its plans to account for IRA provisions that may reduce incentives for generic and biosimilar development.

Tier 2: Strategic Initiatives (Months 6–12)

These recommendations require moderate investment of time and resources but offer substantial benefits to FDA's core mission. They build upon existing programs and authorities while addressing critical needs.

Recommendation 1.1: Expand FDA's efforts to facilitate novel trial designs
FDA should update its pilot programs to allow more programs to benefit, disseminate learnings more rapidly, and better encourage the appropriate use of external control arms.

Recommendation 1.2: Encourage the use of patient preference information to "right-size" clinical trials
FDA should expand its approach of encouraging patient perspectives in medical device applications to all medical products. This

would improve trial design by informing endpoint selection and statistical considerations, allowing trials to better fit the needs of patients.

Recommendation 2.1: FDA should provide greater specificity, consistency and predictability as to how it will assess the evidence for rare disease products
FDA should standardize evidence assessment for rare disease products across all FDA centers and review divisions, potentially supporting legislation to clarify and improve consistency of regulatory approaches.

Recommendation 2.3: Enable greater use of external controls in studying rare disease
FDA should update its guidance on external controls to better facilitate their use in rare disease contexts, including in combination with other novel trial designs (such as trials involving master protocols).

Recommendation 6.2: Further streamline the pathway for interchangeable biological products
FDA should update its policies to provide a clearer pathway for licensing interchangeable products without the need for switching studies.

Tier 3: Long-Term Projects (Year 2+)

These recommendations require substantial resources, coordination with other agencies or longer timelines for implementation, but represent critical investments in FDA's future capabilities and effectiveness.

Recommendation 2.2: Modernize pathways for extremely rare and "n of 1" diseases
FDA should take action to foster more scalable product development, including by facilitating greater use of its new authority to designate platform technologies.

Recommendation 3.2: Designate foreign manufacturing oversight as a core leadership priority and evaluate options for third-party support
FDA should prioritize foreign inspections at leadership level and explore partnerships with nongovernmental third parties to supplement FDA's oversight capacity for long-standing foreign inspection challenges.

Recommendation 3.3: Develop a rating system to incentivize quality manufacturing maturity
FDA should develop facility ratings based on advanced technology adoption beyond minimum requirements to reduce supply disruption risks, guide inspection priorities and inform payor decisions.

Recommendation 3.4: Incentivize and de-risk investment in advanced manufacturing technologies
FDA should reduce the regulatory risk of using advanced manufacturing technologies (AMTs) by clarifying how existing frameworks that were designed for conventional manufacturing techniques apply to new technologies, and update its guidance on AMT designation to expand incentives for using this new statutory program.

Recommendation 4.2: Pursue reform strategies that address programmatic concerns while prioritizing early availability to patients
FDA should continue reforming the accelerated approval program, including by regularizing its procedures and updating processes for withdrawing approval and using advisory committees, while monitoring new policies to ensure they do not unnecessarily delay patient access.

Recommendation 4.3: FDA should minimize unnecessary duplication with other agencies
FDA should enhance the transparency of its decisions to enable agencies such as the Centers for Medicare and Medicaid Services (CMS) to minimize duplicative review and improve regulatory predictability.

Recommendation 5.1: Accelerate the modernization of FDA technical infrastructure and procurement of advanced tools to improve FDA workflows
FDA should accelerate FDA technology modernization to improve internal operations and product reviews, shifting staff time from manual tasks to ensuring consistency with agency policy and precedent.

Recommendation 5.2: Build upon existing frameworks to facilitate innovative uses of AI in safe and effective medical products, including with respect to potential third-party reviews
FDA should utilize existing frameworks and third-party expertise for AI in medical products rather than creating entirely new regulatory approaches.

This prioritization framework provides a roadmap for implementing the recommendations in this white paper in a manner that balances impact with feasibility. While the timing may be adjusted based on evolving circumstances, the overall approach ensures that FDA can make meaningful progress toward enhancing innovation and access while operating within resource constraints.

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