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.