Enabling Expedited Pathways

Overview of current U.S. Food and Drug Administration (FDA) expedited programs, their benefits, and their challenges

Introduction

FDA expedited programs are intended to speed the development and review of drugs, biologics, and devices—particularly for serious conditions and unmet medical needs. These programs are used to shorten time to market, increase collaboration with FDA, and, in some cases, provide incentives for commercialization such as vouchers or market exclusivity.

With increasing demand for improving development efficiency across the biomedical ecosystem, including from the current FDA Commissioner,[1] CTTI formed a small working group of members to review the current landscape of FDA expedited programs and assess whether a full CTTI project would be helpful to address any gaps or challenges in the use of expedited programs.

This booklet summarizes the current expedited programs*, why they are used, and common challenges in applying to and operating within these pathways. The information provided is collected from an informal review of online sources along with discussions within the working group. CTTI may update this booklet as additional information is gathered.

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***For the purposes of this booklet, the term "programs" is a collective term that includes pathways, designations, and other pilots or related initiatives that support expedited review.**

1. Overview of Established FDA Expedited Programs

The table below describes current established expedited programs within the FDA and their criteria for eligibility:

	Expedited Program	Criteria[2-6]
Drugs & Biologics	**Accelerated Approval (P)**	• addresses a serious or life-threatening condition AND • provides a meaningful advantage over available therapies AND • demonstrates an effect on a surrogate or intermediate endpoint that is likely to predict clinical benefit
	Breakthrough Therapy (D)	• addresses a serious or life-threatening condition AND • preliminary evidence demonstrates substantial improvement on a clinically significant endpoint(s) over available therapies
	Fast Track (D)	• addresses a serious condition AND • nonclinical or clinical data demonstrate the potential to address unmet medical need OR • a drug that has been designated as a qualified infectious disease product
	Priority Review (D)	• addresses a serious or life-threatening condition AND • would "significantly" improve safety or effectiveness OR • any supplement that proposes a labeling change pursuant to a report on a pediatric study under section 505A of the FD&C ACT[2] OR • a drug that has been designated as a qualified infectious disease product OR • any supplement for a drug submitted with a priority review voucher
	Regenerative Medicine Advanced Therapy (RMAT) (D)	A regenerative medicine therapy (cell therapies, therapeutic tissue engineering product, and other regenerative medicines), AND • treats, modifies, reverses, or cures a serious or life-threatening condition, AND • preliminary clinical evidence indicates that the treatment has the potential to address unmet medical needs for such disease or condition
	Orphan Drug Designation (D)	Meets the definition of an orphan drug and is: • a previously unapproved drug OR • a new orphan indication for an approved drug OR • the "same drug" as one already approved but with a potential to be "clinically superior" as determined by Office of Orphan Products

	Expedited Program	Criteria[2-6]

Devices	**Breakthrough Device (D)**	• The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions
		• The device also meets at least one of the following:
		  • represents Breakthrough Technology
		  • no approved or cleared alternatives exist
		  • offers significant advantages over existing approved or cleared alternatives
		  • device availability is in the best interest of patients

	Safer Technologies Program (STeP)	• Not eligible for the Breakthrough Devices Program due to less serious nature of disease/condition treated, diagnosed or prevented by the device. AND
		• Should be reasonably expected to significantly improve the benefit-risk profile of a treatment or diagnostic through substantial safety innovations that provide for at least one of the following:
		  • a reduction in the occurrence of a known serious adverse event
		  • a reduction in the occurrence of a known device failure mode
		  • a reduction in the occurrence of a known use-related hazard or use error
		  • an improvement in the safety of another device or intervention

(P) = Pathway: The specific process a product must go through to be legally marketed in the US (steps and requirements for approval)

(D) = Designation: The status granted to a drug or device based on specific criteria that makes it eligible for certain incentives, benefits or expedited review processes.

For additional key features about these programs, see the following FDA guidance documents and program information:

- Expedited Programs for Serious Conditions Drugs and Biologics
- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions
- Designating an Orphan Product: Drugs and Biological Products
- Breakthrough Devices Program
- Safer Technologies Program (STeP)

2. Additional Incentives, Accelerators, and Pilots

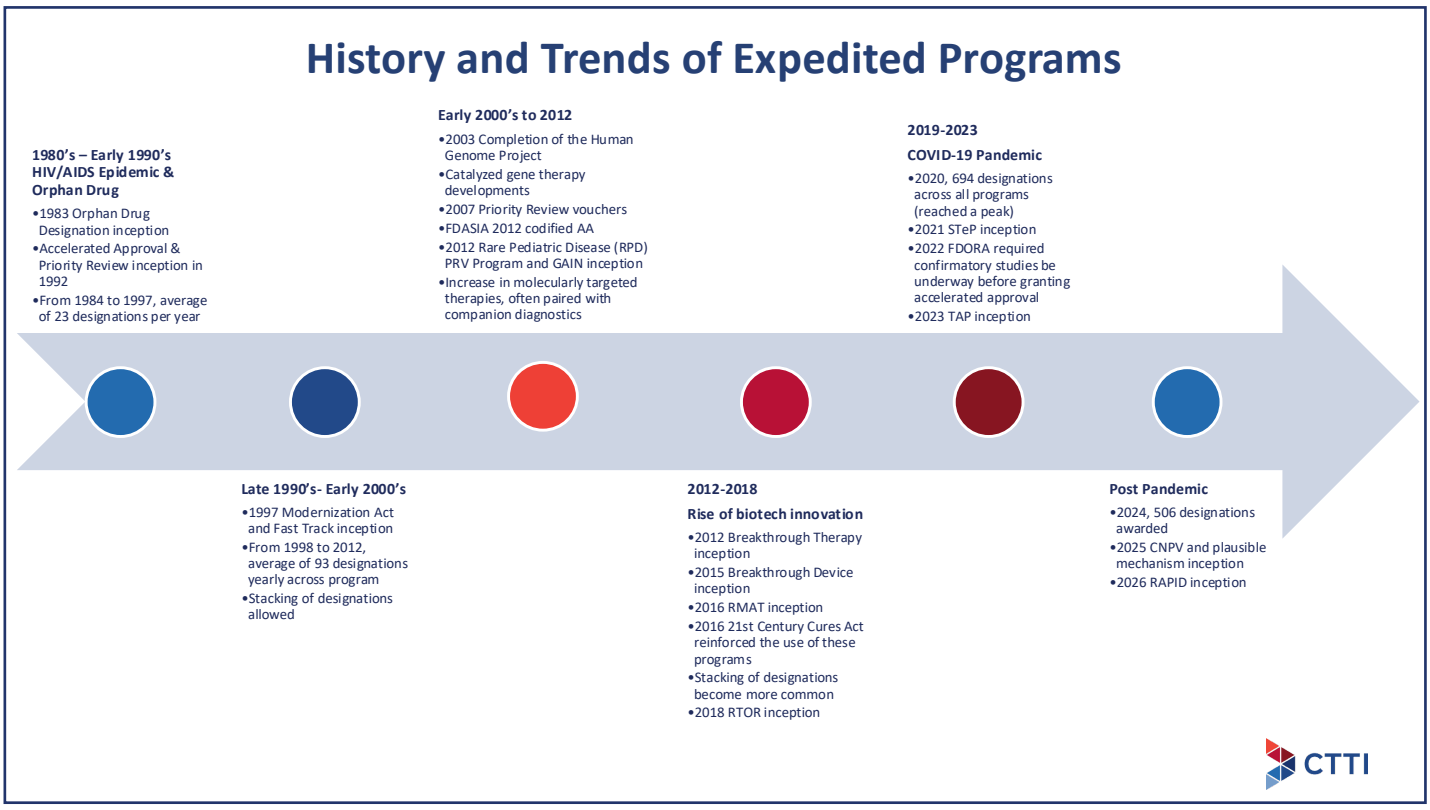
Beyond established pathways and designations, additional initiatives exist that can expedite review processes or provide incentives:

- **Real-Time Oncology Review (RTOR)**
  - Enables reviewers to start analyzing datasets as soon as they are ready, rather than waiting for the entire application.[7]
- **Split Real-Time Review (STAR)**
  - Intended to reduce review times for serious conditions by allowing sponsors to submit data in two parts, core data followed by clinical reports and safety data.[8]
- **Generating Antibiotic Incentives Now (GAIN)**
  - Provides incentives for the creation of new antibiotics, by providing benefits to manufacturers of Qualified Infectious Disease Products (QIDPs) including 5 years of nonpatent exclusivity.[9]
- **Rare Pediatric Disease (RPD) Priority Review Voucher (PRV) Program**
  - Allows for a priority review for a subsequent product application; can be transferred to a third party.[10]
- **Commissioner's National Priority Voucher (CNPV) Pilot Program**
  - Provides a voucher for a 1-2 month review time for drug or biologic therapies that support U.S. national interests.[11]
- **Plausible Mechanism Framework**
  - Intended for diseases for which the biologic cause is known, including the identification of a specific molecular or cellular abnormality, with a well-characterized natural history in the untreated population, and includes a treatment that can demonstrate improvement in clinical outcomes or course that targets the underlying or proximate biological alterations of the disease.[12]
- **Total Product Life Cycle Advisory Program (TAP)**
  - A voluntary pilot to help spur more rapid development of high-quality, safe, effective, and innovative medical devices that are critical to public health. The program provides early, frequent, and strategic communications with the FDA and facilitates engagement with other key parties to advance innovative devices to market.[13]
- **Regulatory Alignment for Predictable and Immediate Device (RAPID) Coverage Pathway**
  - Intended to accelerate beneficiary access to eligible devices with Breakthrough Designation and is available for certain Class II devices participating in TAP.[14]

Some of these initiatives are therapeutic-area specific or are quite new, including recent programs that aim to address unmet needs and conditions that did not meet criteria for existing programs.

3. History and Trends of Expedited Programs

Expedited programs evolved in response to public health needs and scientific advances. The inception of these programs initially started in the early 1980's with the Orphan Drug Act, then in response to the HIV/AIDS epidemic, and later the completion of the Human Genome Project, with more modern initiatives supporting targeted therapies and advanced biologics. Utilization of many of these programs increased substantially during the COVID-19 pandemic and has remained elevated post-pandemic.[15] Collectively, the number of drugs approved through these pathways have also increased, peaking during the pandemic.[14-17]



In 2024, CDER had 50 novel drug approvals with 24 of those (48%) approved as first-in-class. Of those 50 novel drug approvals, 22 (44%) were granted Fast Track, 18 (36%) were Breakthrough therapies, 28 (56%) were designated as Priority Review and 7 (14%) were granted Accelerated Approval. In total, 33 of the 50 novel drug approvals (66%) used one or more of these expedited programs.[16]

4. Expedited Program Utilization

Why Expedited Programs Are Being Used
Stakeholders pursue expedited programs for different, sometimes complementary, goals, such as:

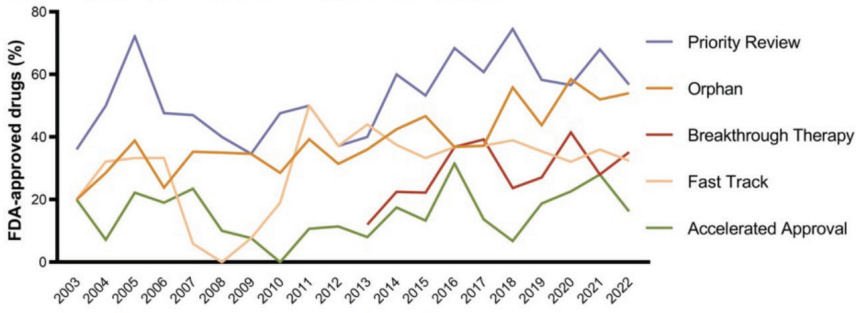
Streamlined processes and faster time to market
- Greater FDA collaboration and clarity through earlier meetings and advice on trial design
- Reduced review times
- Potential to lower development costs when timelines compress

Higher approval success rates in certain contexts
- Orphan products represent a substantial share of new molecular entity approvals.[18-20]

Vouchers and other incentives
- Some designations, e.g. Orphan Drug, confer vouchers that can be sold or used to speed future reviews.
- Orphan drug incentives may include market exclusivity and tax benefits.

More treatments for unmet needs
- Some programs encourage development for rare diseases, serious conditions, and areas with limited therapeutic options.

From: Special FDA designations for drug development: orphan, fast track, accelerated approval, priority review, and breakthrough therapy



Drugs with special FDA approval from 2003 and 2022. *FDA* US food and drug administration. Own illustration

Did You Know?
- Priority Review has been the most frequently used program over time.[15,17] By the 2020's on average, Priority Review was granted to over half of new drug applications.
- The Orphan Drug designation program received the most requests with > 400 per year over the last 5 years.[15]
- Between 2013-2022, 72% of drugs that received breakthrough designation eventually achieved FDA approval[21]
- As of December 2025, CDRH and CBER have granted 1,246 Breakthrough Device designations.[5]

5. Where and When Expedited Options Work Well

A treatment candidate that is well suited for expedited programs involves one or more of the following:

- Addresses a clearly established serious condition and unmet need, including rare diseases
- Involves early indicators or surrogate endpoints that can reasonably predict clinical benefit (common in oncology).
- Has an anticipated benefit that clearly outweighs known and unknown risks when compared to existing treatments for the target patient population.
- Is a novel and highly innovative product.

Scientific Factors Influence Evidentiary Requirements and Program Use

The evidentiary requirements to qualify for expedited programs vary by context and program. Below we highlight a few scientific characteristics that play a role in meeting evidentiary needs, characteristics that ultimately inform decisions around a candidate treatment's submission and acceptance.

1. The time required to measure a clinical benefit

- In diseases in which it takes a long time to measure clinical benefit, meeting the evidentiary expectations for expedited pathways may be more challenging.
- Rapidly progressing disease with measurable near-term outcomes or regulatory accepted intermediate endpoints are often better aligned with expedited development timelines.

2. The sensitivity, reliability, and availability of clinical benefit measures

- Endpoints with a high signal-to-noise ratio and clear clinical relevance are more likely to support regulatory decision-making; for accelerated approval, endpoints should demonstrate they are reasonably likely to predict clinical benefit.
- Diseases with near term outcomes or regulatory accepted intermediate endpoints are often better aligned with expedited development timelines.

3. The maturity of the data

- Some diseases have robust longitudinal data sets showing that the amount of change measured by a biomarker is associated with correlative change in an endpoint. For diseases that do not have established datasets, it may be more difficult to interpret the magnitude and meaning of treatment effects, increasing evidentiary uncertainty.

Use within Therapeutic Areas

Expedited programs have worked particularly well for certain therapeutic areas. Drugs and biologics for Oncology/Hematology are well-suited for these programs because of well-defined surrogate endpoints that are reasonably likely to predict clinical benefit, such as changes in tumor size or progression free survival. Large sponsor companies with oncology expertise tend to navigate these programs effectively, embracing expedited programs as standard practice.

Treatments for rare diseases also highly utilize expedited programs, especially when incentives and feasibility in small populations align. Because rare disease crosscuts therapeutic areas, each is evaluated by FDA on its own merits, balancing the risk of uncertainty against the severity of the disease and the availability of treatments.

Conversely, the use of expedited programs for other therapeutic areas is mixed. In Neurology, drug applications often struggle to meet the "substantial improvement" threshold early on, especially if improvement is based on how a patient feels or functions which can take time and requires larger sample sizes to prove meaningful benefit. In addition, validated surrogate endpoints aren't as common. Thus, sponsors may be more cautious to apply to Accelerated Approval or Breakthrough Therapy due to uncertainties around evidence, unless they have a very compelling early signal.

Exceptions exist. Recently an ALS therapy, Tofersen, was granted Accelerated Approval, Fast Track and Priority Review, and was approved for SOD1-ALS patients based on a surrogate biomarker endpoint of reduction in neurofilament.[22] Thoughtful trial designs, including adaptive designs, enrichment strategies, or designs with pragmatic decentralized elements, and validation are necessary. While expedited programs for neurology drug candidates may have challenges, Neurology is one of the top device areas (along with Orthopedics and Cardiovascular) to receive marketing authorization since the initiation of the Breakthrough Device Program.[23]

For infectious diseases, clinical endpoints are typically well-defined and often rapidly measurable. The outcome is often straight-forward (e.g. the pathogen is cleared). Unless there is an urgent public health need or life-threatening scenario, pursuit of an expedited program may not feel worthwhile. However, this field has opportunities, such as antibiotic resistance, where public need and incentives play a larger role to encourage sponsors to look into treatments that are scientifically feasible but economically unrewarding.

Expedited programs for drugs are more limited in the Cardiology and Metabolic therapeutic areas. It is difficult to compress the development timeline or use surrogate endpoints in Cardiology where improvements are incremental, trials use large sample sizes, and there are hard clinical outcomes (e.g., mortality, MI reduction) which are difficult to achieve within rapid timelines. It is also often hard to demonstrate an advantage over an existing therapy quickly. However, Priority Review is occasionally used for drugs in this therapeutic area that offer a novel mechanism or address an unmet need.

Emerging Initiatives

Despite opportunities for many rare and serious conditions with unmet needs, some diseases with unmet needs, such has long term chronic diseases, are not well suited for the traditional expedited programs. New initiatives, like the Commissioner's National Priority Voucher pilot program (CNPV), are trying to address this gap, especially if they are drug or biologic therapies that support U.S. national interests.[11] Specifically, a therapy may qualify for CNPV if it addresses a large unmet medical need such as a chronic disease crisis in the U.S. or if it demonstrates the ability to deliver a more innovative cure, e.g. a novel immunotherapy to fight multiple diseases.[11]

Scientific and technological advancements, such as improved biomarkers from imaging and modelling and simulation approaches may enable more expedited pathway opportunities for therapeutic areas that haven't been able to meet criteria for traditional programs.

In addition, the following recent initiatives may enable expedited opportunities by helping with justification of benefit and support of evidentiary requirements through innovative approaches. They reflect growing interest and recognition for novel approaches to evidentiary development in rare disease and small populations. These include:

- **Rare Disease Endpoint Advancement (RDEA)**[24]
  - Supports novel endpoint efficacy development for drugs that treat rare diseases.
- **Rare Disease Evidence Principles (RDEP)**[25]
  - Provides greater clarity as to the kinds of evidence that can be used to demonstrate substantial evidence of effectiveness for diseases of known genetic defect.
- **Plausible Mechanism Pathway**[12]
  - Enables the generation of substantial evidence of effectiveness and safety when randomized controlled trials are not feasible due to small patient populations for targeted individualized therapies.

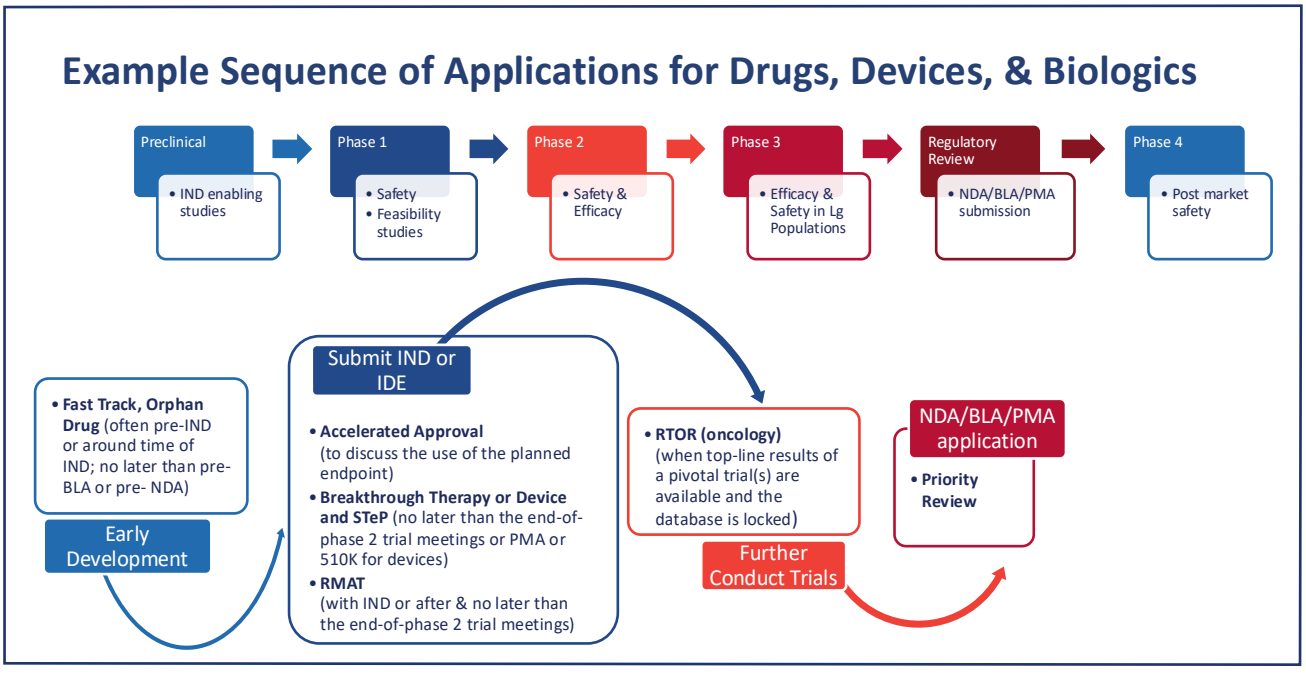
Recent initiatives such as the Regulatory Alignment for Predictable and Immediate Device (RAPID) Coverage Pathway are also creating new opportunities for faster access by allowing innovative products that were accepted as a Breakthrough device designation to have faster coverage decisions and beneficiary access.[14]

Decisions Based on the Development Lifecycle

The timing of submission to an expedited program varies, which may influence a company's decision of when and whether to apply. Sponsors often engage early and strategically, selecting programs that match the development stage and evidence package. This also enables stacking of designations which can be beneficial across the product development lifecycle.

Multiple designations are sometimes stacked because each offers distinct benefits (e.g., interaction, incentives, review speed).

The following image reflects examples of entry points of expedited programs across the development lifecycle.

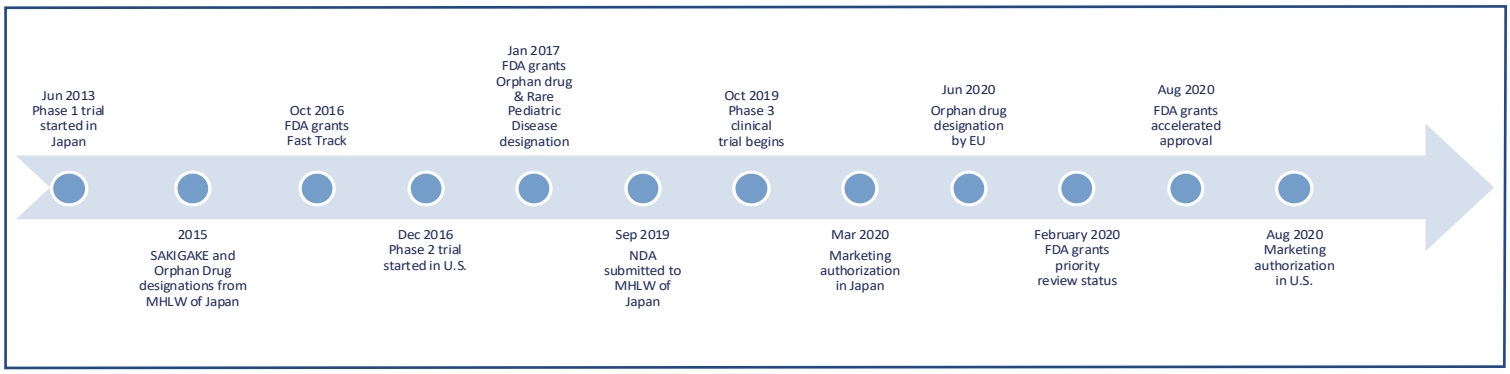


Did You Know?

- The frequency of stacking programs increased after Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012.
- From 2015–2022, over 50% of FDA drug approvals combined Priority Review with at least one additional expedited pathway.[26]
- An Orphan Drug designation is more often than not paired with another expedited program, a benefit for sponsors developing treatments in rare disease.[17,27]
- As of December 31, 2025, the FDA has granted 1,246 breakthrough device designations with 185 receiving marketing authorization. The majority of these designations have been for Cardiovascular.[5]

Case Example: Viltolarsen (DMD)

- Product: Viltolarsen for Duchenne muscular dystrophy (DMD); Company: NS Pharma (subsidiary of Nippon Shinyaku).
- Designations: Fast Track, Accelerated Approval, Orphan, Rare Pediatric Disease designation, Priority Review.
- Evidence basis included 2 studies; Phase 2 primary endpoint was change in dystrophin protein level (increase reported by week 25).
- Timeline included development in Japan and the U.S., with U.S. accelerated approval taking 4 years and 7 years in Japan.



6. Barriers, Challenges, and Examples of Programs with Limited Success

Barriers Applying to a Program

Barriers to applying to expedited programs—some of which were introduced in Section 5 — are listed below. It is important to note that some of the operational challenges may disproportionately affect smaller organizations.

- **Complex eligibility criteria & endpoint selection:**
  - Criteria can be redundant or unclear, creating duplicative sponsor effort.
  - Identifying and gaining acceptance of surrogate endpoints "reasonably likely" to predict benefit can be difficult.[28]

- **Limited clarity on evidentiary standards:**
  - Uncertainty around what constitutes "substantial improvement" or "more effective treatment" for programs like Breakthrough Therapy and Breakthrough Device.
  - Data needs may differ for short- vs. long-term timelines; comparative effectiveness expectations can be challenging.

- **Stacking designations strategically:**
  - Limited insight into sequencing and combining requests can lead to missed opportunities or redundant submissions.

- **Operational burden:**
  - Resource constraints can limit ability to prepare requests and manage frequent FDA interactions.

Challenges Once Accepted into a Program

Upon acceptance, challenges have included:

- Concerns about review quality or internal disagreements in decision-making.
- Difficulty completing confirmatory trials on time.
- Withdrawal risks if confirmatory trials fail, stall, or do not verify benefit.
- Pricing and reimbursement uncertainty; high launch prices, especially for orphan products, can trigger payer resistance and access challenges.
- Payers and clinicians may worry that approving drugs on limited evidence could offer false hope or undue costs if the benefit is not real.
- Risk that accumulating data changes benefit–risk and may affect labels and future eligibility or planned designations.[29,30]

Reasons for Rejection or Market Withdrawal

Once a product is on the market, common reasons for rejection/withdrawal, or failure to convert to full approval, include:

- Safety concerns
- Insufficient evidence or validation
- Failure to meet the endpoint
- Manufacturing issues
- Strategic sponsor decisions (e.g., cost)

Examples of rejections or withdrawals:

Product	Therapeutic Area	Company & Year	Program	Reason
Ocaliva for PBC	Hepatology	Intercept (2025)	Orphan Drug + Fast Track + Accelerated Approval	Safety and insufficient benefit
Rybrevant (SC) for NSCLC	Oncology	J&J (2024)	Breakthrough Therapy + Accelerated Approval	Manufacturing issues
Andexxa for bleeding	Hematology	AstraZeneca (2024)	Breakthrough Therapy + Orphan Drug + Accelerated Approval	Safety
Oxbryta for Sickle Cell	Hematology	Pfizer (2024)	Fast Track + Orphan Drug + Breakthrough Therapy + Priority Review + Accelerated Approval	Safety
Aduhelm for Alzheimer's	Neurology	Biogen (2024)	Accelerated Approval + Fast Track	Insufficient benefit
Drisapersen for DMD	Rare disease	GSK (2014)	Breakthrough Therapy + Fast Track + Orphan Drug + Priority Review	Did not meet endpoint
Vioxx for arthritis	Inflammation	Merck (2004)	Priority Review	Safety
Lartruvo for soft tissue sarcoma	Oncology	Eli Lilly (2020)	Orphan Drug + Fast Track + Breakthrough Therapy + Priority Review + Accelerated Approval	Did not meet endpoint
V-Wave Ventura Interatrial Shunt	Cardiology	J&J (2025)	Breakthrough Device	Insufficient benefit

7. Weighing Uncertainty

Expedited programs can help patients access promising therapies sooner, but they also introduce development decisions that must be actively managed—including the need for timely confirmatory post market evidence, and system impacts such as payer response and trust.

Seeking a balance between flexibility, efficiency and safety is a common occurrence within expedited programs. In an effort to provide flexibility, there may be some uncertainty. Regulators often balance flexibility in proportion to the degree of disease severity, unmet need, and the available scientific evidence, including the feasibility and reliability of confirmatory evidence. Safety must be assessed thoughtfully as some drugs could have irreversible risks.

Regulatory flexibility may shift based on the context. Flexibility may be seen in the type of data or evidence accepted such as the acceptance of real-world data, or in the amount of data required, such as an approval based on a single arm Phase 2 trial as is sometimes seen in Oncology.

There are numerous factors, including uncertainty factors, that must be recognized and balanced with potential benefit of a treatment to inform expedited program decision-making; decision-making on behalf the of the sponsors or CROs, on behalf of the regulators, and on behalf of the patients who receive the product. For example, CTTI often hears from medical product developers about uncertainty around the level of evidence required to prove meaningfulness of an outcome or to support a reasonably likely surrogate endpoint. There is an opportunity to better appreciate uncertainty factors and the decisions that inform expedited program use. There is also an opportunity to better understand how new standards will inform decisions around leveraging expedited pathways in the future, such as FDA's recent announcement that one adequate and well-controlled study will be the default position for market approval, and how new initiatives are being received.[31]

8. Summary

CTTI set out to describe the current landscape and assess gaps in the utilization of expedited FDA programs. Based on the landscape scan and advisory group input this booklet acknowledges that many FDA programs are well utilized. Current gaps in optimizing the use of expedited programs include characterization of decisions around when to leverage which programs, design and logistical support for confirmatory trials, and a better understanding of whether the current pathway options meet the breadth of patient and market need, given advancing technological and trial design capabilities.

The Clinical Trials Transformation Initiative (CTTI) is a public–private partnership with the mission of improving the quality and efficiency of clinical trials. CTTI was co-founded by Duke University and the FDA and convenes leaders from over 70-member organizations to tackle systemic challenges and develop actionable recommendations for the clinical research enterprise. More about CTTI can be found at https://ctti-clinicaltrials.org/about/.

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