

Executive Briefing #5

Expedited Programs for Serious Conditions in the United States (FDA Guidance)

David Schwicker, January 2017

Expedited programs represent the FDA's commitment to **facilitate and expedite** the development of new medicines that address unmet medical need in the treatment of serious and life threatening conditions:

- **Serious conditions** are those that are **life threatening** or associated with **morbidity** that has substantial impact on the **day-to-day functioning**, or the likelihood that the disease will **progress** to a more serious one.
- An **unmet medical need** is a condition whose treatment or diagnosis is **not addressed adequately** by available therapy, or where there is no therapy, including an immediate need for a defined population or a longer-term need for society/public health.
- **Eligible drugs** must be intended to have an effect on a serious condition or a serious aspect of a condition (prevention, diagnosis, mitigation of adverse events).

The above basic principles **apply to all four** FDA expedited programs:

- **Fast track** designation is most beneficial early in development and features frequent interactions with the FDA fast track team regarding study design, safety data, surrogate endpoints, accelerated approval, rolling review, and priority review.
- **Breakthrough therapy** designation is for products where preliminary clinical evidence indicates substantial improvement over available therapy. Its key feature is an FDA commitment of significant resources aimed at rapid development, including access to senior management and the assignment of a dedicated cross-disciplinary project lead.
- **Accelerated approval** is an alternate development pathway that allows drugs to be approved earlier based on a surrogate or intermediate clinical endpoint, with the subsequent requirement for post-marketing confirmatory trials to verify the predicted effect on morbidity or mortality or other clinical benefit.
- **Priority Review** designation directs attention and resources to the rapid evaluation of applications for drugs that, if approved, would be significant improvements in the treatment, diagnosis, or prevention of serious conditions (6 months vs. 10 months standard review).

Fast Track Designation

Fast track designation can be requested at first IND submission or anytime thereafter, but is most beneficial **early in development** given the features offered. The type of information needed to demonstrate the **potential** of a drug to address an unmet medical need will depend on the stage of drug development. Early in development, evidence of activity in a **nonclinical model**, a **mechanistic rationale**, or **pharmacologic data** could be used to demonstrate such potential. Later, **available clinical data** should demonstrate the drug's potential.

Fast track **features** include **frequent interactions** with the FDA review team for a fast track product aimed at discussing study design, safety data, surrogate endpoints, accelerated approval, and priority review. If preliminary evaluation of clinical data determines that a fast track product may be effective, a **rolling review** can be considered, i.e. submitting portions of a marketing application before the complete submission.

Breakthrough Therapy Designation

If **preliminary clinical evidence** indicates that a drug promises **substantial improvement** over **existing therapies** on one or more clinically significant endpoints, including surrogate or intermediate clinical endpoints, breakthrough therapy designation can be considered.

The **key feature** of breakthrough therapy designation is an FDA commitment of **significant resources** to work closely with sponsors. This includes access to **FDA senior management** and the assignment of a **dedicated project lead**, coordinating cross-disciplinary, proactive, collaborative and timely communications. Given the promise of a large effect size over existing therapies, the focus is to **considerably shorten the development program**, with smaller or more efficient trials that require less time to complete and minimize the number of patients exposed to a potentially less efficacious treatment, particularly in **rare diseases**. Additional actions to expedite the process, including **rolling review** and **priority review**, are considered.

Accelerated Approval

Accelerated approval is an alternate **development pathway** that may be granted to a product that has an **effect on a surrogate or intermediate clinical endpoint** that is reasonably likely to **predict an effect on irreversible morbidity or mortality** or other **clinical benefit**.

Accelerated approval has been used primarily in diseases where an extended period of time is required to measure the clinical benefit of a drug. The emphasis is on a more **rapid pace of drug development**, generally involving fewer, smaller, or shorter clinical trials than is typical for traditional approval. **Uncertainty** about whether clinical benefit will be verified and the possibility of undiscovered risks are the reasons that accelerated approval is **reserved** for drugs intended to treat a **serious condition** and that appear to provide a **meaningful advantage over available therapy**. Products that meet standards for traditional approval will not be granted accelerated approval.

As a **condition** for accelerated approval, **post-marketing confirmatory trials** have been required to verify and describe the anticipated clinical benefit. Confirmatory trials must be

conducted with **due diligence**, i.e. as soon as possible and should be underway at the time the marketing application is submitted. The protocol for a post-marketing trial should be developed as early as possible, and timelines for the trial should be specified. Additionally, manufacturers must submit all **promotional materials** (including labelling) intended for the product.

Approval of the product may be **withdrawn** if the predicted clinical benefit is not verified in a confirmatory trial or other evidence demonstrates that the product is not safe or effective.

Whether a surrogate or intermediate clinical endpoint is reasonably likely to predict clinical benefit is a matter of judgment supported by empirical evidence, including clinical data, and the key to determining **eligibility for accelerated approval**. Particularly in **rare diseases**, there may be limited information and little or no experience to inform the interpretation of surrogate endpoints. FDA may consult with external experts in such cases. Therefore, sponsors considering accelerated approval should communicate with the FDA **early in development** concerning the potential eligibility of a drug, proposed surrogate or intermediate clinical endpoints, clinical trial designs, and the integrated planning of confirmatory trials.

Priority Review Designation

A marketing application will receive priority review designation when, if approved, the drug would provide a **significant improvement in safety or effectiveness** or an enhancement of **patient compliance** leading to an improvement in serious outcomes or evidence of safety and effectiveness in a new **subpopulation**. Although such evidence will usually come from randomized clinical trials, a priority review designation can be based on other scientifically valid information, e.g. historical controls.

The key **feature** of priority reviews is the FDA's goal is to take action on the marketing application within **6 months** of receipt, as compared to 10 months under standard review.

It should be noted that expedited programs **do not alter** the current FDA **standards of approval**. As is the case for all drugs, the FDA will review the full data submitted to determine whether expedited program drugs are safe and effective for their intended use before approval for marketing.

Further Information

This executive briefing is a summary of the FDA Guidance for Industry – Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014, available for download at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>

Further information on current early access tools, programs, and initiatives is available at:

<https://www.orphastrategy.com/early-access/>

About ORPHA Strategy Consulting

In rare diseases and for transformative medicines, **early access strategies, benefit/risk and value demonstrations** are often **uncharted terrain**, requiring highly specific expertise and experience.

ORPHA Strategy's principal, David Schwicker (<https://www.orphastrategy.com/biography/>), has industry consulting expertise spanning more than 25 years, and has gained a unique understanding of how early access programs, initiatives, and rare disease and orphan drug incentives can benefit a client's transformative medicine to **prospectively accelerate marketing authorization and market access**. To this is added a focus on **innovative development pathways** that emphasise the use of **real-world evidence**.

Thank you for your interest. To start a strategic discussion on early access, please contact:

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