BEHIND THE BREAKTHROUGH

How the FDA’s Breakthrough Designation Changes a Trial
MOST COVETED OF THE EXPEDITED PATHWAYS

Trials are complicated, with incredibly high stakes. Patients are suffering and doctors are clamoring for a treatment for an unmet medical need.

To accelerate the drug pipeline and commercialization, the FDA offers multiple expedited pathways, that can be used in any combination. Every trial aims for an optimal mix of expedited pathways.

Of all of the expedited pathways, earning Breakthrough Therapy Designation is the most coveted.

This prized designation comes with significant oversight, communication and operational demands. Imaging was used as a surrogate endpoint in 50% of all Breakthrough Therapy Approvals.¹ (Figure 1)

¹ Based on 2015 FDA data.

ANY OF THESE CAN COME INTO PLAY IN A BREAKTHROUGH DESIGNATION

• Priority Review
  The FDA will reduce the review process to 6 months

• Accelerated Approval
  The FDA allows the use of surrogates with the understanding that there will be a post-marketing clinical evaluation (Figure 1)

• Fast Track
  The FDA will review the accumulated data in a rolling fashion

• Orphan-Drug Designation
  Rare disease
On July 9, 2012 the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed. FDASIA Section 902 provides for a new designation—Breakthrough Therapy Designation.

100% of oncology trials that also received Accelerated Approval used central imaging review. For less well-established imaging surrogates, a post-marketing study is required to establish progression-free survival even while the drug is commercialized.

³ Based on 2015 FDA data.

GETTING THE FOUNDATION RIGHT

When imaging results are required for preliminary clinical evidence, they must be performed quickly. Data can be provided to the agency in less than one month. Rapid delivery is everything in this trial incubation phase.

All requests for Breakthrough Therapy Designation are reviewed within 60 days of receipt, and the FDA will either grant or deny the request. Once a drug is designated as a Breakthrough Therapy, the FDA will expedite the development and review of such drug.

A breakthrough therapy is a drug:

• Intended alone or in combination with one or more other drugs to treat a serious or life-threatening disease or condition

• Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development³

If Breakthrough Therapy Designation is granted, the FDA will expedite development and review.

- The FDA will apply all of the Fast Track program features including, the ability to submit a portion of an application prior to the completed version—also known as rolling review (Figure 2)
- The FDA will provide more intensive guidance on an efficient drug development program
- The FDA is committed to involving senior management in such guidance
- The FDA will hold meetings with the sponsor and the review team throughout the development of the drug

**Expect Intensity**

**Standard Review**
Clock starts once FDA receives COMPLETED application.

Individual completed application sections are held until application is complete

Completed application sent to FDA for approval

**Rolling Review**
Clock starts upon submission of first single completed section of application.

Individual application sections are sent to FDA upon completion for rolling review

**Figure 2**

**Breakthrough Therapy Designation is not the same as Breakthrough Therapy Approval.**
To date, only a third of those that have been granted Breakthrough Therapy Designation have earned Breakthrough Therapy Approval.⁴

⁴ Based on 2015 FDA data.
When Breakthrough Therapy Designation is granted, study oversight takes on new meaning, in three key phases:

**Imaging Charter**
Created quickly at the very outset of the study. The imaging charter defines the logic and basis for the independent analysis methodology, and the duties and responsibilities of the individuals conducting the analysis.

**Patient Recruitment**
Imaging can be used to enrich and speed patient recruitment, ensuring that sites only enroll patients that are appropriate for the study. For example, determining if a tumor is measurable on CT scan.

**Image Management**
Images are expeditiously collected, quality control checked, and provided to expert independent readers who will evaluate the images based on the analysis criteria defined in the Charter.

**WHY IS PROJECT MANAGEMENT SO CRITICAL?**

When imaging is a key component of a trial, project management plays a critical role. The best project managers share key characteristics.

**Commitment:** The FDA assigns senior staff to monitor breakthrough therapy trials, from initial request of the designation to submission. The FDA, in turn, expects the same level of commitment from both the sponsor and their vendors. *(Figure 3)*

**Flexibility:** The project manager must be flexible and able to pivot on a dime. If data is needed quickly or the study design has to be altered, the imaging staff must be able to adapt.

**Documentation:** The FDA requires that the sponsor and imaging vendor have clearly documented each key decision. A project journal can capture these decisions in an auditable way.
The central imaging review process plays an instrumental role.

Principal investigators care for the patients. Central imaging review cares for the image, providing critical quality assurance to decrease the variability of image interpretation.

Each reader needs to be specialized in the therapeutic area, trained on the trial’s imaging charter, trained on proper application of the analysis criteria—and most importantly, committed and available for the duration of the study. A plan for adjudicating disagreements and monitoring inter and intra reader variability also needs to be in place.

Even more important, however, is the ability to quickly scale the number of readers trained and able to join the image review team when a study accelerates. Breakthrough therapies often have massive scope changes based on changes to the protocol, an FDA request, or addition of studies. A few dozen enrolled patients can quickly jump to over a thousand, and the reader team may need to grow ten-fold.

**THE NEED FOR TRAINED READERS CAN SCALE QUICKLY**

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7 Breakthrough Therapies achieved approval based on trials with LESS THAN 100 PATIENTS

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5 Based on 2015 FDA data.
From design to endpoint, trials are guided to the best outcome with PAREXEL. Our track record with Breakthrough Therapy trials speaks for itself.

We’ve guided dozens of Breakthrough Therapy trials, and share an insiders’ view of what happens when the stakes, scrutiny, and demand are all sky-high.

DISCUSS TREATMENT OPTIONS AND IDEAS FOR YOUR NEXT TRIAL WITH OUR EXPERTS.

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*Breakthrough Therapy Designation is a remarkable regulatory innovation that changes the economics of drug R&D. It shortens the timeline and reduces the cost of clinical research to the point where one can wonder why any company would want to develop anything else.*

—Bernard Munos  
Pharmaceutical Industry Consultant and Forbes Blogger