Navigating Expedited Regulatory Pathways in the U.S. and Europe

ABSTRACT

Breakthrough therapy designation in the U.S. and PRIority MEdicines (PRIME) in the EU are two programs intended to facilitate and expedite development and review of new drugs to address unmet medical needs. By successfully engaging with regulatory authorities early in the clinical development process, sponsors of eligible investigational drugs can help ensure that their development plans generate the data needed to support expedited development pathways and approval of much-needed therapies for patients.
Background

Innovative companies developing products for a serious disease or condition with unmet medical needs, including rare diseases, may face challenges with the design and execution of early pharmaceutical product development plans. The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have created pathways to encourage early engagement with regulatory authorities to support more efficient product development strategies. The ultimate goal of these expedited regulatory pathways is to achieve earlier patient access to important therapies.

In this white paper, we discuss two similar regulatory pathways – breakthrough therapy designation in the U.S. and PRIority MEdicines (PRIME) in the EU – and how sponsors that potentially qualify for these programs can successfully navigate these pathways.

Breakthrough therapy designation

Breakthrough therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious disease or condition. A serious disease or condition is defined as one associated with morbidity that has a substantial impact on day-to-day functioning. Whether a disease or condition is serious is a matter of clinical judgment based on its impact on factors such as survival, daily functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.¹
Eligibility for breakthrough therapy designation

To be eligible for this designation, preliminary clinical evidence must indicate that the investigational drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint or endpoints. Ideally, this preliminary clinical evidence would be derived from:

- A study that compares the investigational drug to an available therapy (or a placebo or well-documented historical control, if there is no available therapy) in clinical testing, or
- A study that compares the investigational drug plus standard of care (SOC) to SOC alone

Other types of clinical data that could also be persuasive include single-arm studies comparing the investigational drug with well-documented historical experience. For example, data demonstrating that a cancer drug substantially increases overall response rate compared with historical response rate with available therapy may be compelling.

The determination of whether the improvement over available therapy qualifies as substantial is a matter of judgment and depends on the magnitude of the treatment effect (which may include duration of effect) and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy. Some approaches to demonstrating substantial improvement:

- Direct comparison of the investigational drug to available therapy shows a much greater or more important response (e.g., complete response versus partial response) in a trial of treatment-naïve patients or those whose disease has failed to respond to available therapy
- Comparison of the investigational drug with placebo or a well-documented historical control shows a substantial and clinically meaningful effect
- Addition of the investigational drug to available therapy results in a much greater or more important response compared to available therapy
- The investigational drug has a substantial and clinically meaningful effect on the underlying cause of the disease – in contrast to available therapies that only treat symptoms of the disease – and preliminary clinical evidence indicates that the drug is likely to have a long-term disease-modifying effect
- The investigational drug inhibits or reverses disease progression
- The investigational drug has an important safety advantage related to serious adverse reactions and has similar efficacy

Qualification of a clinically significant endpoint

For the purposes of breakthrough therapy designation, a clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM), or on symptoms that represent serious consequences of the disease. A clinically-significant endpoint can also refer to findings that suggest an effect on IMM or serious systems, such as:

- An effect on an established surrogate endpoint
- An effect on a surrogate endpoint or intermediate clinical endpoint that is considered reasonably likely to predict a clinical benefit
- An improved safety profile compared with available therapy (e.g., less dose-limiting toxicity) with evidence of similar efficacy

The sponsor must provide justification for the clinical significance of the chosen endpoint in the breakthrough therapy designation request.
Timing for breakthrough therapy designation requests

Sponsors may request breakthrough therapy designation when an investigational new drug (IND) application is first submitted or at any time thereafter, provided they have sufficient preliminary clinical evidence. Ideally, sponsors should submit a breakthrough therapy designation request no later than the end-of-Phase II meetings. The FDA will respond to these requests within 60 days of receipt of the request. Of note, the designation may be rescinded if the investigational drug no longer meets the qualifying criteria for breakthrough therapy. It is also important to recognize that the standard for breakthrough therapy designation is not the same as the standard for drug approval. The clinical development program must still generate adequate data to establish safety and efficacy, and omitting components of the program that are necessary for such a determination can significantly delay, or even preclude, marketing approval.

Sponsors may refer to the FDA’s Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics for the agency’s recommendations on policies and procedures for breakthrough therapy designation.

PRIME

PRority MEdicines (PRIME) is an initiative launched by the EMA to enhance support for the development of medicines that target an unmet medical need. It was developed in consultation with the EMA’s scientific committees, the European Commission and its expert group on Safe and Timely Access to Medicines for Patients (STAMP), and the European medicines regulatory network. Like breakthrough designation, PRIME is based on increased interaction and early dialogue between regulators and sponsors of promising medicines to optimize development plans and accelerate evaluation so these medicines can reach the patients who need them more quickly.
Eligibility for PRIME

Eligibility for PRIME is restricted to investigational drugs that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. To be accepted for PRIME, a medicine must have demonstrated potential to benefit patients with unmet medical needs based on early clinical data. Of note, there may be cases where it would be possible for a product to be eligible for PRIME through meaningful improvement of safety, rather than efficacy. In such cases, the product may have a similar efficacy to one that is already on the market, but with the expectation of an improved safety profile.

Through PRIME, the EMA offers early and proactive support to sponsors to improve clinical trial designs to generate robust data on an investigational drug’s benefits and risks and to enable expedited application review. Early dialogue also ensures that patients participate only in trials that are adequately designed to provide the data needed for an application, making the best use of limited resources.

Benefits of PRIME

PRIME builds on the existing regulatory framework and tools already available, including scientific advice and accelerated assessment. Sponsors of a medicine that benefited from PRIME can expect to be eligible for accelerated assessment at the time of application for a marketing authorization. When an investigational drug has been selected for PRIME, the EMA will:

+ Appoint a rapporteur from the Committee for Medicinal Products for Human Use or, in the case of an advanced therapy, the Committee on Advanced Therapies. The rapporteur will provide continuous support and help to build knowledge in advance of a marketing authorization application.
+ Organize a kick-off meeting with the rapporteur and a multi-disciplinary team of experts who will provide guidance on the overall development plan and regulatory strategy.
+ Assign a dedicated point of contact
+ Provide scientific advice at key development milestones, involving additional stakeholders such as health technology assessment bodies
+ Confirm potential for accelerated assessment at the time of marketing authorization application (MAA)

While PRIME is open to all companies on the basis of preliminary clinical evidence, sponsors from the academic sector and micro-, small-, and medium-sized enterprises may apply earlier at the proof-of-principle product development stage on the basis of compelling non-clinical data and tolerability data from initial clinical trials. They may also request fee waivers for scientific advice.

Figure 2. Comparison of breakthrough therapy and PRIME

<table>
<thead>
<tr>
<th>Feature</th>
<th>Breakthrough therapy</th>
<th>PRIME</th>
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<tbody>
<tr>
<td>Qualifying criteria</td>
<td>Treat a serious or life-threatening condition and provide preliminary clinical evidence indicating a potential for substantial improvement over existing therapies</td>
<td>Demonstrate a potential to significantly address an unmet medical need or bring a major therapeutic advantage</td>
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<tr>
<td>Regulatory engagement</td>
<td>+ Increased communication and guidance from the FDA during development and review</td>
<td>+ Intensive guidance, including early and ongoing scientific advice on the development plan, with involvement of multiple stakeholders</td>
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<tr>
<td></td>
<td>+ Cross-disciplinary project lead assigned to FDA review team</td>
<td>+ Early appointment of rapporteur</td>
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<td></td>
<td>+ Increased involvement of senior managers</td>
<td>+ Initial kick-off meeting</td>
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<tr>
<td>Submission efficiencies</td>
<td>Rolling review</td>
<td>Scientific advice on key decision points for preparation of MAA</td>
</tr>
<tr>
<td>Regulatory response to request</td>
<td>Within 60 calendar days of receipt of request</td>
<td>Forty days from the start of the procedure (Scientific Advice Working Party meeting)</td>
</tr>
<tr>
<td>Impact on review timeline</td>
<td>May be eligible for priority review if supported by clinical data at the time of submission</td>
<td>If confirmed to be eligible for accelerated assessment, then 150 days</td>
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Navigating the expedited regulatory pathways

Sponsors may benefit from pursuing breakthrough designation and PRIME in parallel, as there is significant overlap in the legwork involved. Pursuing the pathways in parallel also makes sense because the regulators at the FDA and EMA communicate with each other throughout the review and approval process.

Involving an experienced contract research organization (CRO) as early as possible in the clinical development planning process may help sponsors prepare and position themselves for more productive interactions with the FDA and EMA.

How a CRO can help

1. **Regulatory guidance.** Sponsors, especially small biotechnology and specialty pharmaceutical companies, may have limited experience engaging with regulatory agencies. An experienced regulatory affairs team can educate clients on the requirements for these programs and provide customers a critical assessment of the drug product data to ensure suitability for qualification for these opportunities. In addition to providing input on the regulatory aspects of a clinical development plan, a CRO can further assist with interactions with the regulatory agencies.

2. **Medical and scientific expertise.** Medical and scientific experts, particularly those with previous experience in the therapeutic area of interest, can help with understanding of the natural history of the disease and disease pathophysiology.

3. **Operational expertise.** A team with a wealth of experience, especially in rare disease and highly unmet medical need indications. Who are able to leverage this experience to provide sponsors with operational advice on design and execution of the studies.

4. **Informatics and feasibility.** An accurate, robust assessment of the feasibility and achievability of a study is critical to the success of any clinical trial or program, and medical informatics is a core discipline and process. A confidently modeled trial starts with the assessment of all relevant factors that will affect the proposed study, from therapeutic landscape intelligence to historical trial and site metrics. Pivotal information collated and analyzed through medical informatics and discussed with internal therapeutic experts, including drug development services, produces a robust assessment that considers all available data, including recent or historical external clinical trials, published literature, and internal experience with similar studies, to assess the proposed study’s ideal successful strategy. Additional analysis performed by this group would include:
   - Assessment of the top sites and investigators having conducted matching trials by indication or by mechanism of action
   - Research into competing trials by cancer stage, or recruitment rate by cancer stage, where applicable
   - Site-level contact to investigators with a specific set of questions to explore protocol criteria options, impact, and interest

5. **Study design incorporating novel statistical methodologies.** Investigational drugs that qualify for breakthrough therapy designation or PRIME may be well-suited to alternative clinical trial designs such as adaptive designs, an enrichment strategy, crossover or N-of-1 design and use of historical controls, or use of an interim analysis by a data monitoring committee. These trial designs – which may be especially useful in rare disease studies – may enable smaller trials or more efficient trials that require less time to complete and may help minimize the number of patients exposed to a potentially less-efficacious treatment. A CRO with expert statisticians with firsthand experience in alternative clinical trial designs can assist in streamlining the development process.
Conclusion

Persistent areas of unmet medical need – including rare diseases – remain throughout the world. Breakthrough therapy designation and PRIME help sponsors pursue timely patient access to beneficial and safe medicines for unmet medical needs. Both programs seek to leverage early and ongoing regulatory advice with the hope of translating advances in scientific research into accessible patient treatments in an efficient, effective manner. Partnering with an experienced CRO can help with qualification for these expedited review programs and development and execution of a robust clinical trial to generate the data needed to support approval.

References


**Lisa Pitt | Vice President, Global Regulatory Affairs**

Dr. Lisa Pitt is Premier Research’s premier regulatory official, and provides strategic guidance and oversees the company’s regulatory affairs service offerings. Dr. Pitt has more than two decades of experience in the pharmaceutical and contract research industries and extensive expertise in small-molecule and biologic pharmaceutical product development, from early phase through registration and post-marketing.

She oversaw regulatory activity for global product development teams at MedImmune as Director of Regulatory Affairs and served as Director and Principal Regulatory Affairs Consultant at PAREXEL. She also held regulatory positions at Novartis Pharmaceuticals, and immediately prior to joining Premier Research, was a senior regulatory project manager at the U.S. Food and Drug Administration, responsible for drugs and biologic products intended for the treatment of inherited metabolism disorders.

Dr. Pitt holds a doctorate in pharmacy from the University of Maryland School of Pharmacy, a Master of Science and Jurisprudence from Seton Hall Law School, and a bachelor’s degree in biological sciences from the University of Delaware.

**Bassem Saleh | Vice President, Medical Affairs**

Dr. Bassem Saleh is a highly experienced and qualified hemato-oncologist and pharmaceutical physician. He has more than five years’ clinical hemato-oncology experience and more than ten years’ clinical research experience in drug development between CROs and pharmaceutical companies across all phases of clinical development (Phase I - Phase IV). During his time in the pharmaceutical industry, Dr. Saleh has applied his medical expertise in drug development, building customer relationships, identifying new-business opportunities, and managing large teams of medical directors. He has acted as global lead medical monitor, leading global medical and safety teams on more than 40 Phase I - IV hematology/oncology studies.

Dr. Saleh has also been an active member of the Therapeutic Area Expert Group in hematology/oncology and translational medicine teams. He has been involved in assessments of in-house drug development candidates and in-licensing drug candidates. He is trained and certified in hematology, oncology, and pharmaceutical medicine. He holds an MD from the Lebanese University in Beirut, an MFPM and a CCT from the Faculty of Pharmaceutical Medicine of the Royal College of Physicians in the U.K.

**About Premier Research**

Premier Research is a leading clinical development service provider that helps highly innovative biotech and specialty pharma companies transform breakthrough ideas into reality. The company has a wealth of experience in the execution of global, regional and local clinical development programs with a special focus on addressing unmet needs in areas such as analgesia, CNS, oncology, pediatric and rare disease. Premier Research operates in 84 countries and employs 1,000 professionals, including a strong international network of clinical monitors and project managers, regulatory, data management, statistical, scientific, and medical experts. They are focused on smart study design for advanced medicines that allow life-changing treatments.

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