

## **Expedited drug development**

### **An overview of PRIME, Breakthrough Therapy and Fast Track procedures**

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This article provides an overview of PRIME, Breakthrough Therapy and Fast Track regulatory procedures intended to optimise the development of medicines that target an unmet medical need.

#### **1. EUROPE**

##### **1.1 Priority medicines (PRIME) scheme**

PRIME was launched by the European Medicines Agency (EMA) in 2016 to facilitate the development of medicines that target an unmet medical need. Through PRIME, the Agency offers early and proactive support to medicine developers with the aim of optimising the generation of robust data on a medicine's benefits and risks, and enabling accelerated assessment of medicines applications.

The overall goal is to ensure patients benefit as early as possible from therapies that may significantly improve their quality of life.

PRIME focuses on improving the design of clinical trials in order to ensure the efficient generation of the necessary clinical data for inclusion in a Marketing Authorisation Application (MAA). Once a new medicine has been selected for PRIME, the Agency will:

- appoint a Rapporteur from the Committee for Medicinal Products for Human Use (CHMP), or from the Committee on Advanced Therapies (CAT) in the case of an advanced therapy, to provide continuous support during development;
- organise a kick-off meeting with the CHMP/CAT Rapporteur and a multidisciplinary group of experts to provide guidance on the development plan and regulatory strategy;
- provide scientific advice at key points in the development programme. This may involve additional stakeholders such as health-technology-assessment bodies to facilitate quicker access for patients to the new medicine;
- assign a dedicated contact point;
- confirm potential for accelerated assessment of the marketing authorisation application.

In order to be eligible for access to the PRIME scheme, it must be shown that a new medicinal product has the potential to benefit patients with unmet medical needs, based on early clinical data. This might include conditions for which no satisfactory method of diagnosis, prevention or treatment is currently available or, even if such a method exists, the medicinal product concerned will offer a major therapeutic advantage.

While PRIME is open to all companies on the basis of preliminary clinical evidence, applicants from the academic sector and micro-, small- and medium-sized enterprises (SMEs) can apply earlier on the basis of compelling non-clinical data and tolerability data from initial clinical trials.

In order to apply for access to the PRIME scheme, a request for eligibility to PRIME is submitted to the EMA in accordance with submission deadlines published on the EMA website. The request for eligibility consists of the following:

- Pre-submission request form
- PRIME eligibility justification document

The PRIME eligibility justification document, which must not exceed 30 pages, should include the following:

- Background information on the disease
- Background information on the product
- Applicant's justification and claim of major public health interest
  - Epidemiology
  - Available treatments
  - Evidence to address unmet medical need (non-clinical and clinical data)

On receipt of the PRIME eligibility request, the EMA will confirm whether it is within the scope of the scheme, and that the format and content is adequate to support the review of the request.

If the request is acceptable, a Scientific Advice Working Party (SAWP) reviewer and an EMA scientific officer will be appointed, and the review will be conducted through the SAWP. The reports will be forwarded for comments to the SAWP and CHMP, prior to final adoption. The CHMP will aim to have outcomes adopted within 40 days of the start of the procedure. After adoption by the CHMP, the applicant will receive a letter summarising the outcome of the evaluation with the reasons for acceptance or rejection into the scheme. Reports prepared to support the final outcome will not be shared with the applicant.

EMA has published information on the first 12 months of operation of the scheme (April 2016 to April 2017) during which time 96 requests were processed of which 20 were granted PRIME status. Twelve of these were for advanced therapies of which 8 were for orphan medicines. Six of the 20 medicines granted PRIME status were for oncology indications and 6 were for haematology/haemostaseology indications. Insufficiently robust data was cited as the main reason for requests for PRIME status being denied.

## **2. USA**

### **2.1 Fast Track**

Fast Track is a process designed to facilitate the development, and expedite the review, of drugs to treat serious conditions and fill an unmet medical need. The latter is defined as any drug being developed to treat or prevent a condition for which no therapy is currently available.

If there are available therapies, a Fast Track drug must show some advantage over available therapy, such as:

- Showing superior effectiveness, effect on serious outcomes, or improved effect on serious outcomes
- Avoiding serious side effects of an available therapy
- Ability to address emerging or anticipated public health need

A drug that receives Fast Track designation is eligible for some or all of the following:

- More frequent meetings with FDA to discuss the development plan and ensure collection of appropriate data needed to support drug approval
- More frequent written communication from FDA about such things as the design of the proposed clinical trials and use of biomarkers
- Eligibility for Accelerated Approval and Priority Review, if relevant criteria are met

- *Rolling Review*, which means that a drug company can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than having to wait until all sections of the application are available

A company may request Fast Track designation when the Investigational New Drug (IND) application is first submitted or at any time thereafter before receiving marketing approval of their BLA or NDA. The request should include a concise summary of information that supports the Fast Track designation for the indication being studied, including the following:

- The basis for considering the drug to be one intended to treat a serious condition
- The basis for considering the drug to have the potential to address an unmet medical need and an explanation of how this potential is being evaluated in the planned drug development program (e.g., a description of the trials intended to evaluate this potential)

FDA will respond to Fast Track designation requests within 60 calendar days of receipt of the request.

## **2.2 Breakthrough Therapy**

Breakthrough Therapy designation is intended to expedite the development and review of drugs for the treatment of a serious condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). This 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. This can include an effect on a surrogate endpoint considered reasonably likely to predict a clinical benefit, or an effect on a pharmacodynamic biomarker that does not qualify as an acceptable surrogate endpoint but strongly suggests the potential for a clinically meaningful effect on the underlying disease.

A drug that receives Breakthrough Therapy designation is eligible for the following:

- All Fast Track designation features
- Intensive FDA guidance on an efficient drug development programme, beginning as early as Phase 1
- Organisational commitment involving FDA senior managers

Although sponsors may request Breakthrough Therapy designation when the IND is first submitted or at any time thereafter, requests for designation should not be submitted until preliminary clinical evidence is available indicating that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. FDA therefore expects that in most cases Breakthrough Therapy designation requests would be submitted as an amendment to the IND. The request should include a concise summary of information that supports the Breakthrough Therapy designation request for the indication being studied, including the following:

- The basis for considering the drug to be one intended to treat a serious condition
- The preliminary clinical evidence that the drug may demonstrate substantial improvement over available therapies

FDA will respond to Breakthrough Therapy designation requests within 60 calendar days of receipt of the request.

### 2.3 Differences between Fast Track and Breakthrough Therapy designation

The most significant difference is the type of data required. Fast Track can be granted based on preliminary data, such as activity in a nonclinical model or pharmacological data, or a mechanistic rationale. Breakthrough Therapy designation requests must use preliminary clinical data, and therefore activity in a nonclinical model or a mechanistic rationale alone would not be sufficient.

There are also subtle differences in the designation criteria. Drugs seeking Fast Track must only have the potential to address an unmet medical need, while drugs seeking Breakthrough Therapy designation must have preliminary data which demonstrate substantial improvement on clinically significant endpoints over available therapies.

### 3. SUMMARY

	Expedited Programme		
	PRIME	Fast Track	Breakthrough Therapy
Region	Europe	USA	USA
Benefits	Enhanced interaction and early dialogue with EMA  Optimised development plan, accelerated time to approval and facilitation of early access for patients	Actions to expedite development and FDA review  Enhanced interactions with FDA	All Fast Track designation features  Intensive guidance on an efficient drug development program, beginning as early as Phase 1  Organisational commitment involving senior managers at FDA
Eligibility	Early clinical data shows potential to benefit patients with unmet needs  SME can apply earlier in development on basis of compelling non-clinical data <b>and</b> if FIH data indicate adequate exposure for the desired pharmacotherapeutic effects and tolerability	Drug to treat a serious condition  AND nonclinical or clinical data demonstrate the potential to address unmet medical need	Drug to treat a serious condition  AND preliminary clinical evidence indicates drug may offer substantial improvement on clinically significant endpoint(s) over available therapies