

## Client Alert

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### Our latest observation on breakthrough therapy designation (BTD) under the United States Food and Drug Administration Safety and Innovation Act (FDASIA)

#### Facilitation of medicinal products to patients

Market entry timing is crucial in planning for a product launch. Given the valuable but limited period of a product's patent or administrative protection (or regulatory exclusivity), the timeliness of launching a product is essential in maximizing commercial benefit, particularly for medicinal products.

In the United States, there have been several regulatory tools or programs created to facilitate patients' access to medical products with clinical benefits, such as priority review (1992); accelerated approval (1992); fast track (2007); breakthrough therapy (2012); (these first four programs are defined by the United States Food and Drug Administration (FDA) as its four expedited programs for serious conditions); compassionate use; flexible clinical development programs, and so on. Such regulatory programs also provide opportunities for companies to introduce their innovative products. A smart regulatory strategy to utilize these programs paves the best way to expand the validity of a product's commercial life, as well as stir excitement and anticipation among investors.

#### Breakthrough therapy designation

Under the FDASIA, BTD is applicable for a drug or combination products intended to treat serious or life-threatening conditions when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

The FDA interprets the meaning of the preliminary clinical evidence as "evidence that is sufficient to indicate that the drug may demonstrate substantial improvement in effectiveness or safety over available therapies, but in most cases is not sufficient to establish safety and effectiveness for purposes of approval." The agency prefers that a sponsor develop its preliminary clinical evidence from a study comparing the investigational drug to an available therapy (or placebo if no available therapy exists), or from a trial comparing the investigational drug plus standard of care to standard of care alone. If there is no available therapy, and a sponsor likes to show its investigational drug with substantial improvement, the preliminary clinical evidence is required to show a substantial and clinically meaningful effect on an important outcome compared to either placebo or historical control.

The correct understanding of the meaning of preliminary clinical evidence and substantial improvement are factored into the sponsor's decision to apply for BTD. Center for Drug Evaluation and Research Director Janet Woodcock has

contended that the failure to obtain BTM is mostly attributed to the sponsor's submitted results of preliminary clinical evidence that suggest only an incremental and not a substantial improvement over existing treatments.

BTM requests can be submitted as early as at the filing of the Investigational New Drug, ideally not later than the end-of-phase-II meeting, and should avoid being made after a New Drug Application /Biologics License Application filing (There is a prominent exception wherein Gilead submitted its BTM request for the hepatitis C drug Sovaldi late in the NDA review process). After the receipt of the request, the FDA commits to acting within 60 calendar days by issuing either a designation letter or a non-designation letter. In a non-designation letter, the FDA will include an explanation of the agency's decision and may offer advice on subsequent measures to be taken.

If a company has not requested for BTM, the FDA might itself suggest it upon review of the early data submitted. However, a sponsor still needs to make a BTM request itself, and the FDA's suggestion cannot be interpreted as guaranteeing BTM once a request is submitted and reviewed.

On the other hand, the agency also retains the authority to rescind the designation. When a breakthrough designation is no longer supported by emerging data, or the sponsor no longer pursues the development of drugs with BTM, the FDA will notify the sponsor of its intent to rescind but will offer the sponsor an opportunity to justify its product's continued designation. In the event a drug with BTM earns approval, other drugs with BTM targeting the same segment of patients might lose their designations.

## Advantages

All of the benefits of fast-track designation will be available to investigational products awarded BTM. In addition, "intensive guidance" on development will begin as early as phase I. The intensive guidance is reflected by the FDA's commitment through its all-hands-on-deck approach. In this approach, FDA commits to guiding sponsor-awarded BTM in the course of drug development. This all-hands-on-deck approach brings together the needed review disciplines, including chemistry and manufacturing, and involves senior leadership early on. BTM also provides more direct and collaborative engagement with the agency. Our experience tells us that sponsors with BTM have been treated in a very favorable manner. The BTM cases may be attended by director-level officers, and the agency may assemble 20 staff members for BTM engagement, rather than fewer than 10 members during normal proceedings.

The whole framework produces several advantages to a sponsor:

- (1) Shorter development time: The industry's general assumption is to shorten by 30 percent to 50 percent the development time upon grant of BTM. It will substantially increase the net present value of a particular investigational therapy.
- (2) Regulatory certainty: The intensive interaction with the regulatory agency shall be able to increase the predictability of the FDA's decision, and to frame the following clinical investigation in line with the FDA's consideration.
- (3) The image on FDA's endorsement of science: A product with BTM is perceived to have high scientific value from the FDA's perspective. A BTM may present an image of the granted drug with lower failure rate and more stellar future to investors and key opinion leaders.

Through June 13, the FDA's Center for Drug Evaluation and Research received 164 requests for designation, granting 48 and denying 83. The Center for Biologics Evaluation and Research received 31 requests, granting 4 and denying 25 as of May 31. Until this moment, the Center for Drug Evaluation and Research has already approved 6 products with BTM. Roche's Gazyva is the first approved drug.

However, the BTM status does not lead to the final approval directly. Novartis's Serelaxin won BTM last summer but has been issued with complete response letter this March.

In light of these statistics, it is unsurprising that FDA Commissioner Margaret Hamburg concluded, during her last hearing in Congress, that the breakthrough program has been much more popular than anticipated.

## Challenges

Currently, most of the BTMs are granted to late-stage products developed by big pharmaceutical or biotech companies though the program was initially planned to benefit early-stage novel therapies and support small to mid-size companies. When we look back to BTM practiced over the past year, the major hurdles or challenges emerged in the following sectors:

### (1) Payer

Payers express their reservation in accommodating the rising number of products with BTM that from the FDA's perspective may have high clinical benefits. The accelerated rate of introduction to patients may also deteriorate their short-term financial capacity to expand its coverage.

Besides, the current regulatory requirement includes less evidence based on accepted endpoints and in smaller patient populations than what conventional drugs would obtain to gain approval. This will create difficulty for drug developers because this may mean restriction of market access and restriction of reimbursement. The company may also face the difficult decision of whether to aim to win the favor of the payer or the favor of the regulator in their trial design for products with BTM.

Additionally, a sponsor also needs to adjust its product launch timeline to this new drug development scenario of BTM. Traditionally, the company hardly attends to market access issues until the mid-to-late stages of clinical trials, perhaps six to eight years after the commencement of clinical trial. A compressed timeline will not allow the company to formulate a market access strategy for its investigational drug in accordance with its traditional practice. This challenge will especially emerge when they are struggling to reap the benefits of BTM while producing clinical data to prove the value of their products in front of payers.

### (2) Manufacturing / production

The shorter timeline implies that production needs to be able to scale up in a shorter timeframe, or sponsors will not be able to reap BTM benefits. The FDA has already said that manufacturing facilities will likely have to be ready faster than they normally are to cater to BTM. Some companies, such as Roche, highlight the importance of practice by attending manufacturing issues in pursuance of BTM in its portfolio management or research and development planning.

There are still voices that call for a more flexible approach in the FDA's manufacturing requirements. Meanwhile, the FDA is looking for a more systematic solution that would utilize modern approaches to manufacturing.

### (3) Companion diagnostics

Many BTM drugs depend on companion diagnostics to prove their superior efficacy. The FDASIA initially fails to integrate the Center for Devices and Radiological Health (CDRH) in its review process. However, we see CDRH actively utilize other proceedings and commit the center itself to perform priority review on accompanying diagnostics in support of BTM drugs.

In addition, CDRH is introducing the expedited access premarket approval program (EAP). The EAP is a voluntary regulatory program and allows the FDA to exercise its regulatory approval authority in reliance on assessment of a device's effect on an intermediate or surrogate endpoint that is reasonably likely to predict clinical benefit. The EAP program may also reduce required manufacturing information in the premarket approval application, and the FDA may also forgo preapproval inspection of certain manufacturing sites but conduct those inspections after approval.

The implementation of the EAP program will be beneficial to speed up the development of companion diagnostics, and will complement the timeline for the development of products with BTM.

### (4) Bioventures' corporate development

Bioventures are struggling to formulate its corporate development strategy considering the prospect of BTM. BTM compressed the timeline of project development, which has exerted pressure on bioventures to formulate an effective corporate development strategy. The internal project alignment poses an extremely harsh challenge, and the unsophisticated understanding of rising issues due to BTM may lead the company to be lost in its corporate development settings. Moreover, bioventures are struggling to retain sufficient resources and to increase its talent pool. These disadvantages might produce undesirable results because bioventures might find it difficult to follow or utilize the FDA's intensive guidance due to scarcity of resources and talents.

## Stakeholder approach

It has gradually become the norm for the FDA to attend to stakeholders' sentiments in its regulatory decisions, but it remains unclear as to how the FDA could further involve patients in BTM. The agency has commissioned a number of disease-specific meetings with patients and advocates to learn more about unmet needs and disease burden. The communication might serve as the cornerstone to integrate patients' views into BTM decisions in the future.

## Non-US regulators

We do not see any identical program with BTM in other jurisdictions. But there are other regulators that build up comparable pathways to introduce novel therapies to the clinical settings as early as possible.

### (1) European Medicines Agency (EMA) – Adaptive licensing

There have been several existing regulatory paths in Europe to expedite drug development. The most frequently seen approaches include: (1) scientific

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advice; (2) centralized compassionate use; (3) the conditional marketing authorization mechanism (for life-threatening conditions); and (4) accelerated assessment. This March, EMA kicked off a pilot project for adaptive licensing. In adaptive licensing, the sponsor will be granted early marketing authorization in a restricted patient population but is required to conduct several phases of evidence gathering. The sponsor must then update the license to cover broader patient segments. Conceptually, a sponsor will start its project with a core population, and the treatment-eligible population would grow from there.

In addition, EMA will adopt a stakeholders' approach to introduce adaptive licensing, and thereby request input from reimbursement agencies, mostly health technology assessment entities, and in addition, patient groups. The UK's National Institute for Health and Care Excellence has shown strong interest to work together with EMA in adaptive licensing, however, several health technology assessment bodies have not expressed the same level of interest.

(2) Medicines and Healthcare Products Regulatory Agency (MHRA), United Kingdom – Promising Innovative Medicine

This March, MHRA has framed its Early Access to Medicines (EAM) scheme to permit ground-breaking novel medicine to severely ill patients if early clinical studies of this medicine suggest the benefits might outweigh the risks. MHRA will conduct necessary assessment and grant "Promising Innovative Medicine" designation to products that can be benefited under the EAM scheme.

(3) Pharmaceuticals and Medical Devices Agency (PMDA), Japan – a collaborative approach

Unlike in the US or EU, there is no comparable regulatory programs stipulated in statutes to expedite drug development in Japan. In our experience representing clients in such matters, most of the cases come down to how well a sponsor collaborates with the regulatory agency to identify the most efficient path. Based on our observation, the agency itself exercises more discretion than its foreign agency counterparts. Sponsors should be active in consulting with correspondent staff members in PMDA and should be proactive in building constructive relationships with the agency. In the past few years, the PMDA has become more willing to constructively interact with sponsors, and holds to its commitment to strengthen regulatory science capacity. Overall, patients' access to innovative products has continued to improve in Japan.