# Commercialization strategies for early stage drug-related startups

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Drug-related startups face a serious barrier at the early stages of the commercial production of drug therapies (as do those seeking the licensing or purchase of those therapies by established pharma companies).

This barrier is caused by the timing and funding gap between the initial phase of patent acquisition, which provides intellectual property protection for the startup, and the achievement of clinical trial results that demonstrate a credible commercial drug therapy.

Consequently, expediting Food and Drug Administration approval at the earliest stages of a drug's development can be highly advantageous to startups.

For many startups, the prospect of gaining FDA clearance can appear not only intimidating in terms of time and effort, but also questionable as an allocation of resources, because of the substantial costs involved.

However, every drug-related startup needs to keep in mind that FDA clearance is needed before a commercial product can be sold directly to physicians or hospitals and paid for by insurance.

Some startups have tried to avoid the FDA processes by marketing and selling drugs for off-label uses, which are uses for which no FDA clearance has been obtained.

Although doctors can legally prescribe drugs for off-label uses based on their own medical judgment, it is a legally risky decision for any company to engage in the marketing of drugs for off-label uses.

Substantial fines and legal settlements may be the cost of engaging in attempts to market drugs off label.

Moreover, in raising capital from investors to finance the research and development work of the startup, it is a huge advantage to show that the startup has already considered and formed a strategic plan for expedited FDA approval.

Investors are concerned with a range of risks that drug-related startups face, including unknowns regarding anticipated costs between innovations and commercialization; possible high fixed costs to establish regulatory precedent (such as the nature of the content and format of required information for the FDA to perform an evaluation of an innovative drug); the potential existence of other treatments that might advance to market before the FDA process is completed; a shifting regulatory regime; and changes in political control and outlook that can affect FDA policies.

For these reasons, efforts to gain FDA clearance as soon as possible should be considered a key part of a startup's business plan.

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## A COMPLEX PROCESS

Given the complexity of the FDA process, it is generally best practice for a startup to hire an employee who has experience in guiding a drug through the various stages of the approval process.

Alternatively, outside consultants with substantial experience relating to the FDA process are available. Of course, this comes at a cost that may appear tangential to more immediate concerns such as the scientific work necessary to develop a product that is ready for clinical trials.

However, since clinical trials — and their related statutory reporting requirements and FDA assessment — are an inevitable part of the drug development process, formulating an FDA-process strategy at an early stage will ultimately save time and money.

For example, electronic record storage is a crucial practical aspect of FDA compliance that startups frequently do not sufficiently consider. All computer systems that are used to create, change or maintain electronic records and signatures (including mobile electronic devices) are subject to FDA validation.

At any given time, any hardware and software used for record-keeping must be readily available for FDA inspection. In the rush to get things done on time, and hopefully under budget, many startups can neglect the importance of such regulatory systems compliance.



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Early advice that puts in place sound procedures that are then followed as a matter of habit can avoid major problems down the road.

Another consideration for startups is whether to bring a drug to market themselves or instead look to exit at a particular regulatory milestone by selling to a larger pharmaceutical company looking to fill its development pipeline.

When the latter approach is chosen, being able to offer a drug that has been developed in a fully FDA-compliant manner and is geared toward obtaining an expedited approval makes the startup a far more attractive target for acquisition or partnership by a larger pharma.

The latter approach may also have benefits at a very early stage when dealing with potential angel investors who may be concerned about long-term uncertainties that can be reduced by an early exit.

Thus, angel investors will often find startups that have talked with the FDA to assess the regulatory field and formed a strategy based on expert advice to be a more enticing investment.

The multiple approaches to expedited drug review by the FDA enable startups to, in effect, pursue a hedge strategy when considering avenues for drug development.

Even if one approach does not pan out, startups can offer potential acquirers or investors the possibility of an alternative route that can still bring the drug to market on an accelerated timetable.

As a result, in forming their FDA strategy, startups should consider the broadest applicable range of categories for approval. Even though it may be tempting to opt for a single pathway through the FDA maze, applying for the widest applicable scope of approval pathways, in practice, is a superior bet.

## EXPEDITED PROCESSES

It has been estimated that the typical drug development time from patent filing through market launch in the U.S. is around 14 years.[1]

Furthermore, when the costs of inevitable failed research projects are also taken into account, the average total costs involved in developing a new drug for market can run into hundreds of millions of dollars.

It has been suggested that around half of the total costs associated with drug development are associated with the substantial years-long delays in the process of moving the drug through the tests and assessments required by the FDA, and in the context of IP, the U.S. Patent and Trademark Office.[2]

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The FDA has four expedited programs to accelerate the process of bringing drugs treating certain diseases designated serious diseases to market:

(1) priority review.

(2) accelerated approval.

(3) fast track.

(4) breakthrough therapy programs.

Each program has its own distinct features.

Priority review is offered for major advances in treatment over existing therapies (and leads to FDA review in six months as opposed to 10 months for standard review).

Accelerated approval is for treatments of serious or life-threatening diseases that provide meaningful therapeutic benefit over existing therapies and show a surrogate end point reasonably likely to predict clinical benefit (for example, a biomarker known to be associated with positive clinical outcomes indicates that such outcomes are likely even if the clinical data has not been obtained yet).

Usually, one seeking FDA approval typically follows the accelerated approval pathway in instances in which the course of a disease is prolonged and thus requires measurement of the intended clinical benefit of a drug over a significant period of time (even if some positive effects are seen relatively rapidly).

As a result, in cases of accelerated approval, even after the drug is commercialized, further post-marketing trials may be required to ascertain the drug's clinical benefit (and failure of these trials may result in the withdrawal of FDA approval).

Fast track is for therapies that are intended to treat a broad range of serious diseases and that have the potential to fill an unmet medical need. Fast-track designation is conferred based on preclinical data.

Typically, a drug sponsor with fast-track designation for its product will have more frequent interactions with the FDA during drug development and will be able to obtain rolling review.

Finally, breakthrough designation is for treatment of serious or life-threatening diseases that show early clinical evidence of substantial improvement over existing therapies. The key difference between a fast-track designation and a breakthrough designation is that the latter is based on early clinical data.

Therefore, startups may wish to plan to file first for fast-track designation and then file for a breakthrough designation after appropriate early clinical data has been obtained.

The FDA encourages applications for breakthrough designation before the end or at the end of phase II clinical trials and before the start of phase III clinical trials intended to serve as the primary basis for demonstration of efficacy.

However, given that the full benefits of the breakthrough designation come largely from increased close interaction with the FDA, it is preferable to file for breakthrough designation at the earliest feasible time.

Of these four categories of expedited review, breakthrough designation results in the fastest estimated development time, with an estimated median clinical development time of 4.8 years (almost a third quicker than other categories for expedited drug approval by the FDA).

A drug can be designated in multiple fast-track categories, such as breakthrough therapy designation, accelerated approval and priority review.

Breakthrough therapy designation grants extra opportunities to meet with the FDA to discuss study design, safety and efficacy requirements, dose-response concerns, use of biomarkers and other critical development issues.

Therefore, in addition to foreshortening the process, the overall costs of conducting the studies may be reduced through a closer relationship with the FDA.


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## THE BRUKINSA EXAMPLE

On Nov. 14, 2019, the FDA approved a lymphoma treatment from Brukinsa (zanubrutinib), the first time the agency used its accelerated approval program to approve a drug from a Chinese company. Brukinsa has also received a breakthrough therapy designation.

The drug treats mantle cell lymphoma, which is a type of non-Hodgkin lymphoma that begins with lymph node enlargement and may then spread to other tissues such as bone marrow and liver. In the United States, there are around 4,000 new cases of mantle cell lymphoma per year.

The drug application for Brukinsa relied on clinical data largely resulting from trials held outside the United States, which now may be copied by many other pharmaceutical companies, especially those based in China or other foreign countries.

Drugmakers that choose to avoid major U.S. clinical trials can find it easier to swiftly enroll patients in the clinical study groups, especially when there is a relatively discrete group of patient candidates who cannot all be enrolled in multiple trials conducted by different companies.

The success of Brukinsa in obtaining expedited review by the FDA has implications beyond the pharmaceutical industry. Many universities are interested in licensing therapies developed by their researchers for development into commercial drugs.

However, virtually all universities have financial limitations that constrain their ability to pursue every idea or concept that a university research team may come up with.

When considering where to invest limited resources, universities should consider the chances of obtaining expedited FDA review.

In particular, potential inventive therapies that may be candidates to receive breakthrough therapy designation should be given high priority.

The same is true for startups and university spinoffs. In some cases, a university may be willing to allow a researcher who has developed a potential therapy to spin off their own company to pursue it, even if the university lacks the resources to do so.

In these instances, it is also worth considering whether the proposed inventive therapy is also able to receive breakthrough therapy designation from the FDA.

Similarly, in the development of biologics, the ability to receive breakthrough therapy designation and an expedited route to commercial market is a factor that should be taken into account before investing considerable time and resources.

The success of Brukinsa in obtaining the first breakthrough designation by the FDA for a drug primarily developed in China underscores the increasing importance and high profile given to these categories of therapy.

In the future, in assessing the merits of a potentially inventive drug therapy, it will be worthwhile for universities, startups and biologic manufacturers to conduct not only a careful assessment of the IP protection that may be achieved, but also the opportunity to bring a commercial drug product to market under an expedited FDA drug review process. WJ

## NOTES

[1] Dennis S. Fernandez & James T. Huie, *Strategic balancing of patent and FDA approval processes to maximize market exclusivity*, at https://bit.ly/2UlrbaP.

[2] Erin E. Kepplinger, *FDA's Expedited Approval Mechanisms for New Drug Products*, 34 Biotech Law Report 15 (2015).


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