

## Strategy to Register a Drug Product in the US

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### Abstract

Globalization is not a one-way street. US used to be the major driving force in the innovation of pharmaceuticals but many other countries are playing catch-up. This article is intended to describe the necessary regulatory hurdles that need to be cleared before one can introduce a pharmaceutical product into US market.

### Introduction

You have just successfully launched your new product in your country and it is selling like hot cakes. Your board of directors asked: “Hey, why don’t we try to make some money in the US market?” You decided that you are going to give it a try. So where do you start?

First of all, to enter the US market, your product will need to get the approval from the US Food and Drug Administration (FDA). The sponsor (your company) files a market application with FDA. After reviewing your application, FDA will decide whether to grant the product approval. Selling your product without the approval would make you a felony under the US Federal Food, Drug and Cosmetic Act.

### Identify The Application You Would Need For the Regulatory Approval

The application varies depending on the product. If it is a new drug that never has been approved in the US, whether it is a new chemical entity (NCE), a new molecular entity (NME), a new formulation of known drug substance(s), a new route of administration, or a different strength to an approved drug, you will need to file a New Drug Application (NDA). If it is a “me-too” product, also known as generics, then you can file an Abbreviated New Drug Application (ANDA). If it is a biologics, you will file a Biologics License Application (BLA).

However, for a new product that intends to file an NDA, an Investigational New Drug Application (IND) is usually required when:

- you need additional clinical data to support your application;
- the clinical data generated outside of the US may be acceptable based on pre-IND discussion with FDA before you run the clinical studies oversea

There are also cases that a company decides to file an IND in order to conduct a study for publication to help marketing a drug.

IND is filed to start a clinical study (trial). Clinical trials are generally classified into three phases that may run concurrently:

- Phase 1 includes single-dose studies, repeat- or multiple-dose studies, which usually last no more than 28 days. These studies assess such things as: safety and tolerance (maximum tolerated dose); pharmacokinetics, pharmacodynamics, bioavailability and bioequivalence; drug interaction; and food effects. These studies are typically conducted in 20-80 healthy subjects or patients.
- Phase 2 involves safety and efficacy studies conducted with as many as 200 patients who have a targeted disease or condition. It usually involves dose escalation study and safety and efficacy study. The term “early phase 2” or “phase 2a” is sometimes used to refer to pilot studies, and “late phase 2” or “phase 2b” is used to denote statistically powerful, placebo-controlled trials. In some rare cases, FDA has agreed that the sponsor could file an NDA application with Phase 2b data if the drug product showed significant benefit in treating serious or life-threatening disease for which there is no treatment available. At the end of phase 2, there is usually a conference between FDA and the sponsor to discuss phase 3 plans.
- Phase 3, also known as pivotal trial(s), includes controlled safety and efficacy trials in large numbers (up to thousands) of patients. Depending upon the proposed indication, these may be longer-term studies that generate the data needed for NDA approval. Phase 3b studies are typically comparable studies run after NDA has been submitted. Other studies can be performed during phase 3, such as: dose-response, quality-of-life, pharmacoeconomics, special population, concomitant disease and formulation and withdrawal studies. The results from these studies address the labeling issues for the package insert. These clinical studies can last 2-6 years and cost millions of dollars.
- Sometimes, you will also see Phase 4 studies being mentioned in the press releases. It is usually required after the product approval to study special population (pediatric study, geriatric study etc). In the case of accelerated approval, the sponsor will have the obligation for additional Phase 4 studies to obtain extra data on broad population or to collect additional safety and efficacy data.

### **How Much Money Is Needed? How Soon Will The Approval Be Coming?**

Once you are ready to file an NDA, the next question you may ask is how much it costs for the application, and how long the expected review time is. To answer them, let us mention the Prescription Drug User Fee Act (PDUFA). PDUFA was passed first in 1992 to accelerate FDA review of drug applications in response to complaints from the pharmaceutical industry. It required drug and biologics manufacturers to pay fees for drug and biologics applications and supplement. The legislation was subsequently reauthorized in 1997 (PDUFAII) and 2002 (PDUFAIII).

Under PDUFA, the target review time for standard application is 10 months. PDUFA fee for an application with clinical data in 2006 was \$767,400; without clinical data was \$383,700. The establishment fee was \$264,000 and the product fee was \$42,130. However, ANDA for generic drugs is not covered under the PDUFA. For medical devices, Medical Device User Fee and Modernization Act (MDUFMA) passed on 2002 that enables FDA to review Premarket Approval application at faster pace.

Review time clock starts after your application is accepted for filing by FDA. The clock usually starts 60 days after FDA received your complete application and finished a primary review to determine that your application is complete in terms of contents and formats required by the regulation. You will get an acknowledge letter from the Agency regarding the acceptance of your application. 10 months from the date FDA accepted your filing is the PDUFA action date. In recent years, FDA is about 90% plus on time to let the sponsor know on or before the action date whether the application is approvable or not. However, the clock can be reset if you submit an amendment to the application containing important information such as a Chemistry, Manufacturing and Controls (CMC) amendment, or an amendment containing clinical study results which requires extra review time (the extension of review time for a major amendment could be up to 180 days).

There are three outcomes from the review: approved; approvable (extra works needed), and not approvable. An approvable letter usually states what needs to be done and FDA will discuss with the sponsor in detail for the timelines, the scope and the expectations. The other two outcomes are self-explanatory.

In certain cases, FDA may grant a product priority review. In 1987, FDA created an “AA” priority category to classify all applications for potential AIDS therapies to ensure that these products receive the highest priority in the review process. Also, under 21 CFR 314.510, FDA may approve drugs based on surrogate end points that will reasonably predict clinical benefit, or on end points other than survival or irreversible morbidity. This regulation results in the accelerated approval of products that have unmet medical needs. Usually, drugs fall into these categories are for serious or life-threatening diseases. The PDUFA goal for priority NDA review time is 6 months (4 months after accepted for filing).

### **Submission, Going Electronic Or Not**

In recent years, the Agency has updated its computer system to accept submission electronically. Started from last October, FDA requires all product package insert (labeling) be submitted in Structured Product Labeling (SPL) format, signaling the commitment from the Agency towards electronic submission. It is generally recognized that electronic submissions will increase the review efficiency. It allows the reviewers to

access the application materials easily and cuts down paper-clutter around the agency. There was one case that a biotech company submitted its NDA electronically that resulted in a speedy product approval (approved in 6 months after it was accepted for filing). In the future, rolling submission of an NDA should speed up the review process and allow better communications between and sponsor and the Agency.

If an application has been approved in Europe, the Common Technical Document (CTD) format used in the European application is accepted by FDA. Otherwise, the application needs to be submitted at the format deemed by the Agency.

NDA and ANDA content and format requirements can be found in Code of Federal Regulations (CFR) 21 CFR Part 314 – Applications For FDA Approval to Market A New Drug.

### **Appoint A US Regulatory Agent**

A foreign company should hire a US regulatory agent to submit its marketing application, unless it has a US subsidiary to handle the US regulatory affairs issues. The regulation requires the agent has a US address, telephone/fax in the US that FDA can reach during the business hours. It is advisable to hire a reputable company as your US regulatory agent to navigate through the complicated application processes and to get necessary help during the negotiation during the product review and to communicate effectively with the Agency. The regulatory agent also handles submissions and communications after the product approval.

### **Obligations After Your Product Is Approved**

Although you get the approval letter, your job is not finished. You still need to comply with all the regulations and laws by the US government to market your product in the US. For instance, the advertisement and promotion of the product needs to comply with FDA's and Federal Trade Commission (FTC)'s regulations. In recent years, many warning letters have been sent to the sponsors that violated the regulations when they made unsubstantiated or biased claims on their advertisements or their promotion materials. It is very important to adhere to what you have stated in your package insert for your product efficacy and safety information. Always be careful when your sales people disseminate sales aids and promotional materials to make sure your claims are backed by clinical data. For drugs approved under accelerated approval, after 120 days following the market approval, promotional materials must be submitted at least 30 days prior to dissemination. For other drugs, advertising and promotional labeling must be filed to the NDA at the time of initial dissemination/publication.

The sponsor has the obligation to maintain the application by reporting any post-approval changes to the product,

which include but not limit to submission of post-marketing adverse experience report periodically, reporting of death and life-threatening events to FDA within 15-days after initial notification, and submission of annual reports no later than 60 days of the anniversary of the product approval. Every two year (schedule allows), FDA will inspect the manufacturing facilities to make sure the product is made in compliance of current Good Manufacturing Practice (cGMP). FDA also may inspect your contract testing laboratories, your clinical study sponsors, monitors and investigator sites. When you file a supplement towards an approved NDA, it could also trigger an inspection. Any lapse of compliance could bring serious consequences such as loss of marketing right, product injunction, plant closure, product seizure etc. Therefore, it is very important to understand the regulations and the applicable law to avoid unnecessary loss.

There are numerous reports required to keep an NDA update and to ensure your market product is in compliance. The list below summarizes what we mentioned so far to keep the application in compliance:

- Annual reports
- Adverse event reports
- Distribution reports
- Field alerts
- Status reports of post-marketing studies
- Advertising and promotional labeling

In the case when the product is found deviating from the approved specifications, a recall should be initiated. The recall can be initiated either by the company or by FDA. After the recall is completed, a status report is necessary to be submitted to FDA.

### **Conclusion**

Generally speaking, the NDA approval in the US for your new product is exercisable once you have a careful preparation. You can find more comprehensive information at [www.fda.gov](http://www.fda.gov) and the links to the Agency's centers and divisions. You can also find useful information at [www.ich.org](http://www.ich.org), and in Federal Register. Refer to 21CFR from Federal Register for the Regulations covering drug, biologics and medical devices. Another useful website is the Regulatory Affairs Professionals Society website, [www.raps.org](http://www.raps.org).

### **References**

1. 2005 Fundamentals of US Regulatory Affairs, RAPS, 2005
2. 21CFR, some relevant parts--Part 300s (Drugs, IND/NDA/ANDA); Part 600 (Biologics, BLA). Part 200s, Drugs, Labeling, GMP
3. [www.fda.gov/cder/guidance](http://www.fda.gov/cder/guidance)