

APPLIED CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT

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Preapproval Opportunities

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Integrating clinical trials and named patient programs to provide global access to drugs before approval.
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Greater transparency of drug development pipelines, increased media coverage of health care issues, and fingertip access to information about investigational drugs via Web sites and blogs have created a more educated and empowered population of patients. The heightened awareness of drugs in development brings with it an increase in demand from patients, their physicians, and advocacy groups worldwide for access to these potentially promising medications despite their preapproval status.

Global regulations are in place by which a patient may gain access to investigational medicines via their physician. To ensure patient demands are met, companies may choose to institute a prelaunch access program. Companies must carefully orchestrate use of these programs in conjunction with ongoing clinical trials in order to maximize their effectiveness while remaining within strict regulatory guidelines.

This article will describe the differences among early access programs, highlight how regulations can vary from country to country, and describe how programs can operate successfully in parallel with clinical trials.

Preapproval access

Patients can potentially gain access to drugs in a preapproval stage by a variety of mechanisms including clinical trials, expanded access programs (EAPs), compassionate use programs, and named patient programs.

In 1987, the U.S. FDA formally put in place regulations to improve patient access to investigational drugs. These regulations focused on drugs that would address existing therapeutic gaps, including cases in which therapies were not available and those in which patients were unresponsive or not adequately treated with currently marketed drugs.

Nearly two decades later, proposed changes to these rules¹ are intended to clarify the procedures for allowing early access and give patients more latitude in accessing investigational drugs when there are no other therapeutic options. The 90-day window for public comment on the proposed regulation closed in March 2007. While no date has been specified, the FDA is expected to issue a final ruling on these amendments shortly.

An appropriate balance of possibly competing interests continues to be sought: facilitating access to unapproved drugs and minimizing risk to patients while not impeding the progress of clinical trials and data development needed for marketing approval.

FDA-recognized EAPs include treatment investigational new drugs (treatment INDs), treatment protocols, and single-patient INDs. EAPs allow patients who are too ill or do not otherwise qualify for clinical trials to access potentially lifesaving medicines that are still in development when no other medical alternatives exist. While these programs are often grouped under the umbrella of “compassionate use programs,” the FDA does not have a regulation or policy defining a compassionate use program, instead preferring to consider “compassion” an element in all aspects of drug development.²

Treatment INDs and treatment protocols are similar in that they both allow large numbers of patients, who would not otherwise qualify for clinical trials, to gain access to an investigational drug. A treatment protocol is a formal addendum to an active clinical trial, one that sets criteria for allowing large numbers of patients to access the same treatment regimen that is under investigation and is submitted to the FDA by the drug company. In contrast, a treatment IND is initiated by a physician seeking early drug access on behalf of a patient or group of patients who do not qualify for a clinical trial but who may benefit from preapproval access to a new drug.

A single-patient IND is a request from a physician to the FDA that an individual patient be allowed access to an investigational drug on an emergency or compassionate basis—that is, when all other options have failed. The FDA makes it clear that the drug company must agree to the request first and that the FDA does not have the power to compel a company to release a drug for an unapproved use.³

Outside the United States

Named patient (or special access) programs are similar to U.S.-based EAPs but with an international component: Named patient programs enable physicians on behalf of their patients to access medicines approved or nearing approval in other countries that haven’t been granted marketing approval in the patient’s home country. Through these programs, individual patients outside the United States can potentially access, via

their physician, drugs approved or in late-stage clinical trials in the United States for a genuine, unmet medical need.

The 30 member states of the European Union, for example—all of whom nominally come under the jurisdiction of the European Medicines Agency (EMA)—each have their own nationalized regulations regarding the access to unlicensed medications for compassionate use programs (both for individual patients and cohorts). Canada’s Special Access Program provides access to nonmarketed drugs for practitioners treating patients with serious or life-threatening illnesses when conventional therapies have failed, are unsuitable or are unavailable. In Australia, patients can access experimental drugs via the Special Access Scheme; and in Japan, Named Patient Access allows access to drugs with an expectation that the drug be approved in the exporting country.

Named patient programs operate under different rules than those governing U.S. based expanded access programs.

Named patient programs are typically established by pharmaceutical companies if significant demand is expected from overseas markets in which the drug has not yet been approved for use. These requests are typically, but not exclusively, for drugs in the areas of oncology, infectious disease, critical care, and orphan drugs.

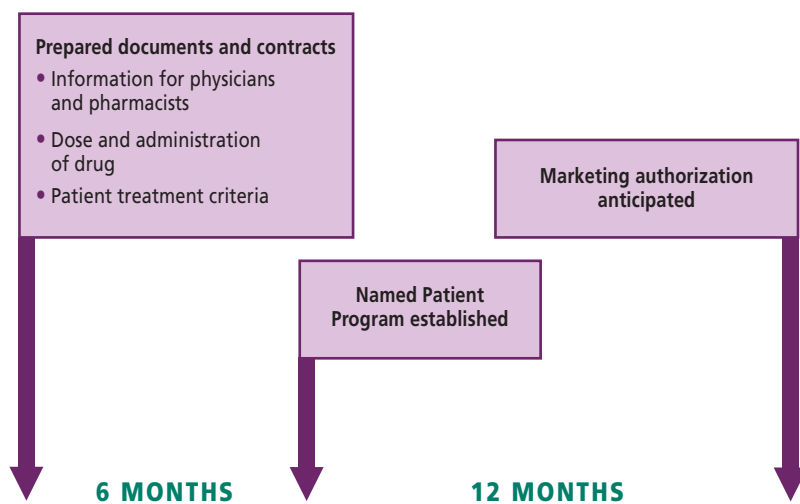
Navigating regulatory complexity

Requests for drugs within the context of a named patient program can originate from any country. As such, the coordination of these programs is complicated by regulations that vary



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Time Frame for Planning a Named Patient Program



Source: IDIS.

Figure 1. The optimal time frame for implementing the program is about 12 months before the drug is expected to receive approval.

from country to country. Furthermore, because they involve the export of drugs out of the United States (in accordance with the FDA guidance document released in July 2007⁴), named patient programs operate under different rules than those governing U.S.-based EAPs.

Once a drug has left the United States, it leaves FDA jurisdiction and enters that of the nation (or nations) to which it is being exported. Most countries legally allow for named patient programs as a means of providing medication to patients when local alternatives are either unavailable or inappropriate. However, the structure of programs within each country can vary widely due to differences in medical practices, resources, funding, and national insurance systems.⁵

Some member states allow both named patient and cohort programs while others allow only named patient programs. In some countries, approval for compassionate use must be provided by a competent authority; in others, an import certifi-

Companies should be aware of the impact expanded access programs can have on patient accrual.

cate may be all that is needed. Country-specific regulations also define requirements for payment, liability, adverse event reporting, and whether a drug must be licensed in another member state before it can be offered via such programs.

Successful integration

Named patient programs can be established while a clinical trial is ongoing, but careful coordination and timing are needed in order to avoid compromising recruitment for the trial. Companies should remain mindful of the impact that any

expanded access program may have on patient accrual to clinical trials. Through an expanded access program, patients can be assured of receiving the drug and not a placebo or control treatment—a factor that may make them reluctant to join a clinical trial.

Named patient programs can be used effectively, however, in concert with clinical trials with minimal impact on accrual, since these programs provide access to patients in countries where there may be no clinical trial in progress.

When run in conjunction with a clinical trial, named patient programs also make the investigational drug available to patients who cannot enter a clinical trial due to their demographic restrictions, such as age or medical factors resulting in exclusion. Detailed screening criteria are used to evaluate patient requests within the context of a named patient program. This screening process can also be used

to assess patients based on the clinical trial entrance criteria and forward those patients who meet these criteria to the sponsor or their CRO for inclusion in the trial.

Named patient programs are generally put in place while a drug is in Phase III trials, after a general safety profile has been established. These programs can provide additional real-life data, including information on interactions and side effects, which can be analyzed for improved safety warnings and recommendations and used to support reimbursement and health technology assessments.

Some hospitals require informed consent forms for patients accessing a drug via a named patient program. This requirement is established by local regulatory authorities. The ultimate liability for use of an unlicensed medicine, however, rests with the physician.

Planning involved

Optimally, a named patient program should be in place about 12 months prior to expected marketing authorization (see Figure 1). If the program is in place too early, the company might not have an adequate supply of drugs available to meet the named patient demand. If the program is started too late, there may not be sufficient use of the program. In cases where demand for the drug is extremely high, however, starting the program within just a few months of expected authorization is warranted.

The planning phase of a named patient program includes:

- Preparing documents and, if needed, establishing a contract with a named patient program specialist
- Developing information for physicians and pharmacists regarding dosing, administration, and restrictions (if the drug is approved in another country prior to the start of the named patient program, the package insert should be

- included in the physician and pharmacist information)
- Establishing treatment criteria to ensure proper selection of patients.

Communicating availability

While the humanitarian motivation for providing preapproval access is to respond to the needs of desperately ill patients, what cannot be ignored is the fact that offering access to drugs still in development creates increased visibility for

Misuse of these programs to secure an even more significant market advantage can result in penalties.

these drugs on a prelaunch basis and initiates early physician and pharmacist engagement. The possibility of a headstart in gaining market acceptance for a drug—key physicians become familiar with the product prior to launch—can be attractive to pharmaceutical companies who choose to participate in these programs.

Although the structure of any expanded access program naturally yields market benefits, promotion of investigational drugs is not allowed. In addition, misuse of these programs, whether intentional or unintentional, in order to secure an even more significant marketplace advantage can subject a company to penalties.

As a result, companies providing access to investigational drugs must exercise caution when publicizing such programs. Companies can provide information regarding preapproval access to physicians at medical conferences for example, but cannot solicit interest from target physicians, advocacy groups or patients; nor can the company use their sales force to promote such programs. Some companies issue press releases announcing availability of specific drugs through these programs, which is acceptable.

Ending the program

The named patient program sponsor should proactively plan for the end of the program. There are a number of options, and the company should select from among them based on what is best suited to the individual drug and the company's own circumstances.

The program can be phased out upon receipt of marketing authorization. If the drug distribution network is not yet in place or the commercial launch is otherwise delayed, a company may choose to continue offering access via a named patient program. Another endpoint option is when reimbursement is obtained in the individual country. This timing can be quite variable among EU countries even though all receive marketing authorization at the same time.

Conclusion

Preapproval access to drugs can provide months and perhaps years of treatment when other therapeutic options have failed. Patients with unmet medical needs can access these drugs from a variety of mechanisms, including clinical trials, expanded access programs, and named patient programs. These programs and associated regulations have been put in place to help ensure patient needs are met in an effective, responsible, and legal manner.

For U.S.-based companies, named patient programs allow access to investigational drugs by patients outside the United States and can effectively supplement the adverse event data collected during the clinical trial period and provide real-life data to support market access strategies. Because these access programs are often conducted in parallel with clinical trials, seamless integration with the corresponding trial is critical to avoid conflicting objectives and maximize the success of each.

Further, drug developers involved in these programs must ensure strict adherence to all regulatory guidelines governing preapproval access and avoid promoting these programs in a manner inconsistent with regulations. For these reasons, many companies choose to partner with a named patient program specialist who offers the expertise and resources to enable response to worldwide demand for investigational drugs in an efficient and controlled manner.

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