

## The Drug Development Process III: Phase IV Clinical Trials

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Clinical trials for the registration of a candidate drug typically take the form of studies evaluating the safety and efficacy of the drug in a narrow spectrum of the overall patient population. Participants in these trials typically include patients with specific manifestations of disease, as well as healthy volunteers. Authorization of marketing of a given drug by a regulatory agency allows for specific claims to be made and recommendations for dosing, formulation, indication, and defined patient populations to be offered, all based on the rigorous studies conducted during the registration process.

Inherent in the registration process, however, is a relatively short study duration, with limited availability of follow-up data. Consequently, if either the sponsoring pharmaceutical company or the regulatory agency has an interest in obtaining additional data outside of and subsequent to the completion of the registration program, other types of postmarketing studies need to be performed.<sup>1</sup> In fact, most drugs approved by regulatory agencies globally undergo some sort of postmarketing study or studies. Loosely, such studies are termed phase IV trials or phase IV commitments. Although several types of studies, all with different conceptual endpoints and purposes, comprise these trials, they are typically initiated after a drug has been approved for at least one indication.<sup>2</sup>

This article on phase IV trials is the final installment in a 3-part series on the drug development process. The first article in the series provided a review of the process by which a newly synthesized compound becomes a pharmaceutical agent intended for patient use.<sup>3</sup> The second article in the series provided an overview of the investigational new drug application (IND) process.<sup>4</sup>

### GOALS OF PHASE IV TRIALS

As previously noted, phase IV trials begin only after a drug is approved for use. The goals of such trials are fairly diverse (Table 1).<sup>5</sup> For example, in the United States, a drug may be legally prescribed for a patient with a specific medical need not listed as an approved

indication if, in the clinical judgment of the physician, a potential benefit is anticipated; however, pharmaceutical companies may not reference, publicize, market, or promote such off-label uses of the product.<sup>2</sup> Additional studies are required to explore these new indications and, possibly, to extend the use of the product into other clinical scenarios.

Phase IV trials also can gather new information about a specific indication of a product in a different patient population or setting. They similarly can help clinical researchers determine the proper use of a drug for specific indications that are similar to the indication already approved and for patient populations not specifically studied in the registration program for marketing authorization.<sup>6</sup> Examples of the latter situation include studies in elderly patients, in patients of different races, and in patients with different concurrent underlying disease states. There is a clear need to understand both the efficacy and the safety profile of the drug in these populations.<sup>2,5</sup> Registration-type studies, in contrast, typically are limited to specific, narrowly defined, more homogenous populations of patients in whom more long-term follow-up has not occurred.

Moreover, phase IV trials may be useful to provide a fuller understanding of adverse effects of the drug, with respect to both frequency and potential idiosyncratic reactions not predicted, given the known biologic properties of the drug.<sup>7,8</sup> Indeed, drug interaction studies often are required, especially in drugs approved for more common indications (eg, hypertension) and in populations of patients in whom impaired clearance may be an issue (eg, patients on dialysis, patients with hepatic failure).<sup>2,5,7</sup> Other goals of phase IV trials include obtaining information about cost-effectiveness of a drug's use and effects on the quality of life of patients receiving the drug; phase IV trials also can act as pilot studies for other potential uses of the product in clinical practice.<sup>5,9</sup>

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**Table 1.** Goals of Phase IV Clinical Trials

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Defining new indications
Education of clinical researchers
Expansion of safety profile
Evaluation of cost effectiveness
Gathering new information
Fulfilling a mandate from a regulatory agency

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Regulatory agencies such as the Food and Drug Administration (FDA) may require phase IV trials either as a condition for approval or in response to information obtained after a drug has already been approved.<sup>2</sup> In the former case, the agency informs the sponsoring pharmaceutical company of the type of information needed; in some cases, the agency may specify the type of study design required and impose a schedule for completion of the requisite studies. These additional requirements may involve information already submitted for marketing authorization. For example, the regulatory agency may determine that gaps in the submitted information exist that, although not sufficiently large to prevent approval, must be filled by further evaluation. Regarding information obtained after the drug has been approved, the regulatory body may request performance of phase IV trials in response to prescription audits, which detect that there is a high level of drug use for off-label indications; the agency may want to gather evidence of and adequate data on the safety and efficacy of the drug for these other indications.<sup>2,6</sup>

#### TYPES OF PHASE IV TRIALS

There are various studies that fall under the rubric of phase IV clinical trials (**Table 2**). Each has a specific purpose and answers a different type of question, as related to the particular goal (*see Table 1*). Indeed, given the myriad of different goals, there are several trial designs that are valuable in assessing drugs after approval.<sup>5</sup>

##### Postmarketing Surveillance Studies

Postmarketing surveillance studies, otherwise known as pharmacoepidemiologic investigations, evaluate the occurrence of adverse effects in very large patient populations (often thousands of patients in hundreds of institutions). These studies are particularly useful for evaluating the incidence of adverse effects in a general population of patients, particularly of unexpected events. Essentially, these studies form the basis of phar-

**Table 2.** Types of Phase IV Clinical Trials

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Postmarketing surveillance studies
Investigator protocols
Pharmacoeconomic evaluations
Usage studies

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macovigilance of drugs in a more diverse set of patients than was studied for initial approval.<sup>8,9</sup>

##### Investigator Protocols

Investigator protocols, designed by independent investigators, are also a major type of phase IV study. Studies are often submitted for consideration to the pharmaceutical company that has gained approval for a particular drug by investigators seeking review, editing, and approval of their study.<sup>5,7</sup> Typically, when company interest in the concept presented for the approved product is high, there will be financial support for the study. Although these studies are similar to investigator IND studies, in which the investigator is a clinical researcher who wishes to evaluate the product for an indication outside the current labeling and not being pursued by the pharmaceutical company, the phase IV study falls within the arena of the original IND and is considered on-label.

##### Pharmacoeconomic Evaluations

Pharmacoeconomic studies evaluate the costs and impact on patient health and economic status of drug usage (and, in some cases, nonusage) in given patient populations.<sup>2,7,9</sup> These studies have become key aspects of the marketing authorization packages for reimbursement and drug pricing, particularly in Europe. They have become increasingly important in countries such as the United States for justification to third-party payers. The guidelines for such studies are currently evolving. This type of phase IV trial represents an exciting area of research within the arena of drug development.

##### Usage Studies

Usage trials document the safety and efficacy of the approved product in real-life situations in the clinical community.<sup>5</sup> These trials can be challenging to design. Although their goal is to reflect the current practice of physicians, a wide range of patterns of use may exist between physicians and between regions that cannot be captured in a strict protocol format. Nevertheless, capturing this pattern of use, as well as any effects

resulting from different patterns of use, is the primary feature of this type of phase IV trial.

#### MONITORING OF PHASE IV CLINICAL TRIALS

As with studies conducted within the registration program, phase IV trials are monitored by the regulatory agency on a regular basis.<sup>2</sup> In the United States, the FDA evaluates the progress and interim results of phase IV trials through review of the annual report of the product IND and of any other commitments made with the agency during the time of trial design. Monitoring becomes particularly essential for studies designed to determine the safety of a drug in patient populations and clinical settings other than those evaluated for market authorization, especially when a large percentage of current use of the product is for indications not specified in the original approval. Monitoring also takes on a particular urgency for studies determining the safety and efficacy of a product when administered with other agents—not only commonly administered drugs, such as oral contraceptives and cholesterol-lowering drugs, but more particularly drugs that are metabolized in a similar manner or that affect the specific clearance mechanisms of the product.<sup>2,5</sup>

#### ACCELERATED APPROVAL

There is a mechanism that makes use of phase IV trials within the registration process called the *accelerated approval track*, which is reserved for medications treating serious and life-threatening diseases; phase IV commitments are used to complete the safety and efficacy package usually obtained in early trials.<sup>2</sup> This method makes use of surrogate end points, which can be obtained more quickly than can data on survival and response to treatment. The FDA has the authority to approve an application based on these surrogate endpoints; phase IV commitments are required, however, to confirm and describe with more robust data the clinical benefits of the therapy. These accelerated approval data are typically based on 24 weeks of therapy, which are necessary to obtain conditional approval, with a minimum of 48 weeks of further trials to obtain additional data on safety and efficacy. Drugs approved

on this basis have more stringent reporting requirements for their phase IV data than those approved in the conventional manner; companies typically must report on the status and results of the commitments for these drugs at least semiannually.<sup>2</sup>

#### CONCLUSION

Phase IV clinical trials represent the final, necessary part of a drug's product development, after the drug has been approved for a specific indication. Studying and evaluating approved compounds in different patient populations and clinical settings, as well as in different formulations and for different indications, are necessary to define the practical usefulness of a drug in physician practice. Such trials are reviewed (and at times mandated) by regulatory bodies. They can provide relevant information on the use and characterization of the approved drug in larger patient populations. HP

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