

Overview

Given the high cost of moving a promising drug candidate through years of clinical trials, it's no wonder that more and more drug manufacturers have begun conducting at least some of their clinical trials in foreign countries. With lower costs and shorter recruiting times, the use of foreign sites is appealing to all drug developers, but especially to those involved in generic and "fast-track" approval programs such as 505(b)(2).

A 505(b)(2) is a new drug application which contains full safety and effectiveness reports, but allows at least some of the information required for approval to come from studies not conducted by or for the applicant. This method gains approval for reformulations and new routes of administration in a fraction of the time required by traditional paths. For drug development companies using the accelerated approval of the 505(b)(2) pathway, filling and completing trials quickly offers both a competitive and a cost advantage.

In 2008, 80% of marketing applications for drugs and biologics approved by the U.S. Food and Drug Administration (FDA) included at least some data from foreign clinical trials, and it is estimated that 40% to 65% of all trials are conducted outside the United States.¹

Why Foreign Data Acceptance is Increasing:

- ✓ The desire to reduce the cost of drug development
- ✓ The need to accelerate the approval of safe and effective drugs
- ✓ The increasing ethnic diversity of the U.S. population
- ✓ The ability to determine a medication's safety, efficacy and metabolism across ethnicities
- ✓ Expanding medical knowledge allowing the characterization of ethnic factor influence on a given drug

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline, entitled "Ethnic Factors in the Acceptability of Foreign Clinical Data," notes that while some medications have comparable characteristics across ethnicities, in other cases ethnic differences may affect safety, efficacy and metabolism.

Factors to consider:

Intrinsic ethnic factors

Intrinsic ethnic factors include genetic or physiological factors that are inherent to the drug, its class or the disease under study. These are factors that help to define and identify a subpopulation

and may influence the ability to extrapolate clinical data between regions. Examples of intrinsic ethnic factors include:

- Gender predominance
- Genetic differences in receptor sensitivity
- Genetic polymorphism of drug metabolism
- Racial differences in disease manifestation

Extrinsic ethnic factors

Extrinsic ethnic factors in a population must also be considered. These are factors associated with the environment and culture in which a person resides and are less genetically and more culturally and behaviorally determined. Examples of extrinsic factors include:

- Climate
- Diet
- Exposure to pollution and sunshine
- Socioeconomic status
- Use of tobacco and alcohol

When intending to use data from foreign clinical trials, it is important to plan and supervise the trial design and conduct. When developing the protocol, researchers must take into account prevailing medical factors such as diagnostic criteria or social acceptance of the disease, the population's compliance with prescribed medications or non-medicinal therapies that may contribute to differences in trial results.

Appropriate Drug Characteristics

Which drug candidates can be effectively pursued using foreign trial data is partly a matter of choosing compounds which are less likely to be sensitive to ethnic factors.

These include compounds with:

- A wide therapeutic dose range
- High bioavailability
- Linear pharmacokinetics (PK)
- Little potential for drug-drug and drug-diet interactions
- Little potential for inappropriate use
- Low potential for protein binding
- Non-systemic mode of action

If the FDA determines that a compound is not ethnically sensitive, bridging studies may not be required or pharmacologic studies (pharmacokinetics/pharmacodynamics) may suffice.² If ethnicity is a factor, controlled clinical trials may be needed to confirm the findings in an ethnically-relevant group of patients.

Foreign Trial Site Selection

Ethnicity, however, is not the only concern for sponsors considering global trials and incorporating foreign trial data. The huge rise in the number of foreign trials has also led to a large rise in the number of complaints regarding the conduct of trials.³

According to the FDA's Center for Drug Evaluation and Research, complaints pertaining to foreign research sites include informed consent issues, failure to follow protocol, inadequate records, unqualified personnel, failure to get review board approval, drug accountability and recruitment practices, among many others.⁴

As part of the application review process, the FDA often requests an inspection of the clinical site. If a notice of observations, known as FDA Form 483 is issued, corrections must be made or a warning letter will be distributed. In cases where deviations can affect the study outcomes, the FDA will disallow data from a clinical site.

The increasing prevalence of foreign clinical trials has brought forward an awareness that in some developing countries there may be minimal regulatory supervision.⁵ Keeping in mind these trials often provide lower costs and faster completion times, it's still crucial that local institutional review boards can adequately monitor data integrity and protect the privacy and welfare of study participants.⁵ Others question the degree to which results from developing nations can be applied to the U.S. population.

Summary

When conducting trials where most or all of the data will come from outside the United States, it is important to be sensitive to issues surrounding globalization and to carefully manage the ethnic factors in a study. If you choose to work with an outside research partner, it is vital to look for one with:

- Global experience
- A site-centric approach to study management
- Flexibility to work under multiple types of contractual and operational requirements

Technology systems and worldwide communications capabilities are also critical when dealing with probable requirements for a standardized electronic format for data collection.

Conclusion

The pharmaceutical industry will need to shift and take steps to integrate foreign data into more effective drug development research. Working closely with the FDA throughout the trial to ensure the acceptability of data is only logical, and seeking ways to expand FDA oversight of foreign clinical trials is something that will benefit the industry and ultimately, worldwide health.

The impact of foreign trial data harmonizes regulatory requirements between countries, aids in the transfer of technology, develops global treatment guidelines and facilitates the development of best practices.

About Camargo Pharmaceutical Services

Camargo Pharmaceutical Services is an end-to-end drug development services company, specializing in the 505(b)(2) drug approval pathway. For more information, visit www.camargopharma.com or the President's blog at www.camargoblog.com.

To get started on your next 505(b)(2) drug approval, contact Rick Bell at rbell@camargopharma.com or 1-513-618-0333.



References

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