A number of different public agencies have an interest in the pharmaceutical industry, including those responsible for verifying whether new treatments are safe and effective, those charged with monitoring promotional practices, and those overseeing public health services and government insurance programs.

Although the industry has always taken a more flexible approach toward Phase IIIB and IV research than to registration research, as we will see in the first section of this chapter, it would be a mistake to think of strategic research as being unregulated and lawless. In fact, in addition to principles of good clinical practice, strategic research is subject to its own unique laws (many enforced by significant financial and criminal penalties) that vary significantly from country to country and primarily relate to off-label promotion, product supply, financial inducement, and patient privacy.

Clearing the Bar

The International Conference for Harmonization: Good Clinical Practice (ICH-GCP) established a minimum standard for clinical research in May 1996. Although most countries recognize ICH-GCP as the international ethical and scientific quality standard for the conduct and reporting of trials that involve the participation of human subjects, practical interpretation of this standard has been subject to local regulatory debate since it was finalized. Most regulators have their own ideas about what ICH-GCP actually means in practice, but local interpretations are united in their conservative attitude toward applying ICH-GCP to registration research. This consistency breaks down in Phases IIIB and IV, however, with regional differences so great that a study design demanded as a condition of approval by one country may be illegal to conduct in another.

In the United States, the FDA has developed volumes of notifications and advisories that expand on these guidelines. Other nations have their own interpretations of the guidelines: the European Union has adopted the European Clinical Trials Directive (EU-CTD) and its European Medicines Evaluation Agency (EMEA) is continually expanding on this directive; Australia has adopted the National Health & Medical Research Council’s Guidelines for Good Clinical Research Practice (GCRP); and Japan is still subject to the idiosyncrasies of the Pharmaceutical Affairs Law despite adopting ICH-GCP in the late 1990s.

Although ICH-GCP sets a minimum standard for the conduct of clinical studies, most sponsors have created their own standard operating procedures (SOPs) that not only meet the standards set by GCP but also attempt to address more detailed local standards and FDA/EMEA precedents established over the past 25 years. In an attempt to address these different standards and interpretations, most corporate SOPs set a much higher bar than ICH-GCP or the EU-CTD.

The gap between a sponsor’s processes and those established by ICH-GCP represent the additional lengths to which a sponsor is willing to go to minimize the risk of a technical rejection of submission data. It is not unusual for registration studies to be loaded with $10
million to $20 million of additional activity not explicitly required by regulatory agencies. Of the few companies that have attempted a less conservative approach, most have learned the hard way that taking risks with a new drug application is simply not worth it.

Since many of these costly additional procedures do little to protect patient safety or data quality, many sponsors are more comfortable taking a more practical view of ICH-GCP once the regulatory hurdle of product approval has been overcome. Recognizing that process for process sake is both expensive and a poor use of physicians' time, many pharmaceutical companies are establishing Phase IIIB and IV SOPs that are designed to comfortably address the spirit of the ICH-GCP guidance while providing much greater latitude for study design and cost containment.

Many people incorrectly assume that a "Phase IIIB/IV" approach must be less clinically robust. This is not so. It simply reflects an understanding that ICH-GCP allows for context-sensitive research practices. Some Phase IIIB and IV studies may need exactly the same level of administrative due diligence applied as do registration activities, but not all. Inappropriately applied processes can increase the burden of strategic research to patients and investigators, sometimes jeopardizing research feasibility without improving clinical robustness.

**Promotional Regulations**

Phase IIIB and IV research activity can benefit from greater operational design opportunities (as explained in the previous chapter) and a more practical interpretation of ICH-GCP than earlier phase clinical trials, but this research can also be subject to a range of geography-specific regulatory considerations not applicable in earlier phases. Over the past 25 years, most countries have introduced regulations governing the sales and marketing of pharmaceutical products. These regulations cover a wide range of matters, including justification of claims, off-label prescribing, medical education, and potential conflict of interest by companies in their interactions with physicians.

Most importantly, because strategic research is conducted in parallel with intense promotional activity, the research is subject to the same promotional regulations that apply to the sponsor’s sales and marketing activities. Studies must be designed with sufficient rigor to avoid even appearing to encourage off-label prescribing or to perpetuate false
Clinical Trial Monitoring

Most regulators have an expectation that studies conducted in support of marketing authorization are subject to 100 percent source-data verification performed through frequent on-site monitoring visits. ICH-GCP taken on its own, however, does not insist upon this. Rather it allows for various forms of monitoring depending on the study being conducted.

“The determination of the extent, and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring, before, during and after the trial; however … central monitoring in conjunction with procedures such as investigators’ training and meetings and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable for selecting the data to be verified …” (ICH-GCP).¹

Although most companies do not take advantage of this freedom to choose a monitoring method during registration trials, a number of large companies are starting to explore processes in strategic research such as computerized monitoring (of electronic data) and structured remote telephone monitoring that can significantly reduce the frequency and cost of on-site visits while maintaining data quality and protocol compliance.

Product Supply

Many countries have different rules regarding the supply of investigational product during different phases of clinical research. The study sponsor almost always supplies pre-approval investigational product; post-marketing studies are often conducted using the commercially available product. This is particularly common when performing naturalistic studies: where the supply of study drug may influence product compliance and persistency; where maintaining a wide product inventory for naturalistic dose titration is not practical; or when an investigational product is to be evaluated against naturalistic “standard care.”

A number of countries, including Germany, attempt to prevent sponsors’ using reimbursed field stock to support Phase IV research, even for post-marketing safety surveillance activities that require very large patient numbers.

Financial Inducement

Some countries have taken a hard-line approach to studies that directly influence prescribing of state-reimbursed medication through the conduct of the study. The United States, for example, has applied the Anti-kickback statute, which likens any payment to an investigator for the purpose of inducing the prescription of federal or state reimbursed product, to bribery of a government official in anticipation of financial gain, an offense with significant civil and criminal penalties.
Seeding studies, once popular in the United States, have been directly targeted by these anti-kickback measures (see the appendix). These studies, frequently associated with large numbers of investigators and sites, involve paying physicians sums of money to initiate patients on reimbursed product while only asking them to collect nominal information. Unfortunately, applying anti-kickback laws to studies has affected many legitimate study designs and is beginning to affect patient access to medication in expanded access programs and open-label extension phases.*

Not all regions take this hard-line approach, however, as indicated by the findings of a 2001 report by the Netherlands Health Care Inspectorate. This report, which involved an analysis of corporate marketing plans, estimated spending on seeding studies to exceed 20 percent of annual marketing budgets for Netherlands-based pharmaceutical companies. Although the European Council Directive 92/28/EEC has prohibited pharmaceutical companies from using direct or indirect financial inducements to influence prescription practices since 1992, lack of enforcement has allowed seeding studies to remain a common part of the marketing landscape in many European countries.²

Privacy

Over the past five years, legislatures have taken a range of measures to protect individual privacy in an age of increasing data collection and sharing. Some of these measures have been specifically addressed in the Health Insurance Portability and Accountability Act of 1996 (HIPAA) in the United States and the European Union Privacy Directive. These measures have been designed to target all healthcare interactions, and clinical research activities must operate in compliance with them. Differences in privacy legislation across countries require differences in the study start-up process, patient consent activities and data collection and processing, thus making it complex when data must cross borders either for off-shore entry or for management in a centralized database.

Conclusion

In meeting regulatory requirements, there are more gray areas in the practice of strategic research than in registration research. There is greater freedom to design a range of clinical studies and less fear of not meeting a regulatory bar. But strategic research is no regulatory panacea. There is a wider field for opportunity, but it is filled with landmines in new locations because the product is simultaneously in commercial distribution and research settings.

* These are added to Phase III and IIIB studies so that patients can continue to benefit from treatment until a product is finally approved.
References


* Note: All citations to websites listed in this book were verified in May of 2005.