Phase I Clinical Trials in Canada

The Promise of the New CTA Regulation

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Clinical trials are big business expenditures for the biopharmaceutical industry, and Phase I clinical trials play an important role in screening new therapies for further development. Research and development spending by pharmaceutical and biotechnology companies has been estimated at more than $25 billion per year[1]. In 2000, between 1,500 and 1,750 unique and new therapies were tested among patients in all pre-approval clinical research phases[1]. Of the 7,000 drug candidates in R&D worldwide, only one out of every 1,000 drugs that enter animal testing ever begin Phase I clinical trials in humans[1].

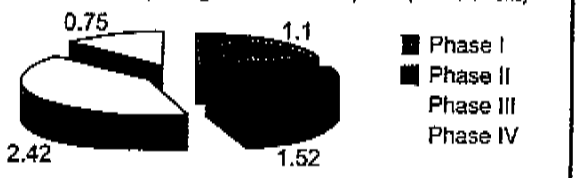
What are Phase I Clinical Trials?

Most experimental drugs proceed through four phases of clinical trials, as described in Table 1.

Phase I clinical trials are the first series of trials required to obtain marketing approval from a regulatory agency for an experimental drug. Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range and identify side effects. This trial is typically followed by other clinical trials, including dose-ranging and pharmacokinetic studies[1]. Based on Phase I clinical trial data, experimental drugs that are found to be unsafe or not meeting the target safety and pharmacokinetic profile would normally not make it to Phase II.

There is continued pressure for pharmaceutical and biotech companies to compress their clinical development cycle at every phase to maximize return on their investment dollars. With an average 20-year R&D cycle and cost of $635 million US for developing a single drug, there is a lot at stake at every phase of the clinical development cycle[2]. For the average blockbuster drug, delaying the start of sales by even one day could cost a company $1.3 million US in lost sales[2]. Add to the mix that the probability of successfully completing each phase varies — 70 per cent for Phase I, 50 per cent for Phase II and 80 per cent for Phase III[2] — and only 28 per cent of products entering Phase I successfully complete Phase III trials. To compress this development cycle, move more products through the cycle and stay lean, companies are increasingly relying on contract research organizations (CROs) to conduct clinical trials. As a result, the compounded annual growth rate of worldwide clinical spending has reached a healthy 21 per cent for CROs, whereas only a seven per cent growth rate has been posted for internal resources of pharmaceutical and biotech companies[2].

Figure 1. Total Pharma Spending on Clinical Development, By Phase



(Source: PhRMA, Tufts Center for the Study of Drug Development Centerwatch Analysis, 1998)

Table 1. Four Phases of Clinical Trials in Drug Development

Study Phase	Number of Patients	Duration	Primary Purpose
Phase I	20-100 healthy normal patients	Up to One Year	Safety
Phase II	Up to several hundred patients	One to Two Years	Safety & efficacy
Phase III	Several hundred to several thousand patients	Two to Four Years	Efficacy & cost benefits
Phase IV (Post-Marketing)	Several hundred to several thousand patients	Two to 10 Years	Cost benefits & outcomes

(Source: FDA 1997; *Centerwatch: Industry in Evolution for Clinical Development Cycle*, 2nd Ed. FDA; 1997.)

Because of the international operations of most pharmaceutical and biotech companies, Phase I clinical trials have traditionally been conducted not just in the headquarters of these companies, but also in North America and Europe. Phase I trials are not new in Canada, what is new is that an increasing number of them are coming here, thanks to the new Clinical Trial Application (CTA) regulation.

What is the New CTA Regulation?

The new CTA regulation, as described in Division 5 of the Food and Drug Regulations, came into effect on Sept. 1, 2001[3]. The Health Products and Food Branch of Health Canada is the agency responsible for implementing the new regulation, which describes the approval process for Phase I-III clinical trials to be conducted in Canada. The key elements of the approval process are as follows:

- A CTA must be filed prior to starting the clinical trial in Canada;
- The CTA will be approved or rejected within 30 days (default review time);
- The target review time for CTAs of Phase I clinical trials and comparative bioavailability studies involving healthy, adult volunteers is seven days, except for somatic cell therapies, xenografts, gene therapies, prophylactic vaccines or reproductive and genetic technologies;
- All clinical trials (including Phase IV) must be conducted in accordance with Good Clinical Practice;
- Each clinical trial requires its own CTA, although previous CTAs can be cross-referenced;
- A CTA is not needed for Phase IV clinical trials.

Why is the New CTA Important for Canada?

The decrease in the CTA default review time from 60 to 30 days is the single most important driver of the increase in Phase I clinical trials in Canada.

This new CTA regulation makes Canada a more attractive location than Europe or the U.S. for North American companies to conduct Phase I studies. Prior to this new regulation, Canada was not considered an ideal trial location, since the previous 60-day IND review default meant lost product approval time for market entry, and lost sales opportunity for time-sensitive and profit-focused pharma and biotech companies.

Instead, these companies were turning to certain European countries, such as the U.K., where no IND was required and the ERB protocol review was the key review mechanism prior to the study's start. This advantage is losing ground, as a comparable IND review process is underway for Phase I clinical trials in the U.K. Canada's attractiveness as a Phase I trial location is further enhanced by its proximity to U.S.-based study sponsors and monitors, who prefer not to lose time crossing the Atlantic Ocean to monitor a study or meet with the study investigator.

Some companies were conducting their Phase I studies in the U.S., where the IND review default was 30 days. However, the new CTA review default is now on par with the U.S. one. Canada's currency is also a boost to many U.S.-based study sponsors, who can take advantage of the value that the Canadian dollar brings to the overall study cost. The location is also of convenience to U.S.-based study sponsors, especially in relation to the major American pharmaceutical and biotech centres, namely New Jersey, New York, Massachusetts, Pennsylvania and North Carolina. For example, Toronto and Montreal, where no less than seven Phase I CROs are based, are within 1-2 hours flying time from the major cities in these hotbeds. Additionally, being in the same time zone allows for easier communications between CROs and study sponsor personnel, while an added bonus is the demographically similar subject population and minimal language barrier, since English is largely spoken everywhere.

Canadian biopharmaceutical companies, especially start-ups based in Toronto, Vancouver, Ottawa and Montreal, are poised to benefit since the option of where to place their next Phase I clinical trial has expanded to include local CROs, thereby allowing them to take advantage of any R&D tax credits and cost savings related to currency, travel and monitoring. The close proximity of Phase I CROs to these companies would also facilitate closer interaction between scientists, sponsors and CROs.

The Canadian CRO industry has been anticipating the finalization of the regulation for the last three years, and has prepared for this by opening up Phase I clinical facilities just prior to September 2001. The industry is dynamic, young and growing, with a high concentration of highly trained technical and scientific workers dedicated to conducting clinical trials.

The new CTA regulation helps ensure the continued growth of this industry and puts forth advantages that essentially boost Canada's role as an international R&D hub. In turn, high-paying and highly technical jobs are retained within Canada's borders, as well as further technological innovations and investments.

This type of change has significant impact on highly regulated industries such as the biopharmaceutical and supporting CRO industries. Such positive changes are welcome in these times of widespread business failures. Without the new CTA regulation, Phase I clinical trials wouldn't have come to Canada at all, and those Canadian CROs focused on Phase I clinical trials may have lost yet another business opportunity.

References

1) Spera, Allan, ed. *CenterWatch Directory of Drugs in Clinical Trials*. First Edition. Boston: 2000.

2) *CenterWatch: An Industry in Evolution*. 2nd Ed., 1999.

3) Health Products and Food Branch. *Draft Guidance for Clinical Trials: Clinical Trial Applications*. Ottawa: 2001.

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