
Comparison of clinical trial costs between Canada and the US.

A critical analysis and review

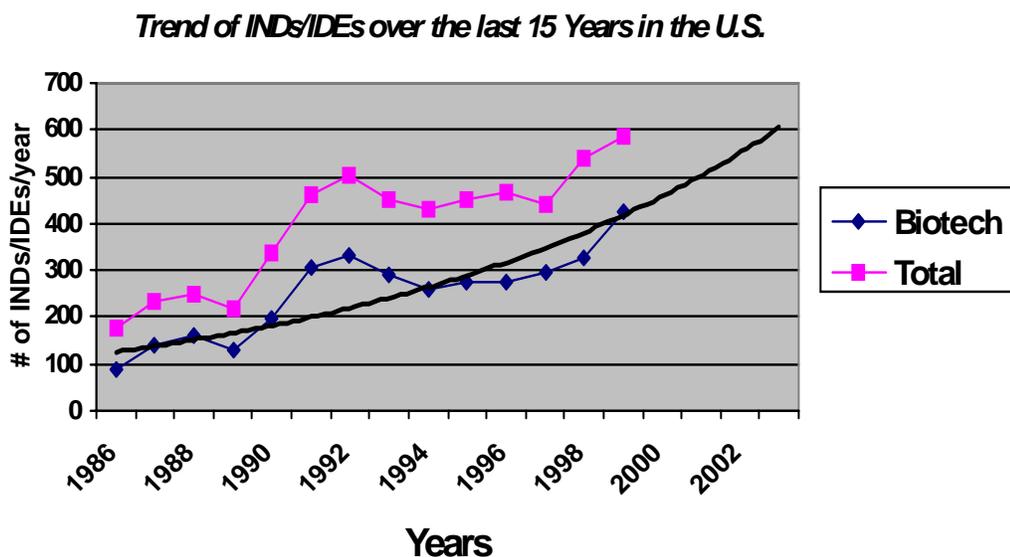
by Richard J. Meadows M.Sc., M.B.A¹.

Executive Summary:

There is a growing need for increased capacity as well as productivity in clinical trials. The amount of funds being spent on R&D by the biopharmaceutical industry estimated at \$33 billion in 2001, is growing by 15% per year: approximately 40% of which is accounted for by clinical trials.

This need for increased capacity and output is being driven by three factors:

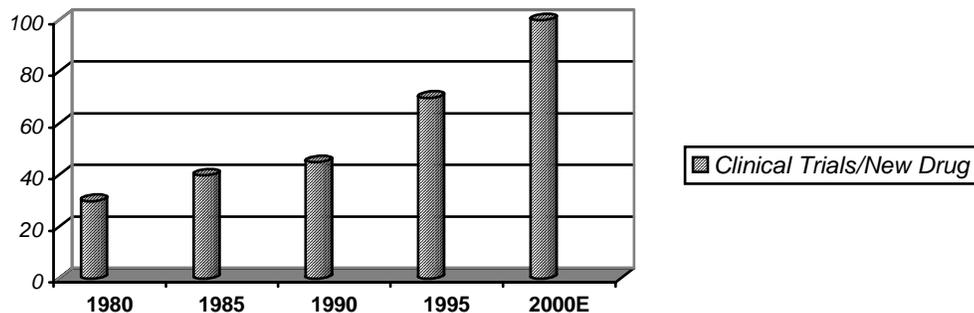
1. The number of drugs and devices entering clinical development is increasing, as the graph below indicates. Furthermore, the main driver for growth is coming from the biotechnology side (the lower curve in the graph) of the drug industry².



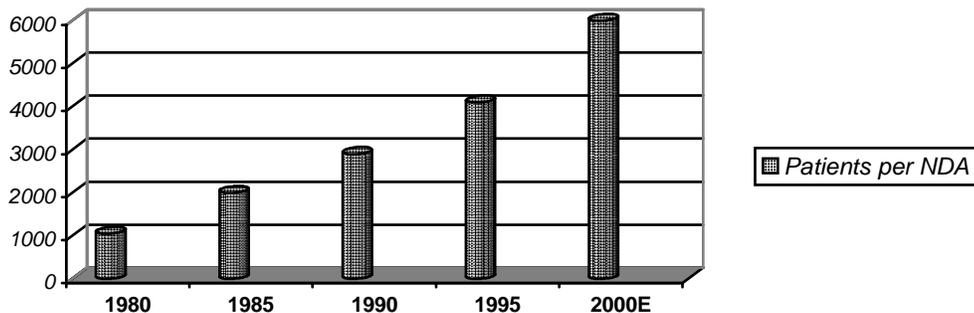
¹ Currently, Venture Advisor, for CDP Capital Technologies; Director of – BIORTHEX Inc., THERION BIOLOGICS Inc., MOLECULAR MINING Inc., and MERIX Biosciences. Consultant to PHARMAGAP (NRC spin-off).

² INDs are Investigational New Drug Submissions and pertain to drugs; while IDEs refer to Investigational Device Exemptions and apply to medical devices.

2. There are more clinical trials being conducted per New Drug approved.³



3. There are more patients per drug being accrued⁴ into clinical trials.



In addition, it is estimated that pharmaceutical companies spend \$1.3 billion USD per year on recruitment (\$1.0 billion on patient and \$300 million on physician recruitment) for clinical trials, because 75% of clinical trials do not reach their deadlines⁵.

These four factors are putting enormous economic pressure on pharmaceutical firms and consequently, the cost to develop a new drug is estimated currently at anywhere between \$659⁶ and \$800⁷ million US.

The cornerstone of clinical trials is patients, and more precisely collecting data from those patients in the most cost efficient manner. Getting data from patients in turn, involves employing advanced data gathering techniques and processes, reliable and efficient study processes, and superior economic metrics.

³ Source : Boston Consulting Group, Food Drug Law Journal 1997, Center Watch 1994

⁴ ibid

⁵ Source : ACURIAN

⁶ Boston Consulting Group

⁷ Probabilized spend by phase. Source: Eli Lilly Business Development Group.

Canada is well positioned to take advantage of this burgeoning opportunity; because of a variety of tactical factors listed below. However, these factors for the most part, spill out from four primary “structural” or strategic elements which favour Canada over the U.S.:

- A positive exchange rate variance, which at one time was as high as 40%; yet even at 30%, favors Canada over the U.S.⁸.
- Subsidized public healthcare, which results in lower diagnostic and interventional costs per patient.
- Lower labour rates for nursing and medical staff, and
- Financial infrastructure which makes funds available for clinical trials from government sources (Technology Partnerships Canada (TPC), Canadian Innovation Foundation, Canadian Institutes for Health Research⁹ (CIHR), BioLevier¹⁰), local venture capital pools and “big pharma” support.

Some of these tactical factors are:

- a growing number of high quality clinical sites as measured by level of GCP training,
- common standard-of-care which allows for easier integration of clinical trial data over many sites between the two countries
- well characterized patient populations e.g. hyperlipoproteinemia in Quebec, breast cancer in Ontario, leukaemia, etc.
- presence of Centers of Excellence such as the Canadian Genetic Diseases Network¹¹, the Canadian Stroke Network¹²; the Canadian Leukemia Studies Group¹³ with access to high quality clinicians and patients; as well as some 50+ institutional sites, CTOs¹⁴ and SMOs¹⁵ listed in the Canadian Clinical Trials – Facilities and Capabilities Handbook¹⁶
- institutional overhead costs, expressed as a per cent of gross study charges of 25%-40%, often well below those of comparable facilities in the U.S.¹⁷. (this is usually available on a site-by-site basis)
- lower labour costs especially research nurses¹⁸ with GCP¹⁹ training

⁸ « Competitive Alternatives » Comparing Business Costs in North America, Europe and Japan. G7 –2002 Edition. KPMG 2002.

⁹ CIHR has a program in collaboration with the Canadian Pharmaceutical Industry to subsidize in part clinical trials reviewed for their scientific merit by their peer review committees.

¹⁰ A \$100 million fund started March 2002, by the PQ government of the Province of Quebec to specifically subsidize in part Quebec biotech companies proceeding on to proof-of-principle human clinical trials.

¹¹ Dr. Michael Hayden, Scientific Director.

¹² Dr. Tony Hakim, Scientific and Clinical Director, Ottawa General Hospital.

¹³ Dr. Richard Van der Jagt, Chairman, Ottawa General Hospital.

¹⁴ CTO = Clinical Trial Organization

¹⁵ SMO = Site Management Organization; usually small group of physicians in hospitals or academic sites who organize themselves to conduct clinical trials e.g. Royal Ottawa Hospital to do psychotherapeutic trials.

¹⁶ Published by Industry Canada, CIHR and Genome Canada.

¹⁷ CROs report some sites on the East as well as West Coast charge as much as 110- 150%, overhead charge to cover use of their facility and staff.

- lower procedure fees for diagnostic and therapeutic interventions²⁰
- lower monitoring and project management fees for CROs in Canada²¹ to monitor sites in Canada and the U.S.
- patient accrual rates which can be higher depending upon the nature of the site and condition to be studied²²
- per patient costs which are a fraction of their U.S. counterparts
- recruitment fees for patients, if paid, are lower in Canada²³
- actual cost of monitoring Canadian sites are cheaper than in the U.S. (ceteris paribus) taking into account aggregate travel expenses
- infrastructure in place for centralized IRB reviews²⁴
- cost of routine diagnostic procedures e.g. blood chemistry, virology, diagnostic microbiology may be covered under provincial health plans if the study does not add to the burden of patient treatment cost.
- when all factors are costed-out - in a study employing a higher proportion of qualified Canadian sites will be cheaper than if the proportion favored US sites. The impact of these factors is approximately 30-45%, but can be higher depending upon the nature of the disease to be treated, the length of trial and the complexity of the primary and secondary endpoints of the trial. Please refer to the Case examples in the final report.

As the report drafted by KPMG entitled “Competitive Alternatives” illustrated, Canada enjoys a significant cost advantage over other countries in the G-7, especially in so far as R&D is concerned (30.6% over the U.S.).²⁵

¹⁸ A research nurse with two to four years experience, can be expected to make between \$35,000. to \$45,000. CAD, excluding benefits of about 15% of gross salary in an academic/institutional research site versus \$50,000. - \$60,000. USD for a comparable nurse in a U.S. hospital or clinic site. CRAs in a U.S. based CRO can be expected to make \$60,000. - \$75,000.USD according to industry recruitment web sites, and those with five or more years experience can earn north of \$77,000. USD according to Salary.com and BioMed Network.

¹⁹ Good Clinical Practice, required in order to ensure high quality collection and oversight of clinical trial protocols and data collection.

²⁰ CMAJ - for example the Ontario Health Insurance Plan (OHIP) fee for an *MRI scan of the lumbar spine* is approximately 40% -50% of that of the median charge of the Minimum Fee reimbursed by Medicare and the Maximum of a private Insurance Company.

²¹ Monitoring fees vary from CRO to CRO although in broad terms they tend to cluster around certain price points depending upon whether it is a Canadian or American CRO. In the case examples provided in this report for example, a per day monitoring fee of \$1500.00 CAD for a small-to-medium CRO is expected. In contrast, a U.S. based CRO would charge on average \$2500.00 USD per day.

Moreover, when taking travel costs into consideration, Canada enjoys a significant cost advantage over the U.S. e.g. hotel costs in Montreal or Toronto where you would expect to find major medical/academic sites for example range about \$150 - \$180 CAD; in a comparable U.S. city say Boston or Philadelphia this would be \$179 USD and up; and at current exchange rates this would be the equivalent of \$260 CAD. Factor in food, airfare, car expenses etc. and added over even 10-30 sites and the savings are significant.

²² CLSG/Pharmacia AML study 1997-2002.

²³ Recruitment fees can be anywhere from \$500 - \$1000 USD per patient in the U.S.; Canadian fees are not available but are expected to be significantly lower even on a straight dollar number conversion (industry sources)

²⁴ University of Ottawa and Ottawa Hospital, General Campus

²⁵ « Competitive Alternatives » Comparing Business Costs in North America, Europe and Japan. G7 –2002 Edition. KPMG 2002.

The Comparative Cost Index for Biomedical R&D varied from 66.3 in Halifax N.S. to 76.8 in Toronto ON., where 100 was the Overall Index for the U.S. (the index values ranged from a low of 82.5 for San Juan PR, to a high of 136.4 in San Jose CA).²⁶ The primary reason for Canada's strong showing is its low overall labour cost.

Clinical trials, whether they are earmarked for registration of a medical device or a drug, represent significant logistic challenges. They require the articulation of explicit objectives, clear trial design with relevant and measurable primary and secondary endpoints as well as the number of patients required to meet statistical - and by corollary - scientific proof of efficacy. Moreover, detailed site planning and monitoring, and a fully transparent cost structure reflecting variable and fixed costs as well as the proper attribution of each towards carrying out the study protocol, is essential.

The three case examples included in this report, cover a medical device used in orthopaedics, and two cancer clinical trials. One of the cancer trials involves the longitudinal study of a cocktail of drugs used to combat Non-Hodgkins Lymphoma (NHL); the other an agent to arrest the progression of a solid tumour cancer i.e. non-androgen dependent, prostate cancer. These trials were chosen because they are timely. They also represent the "hot" areas of clinical and therapeutic research in the world; and two of them were conducted in Canada.

These working cases also serve to illustrate, with different starting assumptions regarding number of patients, number of sites, type of diagnostic measures of therapeutic effect etc..., the impact of employing varying proportions of Canadian versus U.S. sites, as well as utilizing a Canadian based versus U.S. based CRO.

For example, in the medical device trial which employed 400 patients recruited from 10 sites, 6 in the U.S. and 4 in Canada. By using a Canadian CRO to recruit the sites, as well as monitor the study and using a central site in Canada to interpret the diagnostic MRIs carried out at all 10 sites, an overall cost savings of 30% was achieved. An additional 25 % saving could be achieved by increasing the proportion of Canadian Investigative sites by 50% i.e. shifting the proportion from the original 6:4 in favour of the U.S., to 6:4 employing a majority of Canadian sites.

There were still cost savings in the order of 14% in the latter scenario even if a U.S. based CRO was used to oversee the trial with a majority of Canadian sites.

In the case of the NHL trial, the Canadian Co-Operative group's expenses to carry out the trial, using electronic data capture, were calculated to be a little more than a quarter of the comparable costs to conduct the same study employing U.S. sites. The major cost savings arose from site-related fees.

And, in the second cancer trial, it is estimated that a 30% savings could be realized by using a majority of Canadian sites, regardless if the CRO monitoring the trial was

²⁶ Boston MA's Index was 119.1.

Canadian or U.S. based. This being said, a sensitivity analysis, reveals an overall cost efficiency of 36% if both a majority of sites used, as well as the CRO are Canadian.

Clinical Trials in the U.S. and Canada.

Context:

Overview – size and trends:

Clinical trials represent the most significant cost element of drug development for pharmaceutical companies worldwide. They account for over 40% of the total R&D budget and an aggregate global expenditure of some \$30 billion annually. This figure, by all industry accounts continues to grow; and most industry watchers concur that the compound annual growth rate of the market will be at least 10 -12 % per year.

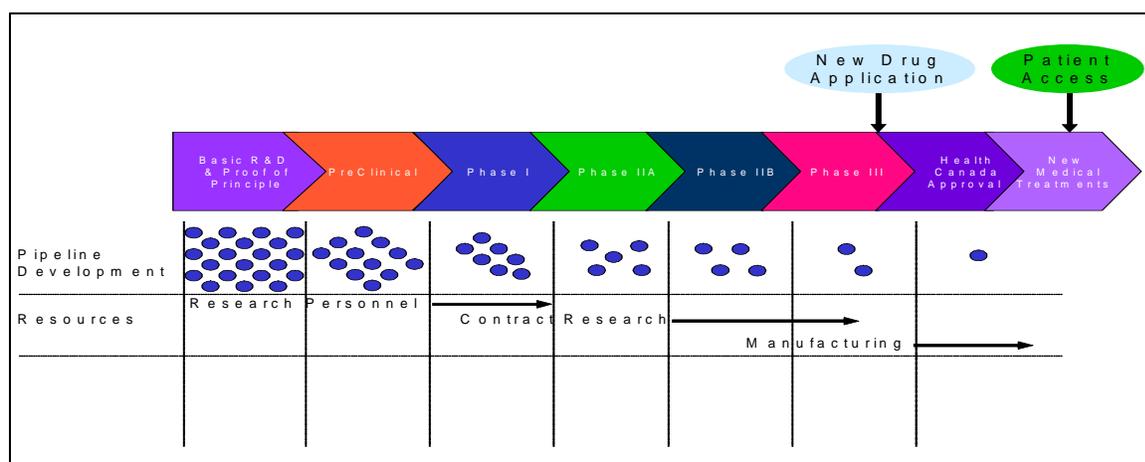
The average cost from bench to market, to develop a commercial drug is believed to be approximately \$800 million US²⁷. Of this amount, a significant proportion is attributable to the cost of clinical development and more specifically designing, conducting and monitoring clinical trials in human subjects.

Overview – stages of drug discovery and development; and key issues:

The goal of drug discovery is to discover novel new compounds from natural and/or synthetic sources, determine if they bind to unique biological targets, elucidate their structure and uncover lead agents which can pass the muster of selectivity and potency and enter into pre-clinical development.

Pre-clinical development is a separate well defined stage which acts as the critical bridge between the drug discovery part of the R&D chain and clinical development in human subjects. Pre-clinical development typically involves work in animals to further elucidate the mechanism of action of candidate drugs, test them for toxicity and clarify certain physiological and biochemical properties.

The stages of Drug Discovery and Development are shown in the chart below:



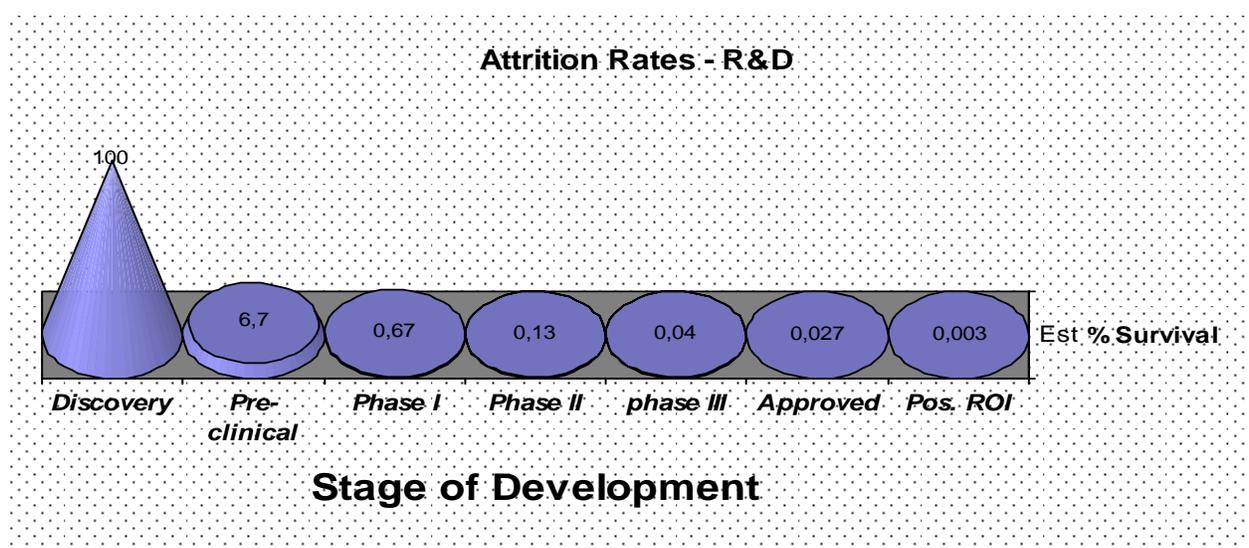
²⁷ Tufts University estimate

The latter part of the pre-clinical stage, which has the acronym **ADME/Tox**²⁸, has recently become a critical step to address the bottleneck within “big pharma” at which literally thousands of compounds emerging from larger and larger combinatorial libraries in the Discovery phase must be methodically screened in order to find the 10-20 lead candidates which can enter preclinical development. It is at this juncture that a sizeable number of candidate compounds fail - fully two thirds, due to adverse ADME/Toxicity²⁹.

This has the result of raising expectations for those leads which make it through ADME/Tox to succeed in clinical development.

The attrition rates continue to be high as “leads” become candidate drugs. For example, a little less than 7% of the compounds coming out of discovery actually make it into pre-clinical testing. These are the ones which have made it past the vast array of semi-automated chemical and biological tests conducted first *in vitro* and then *in vivo*, to demonstrate activity and specificity to a particular biochemical and biological target.

That 7 % number dwindles down even further to one tenth of 1% by the time phase II is completed, as the chart below illustrates.



In conclusion, currently 24 out of 25 drugs entering clinical development will fail to reach the market³⁰.

²⁸ Absorption – measures the ability of a drug to pass the digestive tract into the bloodstream; Distribution – measures the amount of a drug that different tissues take up from the blood; Metabolism – identifies the chemical changes the body makes to the drug (primarily in the liver); Elimination – shows how the body expels the drug in its native form or metabolite; and Toxicology – determines the adverse effects of the drug on the body, even to its propensity to cause cancer in certain circumstances.

²⁹ Source : Verkatish S, .Lipper R.A. J. Pharm Sci. 2000 Feb; 89(2):145-54.

³⁰ Shillingford C.A., Vose C.W. “Effective decision making: progressing compounds through clinical development” Drug Discovery Today September 2001,6,(18): 941-946.

Overview – phases of clinical drug development; and key success factors:

There are four well defined phases of clinical development – Phases I to IV. The italicized points appearing below each stage are those critical success factors which companies must pay strict attention to if they are to exit each stage successfully.

Phase I - initial safety trials in normal healthy human volunteers (however in the case of a cancer or HIV drug is usually conducted in actual patients) to establish the safe dose range for a drug³¹.

- *quick access to normal subjects i.e. access to a broad population who can come accessed quickly*
- *facilities and specialized equipment to carry out blood and pharmacokinetic analyses*
- *well-educated technologists who are GCP trained³²*
- *quality control processes and documentation*
- *low labour and transportation costs*
- *low facility costs*
- *cost and speed, part of which applies to the regulations of the country in which the study is to be conducted³³.*

Phase II – pilot clinical trials to evaluate efficacy and safety in a small number (about 100- 300) of patients with the particular condition to be treated.

- *ability to identify and quickly recruit³⁴ the type of patients which are being targeted and that fit specific inclusion criteria e.g. stage of disease, age, concurrent medical problems, ethnic origin, exposure to previous drugs in the category under study or in other drug classes (e.g. anti-hypertensives)*
- *access to well-trained clinicians in the field who have participated and successfully completed clinical trials in the therapeutic area being studied and have ready access to well-characterised patients*
- *clinicians who have well organised offices or clinics with research nurses who have done previous trials and have experience in completing and maintaining patient trial documentation and (e.g. Case Report Forms).*

³¹ This clinical stage is a natural entry point for firms who have developed expertise and own infrastructure in the medical testing and diagnostic fields e.g. MDS Laboratories, who now owns Phoenix Life Sciences; Canadian Medical Laboratories (CML) who spun out Pharma

³² **Good Clinical Practice.** A standard for the design, conduct, performance, monitoring, auditing, recording and analysis of clinical trials that ensures that the data collected are accurate and credible and that the rights of the test subjects are protected.

³³ Until recently the time to get approval to conduct a Phase I trial in Canada was 60 days or more; this compared unfavourably with Europe and the United States which was 30 days. It is presently in line with these two countries. In pharmaceuticals there is no better example of the adage “time is money”. At an opportunity cost of almost \$1.3 million US per day for a regular drug and over \$11 million US per day for a blockbuster like ZANTAC or VIAGRA, a delay of over 30 days could mean a loss of sales of anywhere from \$50 to over \$300 million dollars US. This amount may be difficult, if not impossible, to recover over the commercial life of the approved drug

³⁴ 80% of clinical trials fail to recruit subjects in the desired time frame – as reported in Marks R.G., Conlon M., Ruberg S.J. “Paradigm shifts in clinical trials enabled by information technology” *Statistics in Medicine* 2001; 20:2683-2696

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- *GCP trained research nurses who will monitor the investigational sites*
 - *access to hospital laboratories which can carry out various analytical assays quickly and at reduced cost*

Phase III – multi-center studies meant to measure efficacy and safety in populations of 1,000 – 10,000 patients for whom the drug is eventually intended. The design of the trial is critical and the data collected will, in large measure, determine the information required for the labelling of the drug and the package insert.

Much the same criteria as indicated in phase II above, but with the added caveats of:

- *access to and an ability to recruit certain types of patients*
- *being able to follow-up on patients, ensure they return for the various prescribed visits and complete their various tests etc..*
- *logistics organization; CROs must have the capacity and network to monitor the trial cost-effectively, since monitoring costs represent anywhere from 30-50% of a clinical trial's budget³⁵.*
- *access to bio-statistical expertise and data integration*
- *means for economical data collection and storage with rapid information exchange over many sites i.e. >40*
- *ability to have a “relatively seamless” regulatory connection between countries, especially in the case of Canada and the U.S. - so for the most part, data collected in one country, is accepted by the other.*
- *common approaches to medical care and the use of drugs³⁶.*
- *access to consistent levels of quality medical and hospital care*
- *computerization of offices and records*
- *centralized IRB (Institutional Review Board) approval.*

Cost – and the Risk/Reward argument for clinical Trials

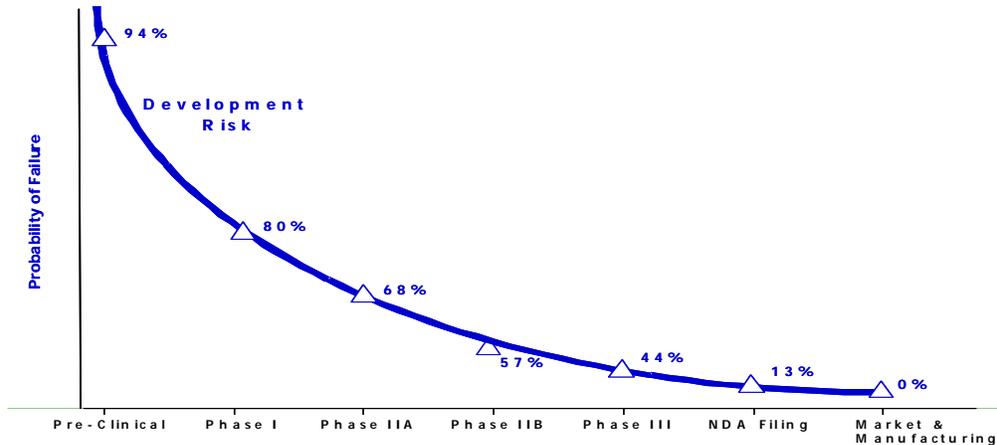
The objective of clinical trials is to secure regulatory approval for the sale of a new drug. This notwithstanding, the means to achieve this end is accomplished through a dynamic iterative process, which serves to maximize the value of a potential saleable drug while minimizing the inherent risk in its development. In the day-to-day reality of bringing a drug from research into clinical development, development risk is made up of an amalgam of factors; of which cost is just one; albeit the most important one. Other factors, such as subject recruitment and patient accrual rates, monitoring, access to quality patients and investigators eventually play out in terms of cost also.

³⁵ Just taking travel costs into consideration, Canada enjoys a significant cost advantage over the U.S. e.g. hotel costs in Montreal or Toronto where you would expect to find major medical/academic sites for example range about \$150 - \$180 CAD; in a comparable U.S. city say Boston or Philadelphia this would be \$179 USD and up; and at current exchange rates this would be the equivalent of \$260 CAD. Factor in food, airfare, car expenses etc. and added over even 10-30 sites and the savings are significant.

³⁶ Patent-based drug manufacturers believed that French physicians, prescribed more antibiotics per head than their North American counterparts and for quite different conditions. This was not the case for Canadian and U.S. based doctors.

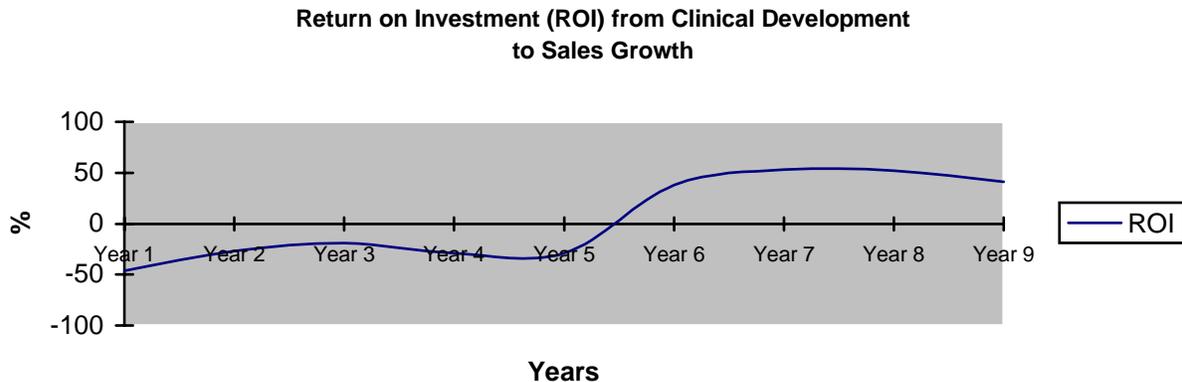
The cost to develop a new drug, from bench to commercial launch, has been variously estimated at anywhere between \$550³⁷ and \$880³⁸ million US.

Development risk is adequately compensated by reward at the point where the first trial in humans demonstrates some measure of efficacy as its primary endpoint i.e. Phase IIB. This is the juncture where, theoretically at least, risk/reward is balanced i.e. probability of failure is about 50% (refer to graph below).



Source: Adapted from Biopharmaceutical Drug Development Accelerator; September 2002

At the Phase IIB stage there is adequate future financial return for the level of developmental risk. However, this initially negative return on investment, becomes positive over time as the drug proceeds through clinical development and on to eventual commercialization. This is shown in the graph below.



Source: ROI for a product from clinical development in a biotech company (Years 1 through 5); through to early sales and marketing Years 6 –9.

³⁷ Lasagna L., Tufts University Estimate

³⁸ Boston Consulting Group

Coincidentally, it is at this point that the greatest “lift” in value occurs³⁹ for biotechnology projects as well. The market rewards big pharma and biotech firms for getting to these significant developmental milestones. Moreover, for a middle stage biotechnology company this represents the critical juncture at which point it has enough to offer to a potential collaborator or development partner to entice them into a significant development deal.

This is also where, according to some deal makers in biotech⁴⁰, the maximum value of a drug is realized (it can be some multiple of some 10-100 times the value of the post pre-clinical phase) and provides the needed up front cash and milestone payments needed to fuel further development, as well as arm the originating company with proof-of-concept for their drug discovery platform.

Two critical questions arise from the dual observation that the greatest value-added occurs at the latter stage of phase II; and that development costs rapidly escalate as well from early phase II onwards⁴¹. The first question is - what factors of input are key to ensuring that the ROI (Return on Investment) for a company`s clinical development program is realized, whether that is in “big pharma” or small biotech And the second question is - are these factors effected by geographic location?

Key operational trends and issues to consider when planning clinical trials:

The answers to these two questions must be considered in the context of the following operational issues and trends.

First, the time-to-approval for new drugs appears to be getting longer. PhRMA reports that in 1999 it took 12.6 months to secure approval for a new drug in the U.S.⁴²; a year later that figure had risen to 17.6 months. Although 2001 saw an improvement towards an average approval time of 16.4 months; 2002 has since slipped down to 19 months - an unsettling divergence from the 1999 performance.

Second, the increasing number of trials in certain therapeutic areas e.g cardiovascular and various forms of cancer has had the effect of increasing competitive pressures for new patients; and consequently, pharma is beginning to see significant drops in average monthly recruitment rates per site⁴³. Consequently, companies are starting to move their trials to other regions of the world e.g. Eastern Europe⁴⁴.

³⁹ Personal Communication, Venture Capital Partner, a Canadian Biotech Investment Fund.

⁴⁰ Personal Communication, Senior V.P. Medium Sized Biotech Company

⁴¹ According to the Boston Consulting Group in their report on “The Impact of Genomics on R&D”; of the \$880 million - \$370 million is spent on Biological Target Identification and Validation; another \$160 million is spent on screening and lead optimisation; \$90 million in pre-clinical development and the remainder of \$260 million in clinical development. Phase I can be expected to account for about 10% of this clinical development figure, with approximately 30-40% for phase II and 60-70% for phase III.

⁴² From submission of the New Drug Application (NDA) to the FDA to receipt of the letter of compliance.

⁴³ Source : ACURIAN

⁴⁴ MDS Pharma Services Clinical Research, Central and Eastern Europe. Lilly, Area Medical Center, Vienna

Third, the market conditions of the last 2 years have made it very difficult and in most cases virtually impossible for biotech companies to raise enough money to get into the critical phase II stage of development. This has forced them to rely more on big pharma to take promising new compounds into development. Furthermore, biotech firms are not as financially well-heeled as their big pharma competitors. Consequently, they are not in as strong a position to weather a clinical setback⁴⁵ of one of their limited number of drug candidates.

Fourth, big pharma has recently suffered some high profile development failures in managing the clinical development process and maximizing the feedback from regulatory agencies in order to expedite the development process. Drug companies want increased predictability of FDA reviews particularly after Phase II trials. Consequently, the FDA will likely be consulted earlier. The FDA has already put in place a special protocol approval for certain drugs in cancer.⁴⁶ This will it is hoped, have the result of making the development process more transparent and predictable.

Fifth, the much anticipated payoffs of combinatorial chemistry, tapping into the power of genomics and the drug discovery process acceleration promised by high throughput screening has not been realized. All failed, singly or in combination, to increase the number of high quality compounds making it into clinical development⁴⁷. This has put a lot of pressure on big pharma to seek more effective decision-making and development strategies with respect to drug candidate selection as well as clinical development.

The planning and costing out of clinical trials:

⁴⁵ In 2002 clinical failures occurred all too frequently - 30 biotech drugs failed to achieve their primary endpoints in Phase II and/or Phase III⁴⁵. This is as many as were approved annually by the FDA between the years 1994 to 2000. Cancer drugs accounted for 27% of failed late-stage trials, although there were also failures in all therapeutic areas including rheumatoid arthritis, Crohn's disease, cardiovascular and CNS; as well as diabetes and infectious diseases.

⁴⁶ Personal Communication, Feb. 2003.

⁴⁷ Pigliucci R. Discovery Partners International. Presentation to SCREENTECH 2002, March 4, 2002, San Diego California

The critical factors for success within each stage of clinical development were itemized and elaborated previously; these factors and their operational sequelae have been subsequently translated into the critical checklist below.

<i>Key Activity</i>	Responsibility/ Cost⁴⁸	Comments
Identification, vetting & Negotiation with clinical sites i.e. drafting Clinical Trial Agreements	Sponsor/CRO	Identify hospitals and appropriate clinicians at appropriate clinical sites ~ 15 = <i>a</i> days; Establish contact person at each of 15 sites; letter to each site, arrange meetings, telephone follow-up = <i>b</i> days; Visit 10 sites do GCP audit and follow-up documentation = <i>c</i> days; Finalize negotiations, with 5-7 sites = <i>d</i> days; Total <i>a + b + c + d</i> days @ \$1500.00/CAD/day. Travel is billed to Sponsor
Setting up, choosing members establishing SOPs for Data Monitoring Committee	Sponsor/CRO	Preparation = <i>e</i> days; Establish SOPs = <i>f</i> days; Establish compensation, Identify 5 members and Chairman = <i>g</i> days; Meet and vet members = <i>h</i> days; Review SOPs, set up schedule for meetings = <i>i</i> days. Total <i>e + f + g + h + i</i> days @ \$1500.00/day. Travel is billed to Sponsor.
Validation of Trial Design	Sponsor/CRO	Selection, vetting and engagement of Statistical Consultant = <i>j</i> days.
Study Protocol Review and Critique	Stat Consultant \$?	Study design, validation and plan for the collection of clinical data to meet endpoints and meet regulatory guidelines for approval
Recruiting of Monitors	CRO	
Organize Investigators' Meeting	CRO	Attendance at meeting by Sponsor's personnel, <i>k</i> days Travel is billed to Sponsor
Design, Validation, of CRF ⁴⁹ s	Sponsor/CRO	Part of EDC ⁵⁰ solutions -
Trial Monitoring	CRO	EDC ⁵¹ will reduce significantly the frequency and nature of trial monitoring.
Project Management	Sponsor/ CRO	<i>l</i> days/ month x <i>m</i> months = <i>n</i> days @ \$1500.00/day
Arrange for IRB ⁵²	Sponsor/ CRO	Central IRB in Canada and the U.S. Regional IRB approvals for <i>o</i> sites. <i>p</i> days @ \$1500.00/site
Data Collection and Data Management	Sponsor/CRO \$?	Cost to identify and vet an EDC provider and negotiate the appropriate cost model to meet Sponsor's short and long term needs <i>q</i> days @ \$1500.00/day = <i>r</i> \$
Identify, and negotiate for central blood and/or diagnostic analysis at a site in Canada.	Sponsor/CRO	<i>s</i> days @ \$1500.00/day .
Prep and attendance to FDA	Sponsor/ CRO	

Critical Success factors for Clinical Development in the Global perspective:

⁴⁸ Subject to final review and requires detailed quote from EDC supplier

⁴⁹ Case Report Forms

⁵⁰ EDC - Electronic Data Capture – Capturing clinical trial data in an electronic medium directly and transmitting it to a central databank for conservation and subsequent analysis.

⁵⁰ Institutional Review Board – each major academic site, hospital, research Institute has one which reviews experimental protocols to ensure the highest ethical standard and protect the rights of the participating subjects.

⁵¹ ibid

⁵² IRB - Institutional Review Board – each major academic site, hospital, research Institute has one which reviews experimental protocols to ensure the highest ethical standard and protect the rights of the participating subjects.

The abovementioned factors are as critical to Global Clinical Development as they are for registration in local markets. The stakes are however higher.

Global drug development requires very tight process control, integrative monitoring and data collection systems, recruitment of a large number of patients and of course the production of high quality data.

Data, as one entrepreneur, who co-founded one of the most successful CROs in recent biotech history, must unfortunately be acquired through patients. It would be a lot cheaper and easier to get data if you did not have to rely on human subjects⁵³; but alas that is not the case. And rapid access to high quality subjects ensures in turn, production of high quality data. This is not always self-evident, but it is the single most important element which gets the company to NDA review and approval quickly and effectively.

Importance of Patient and Investigator Recruitment

Patients must be scrupulously identified, carefully developed and nurtured in order that biopharma has the ability in the later stages of development to compare the advantages and disadvantages of different drugs and treatment regimes.

Recruitment of patients and investigators for participation in clinical trials is a \$1.3 billion USD business in the United States. Furthermore, 75% of clinical trials it has been reported, miss their development timelines because of poor recruitment.

Rapid access to qualified patients through a network of well trained and experienced clinicians is key. Many of these networks, in Canada at least, are informal e.g. Canadian Leukemia Studies Group (CLSG)⁵⁴, but can be formalized into albeit loose affiliations of specialists such as the American groups are - Eastern Cooperative Oncology Group (ECOG), South Western Oncology Group (SWOG), to mention just a few.

Canada does possess a number of these networks. Some are organized officially, others are loose informal groups of clinicians with specific expertise who can be marshalled together quickly to carry out a trial.

Canada also has the salient potential to create additional specialized networks from existing groups, as well as academic and institutional affiliations which exist at the scientific level. Noteworthy examples are the Centers of Excellence e.g. Canadian Genetic Diseases Network⁵⁵, and the Canadian Stroke Network. Some specialists have

⁵³ Personal Communication.

⁵⁴ Dr. Richard van der Jagt, Ottawa Hospital, General Campus.

⁵⁵ Dr. Michael Hayden, Scientific Director.

attempted to organize themselves into small but highly productive sites for patient recruitment in psychiatry⁵⁶, heart disease⁵⁷, woman`s health⁵⁸, etc..

Canada`s performance in a primary care trial:

An example of the performance metrics of one of these spontaneously organized networks of clinical investigators is seen in one of the few large scale published trials, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), designed as a phase IV trial but with the scientific rigour of a phase III trial. This trial was meant to study the clinical outcome of antihypertensive and anti-hypercholesterolemic medication in a diverse older population (>55 years of age) with a particular focus on women and African-Americans which included sites in Canada.

The recruitment performance in the ALLHAT trial is shown in the table below⁵⁹.

<i>Location</i>	<i>Number of sites</i>	<i>Pts./week per Clinic at 6 mos.</i>	<i>Median Days from Approval to First Randomization</i>	<i>Median # of Randomizations/site</i>	<i>Median Months to recruit</i>
NE US	106	0.7	55.0	36.5	34.0
South US	131	0.7	44.0	41.0	34.0
NW US	239	0.8	46.0	42.0	35.0
West US	84	0.6	46.0	37.0	32.5
Canada	30	0.5 (0.6) ⁶⁰	63.0 (56.0)	19.0 (23.0)	10.0 (9.0)
Caribbean	33	2.4	41.0	109.0	22.0
Canada ⁶¹ Indexed to US	22	86	86	41	170

This was a primary trial in which frontline physicians don`t normally take part. Consequently, it might be expected that these physicians would not to be as well equipped, prolific or as well organized as more experienced academic sites; nevertheless, the logistics of the trial speak to its daunting challenges and unique achievements: over 42,000 patients enrolled, over 6 years of follow-up, and more than 600 sites spread over the western hemisphere.

Canada`s performance is noteworthy in two significant respects. The first is in the recruitment rate, this was 86% of the average of the US sites, despite the fact that the Canadian sites had a lower likelihood (demographically) of being able to recruit African

⁵⁶ As communicated by Groupe SECOR.

⁵⁷ Dr. Salem Yusif, McMaster University, Hamilton, ON

⁵⁸ Ottawa Hospital, Civic Campus

⁵⁹ Wright J.T., Cushman W.C., et al.. "The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT): Clinical Center Recruitment Experience. *Controlled Clinical Trials* 22:659-673 (2001).

⁶⁰ Weighted figure to take into account the difference in number of sites between Canada and the US average and thus equilibrate it to the US situation for purposes of head-to-head comparisons.

⁶¹ Canada`s performance indexed to the average of the US sites.

Americans⁶² (the primary target population of the trial) into the study. The second, is in the recruitment speed which was 170% faster than that of their US counterparts. This was achieved with only 22% of the sites that the US had (figure in the lower left hand box of the last row).

Both recruitment rate and recruitment speed are considered key to global competitiveness⁶³ in clinical trials. The performance of key academic/university sites in Canada, who have had prior experience in the conduct of clinical trials, is known to exceed that of primary care centers.

Monitoring as a key expense component of a clinical trial

In addition, monitoring is a key expense of multi-center trials and can account for up to 40% of a clinical trial's cost. The cost of travel to these various sites is a material expense and is usually accounted for separately either as a pass-through cost to the sponsor, if the monitoring is contracted out to a CRO; or as a direct expense on the cash flow statements of the sponsoring company.

Company competitiveness is furthered by being able to conduct these trials in as efficient a manner as possible while attempting to minimize monitoring expenses. One way to achieve this is to move from paper-based trials⁶⁴ to using Remote Data Entry by either employing modems or submitting and validating data right on the web through secure network collections.

It has been estimated that by using electronic data capture, 20% of monitoring, and 40% of data pick-up and handling costs can be saved.⁶⁵ These time savings, can be substantial e.g 18 weeks for monitoring; 6 weeks for patient recruitment, 3 weeks for site recruitment and 38 weeks for data management⁶⁶. This in turn translates into real cost savings. The savings in direct expenses of an average trial is estimated at about \$15,000,000.USD. The opportunity cost gain, assuming a successful product launch can be up to \$550,000,000.USD⁶⁷. Canada with its well developed IT sector, it's superior connectivity as far as the world wide web is concerned, and the preponderance of computers in the health care setting; is well positioned to take a leading role in the development, use and dissemination of EDC in human medicine.

⁶² Target of >55% from this ethnic group

⁶³ Personal Communication, Dr. William Neilson, Former Director of Worldwide Product Development for FERRING Pharmaceuticals, Denmark.

⁶⁴ 85% or more of pharmaceutical drug trials still use paper

⁶⁵ Green J.A. "The EDC value Proposition to the Pharmaceutical Industry". DataTrak International July 9, 2001.

⁶⁶ Source PJB, 2001

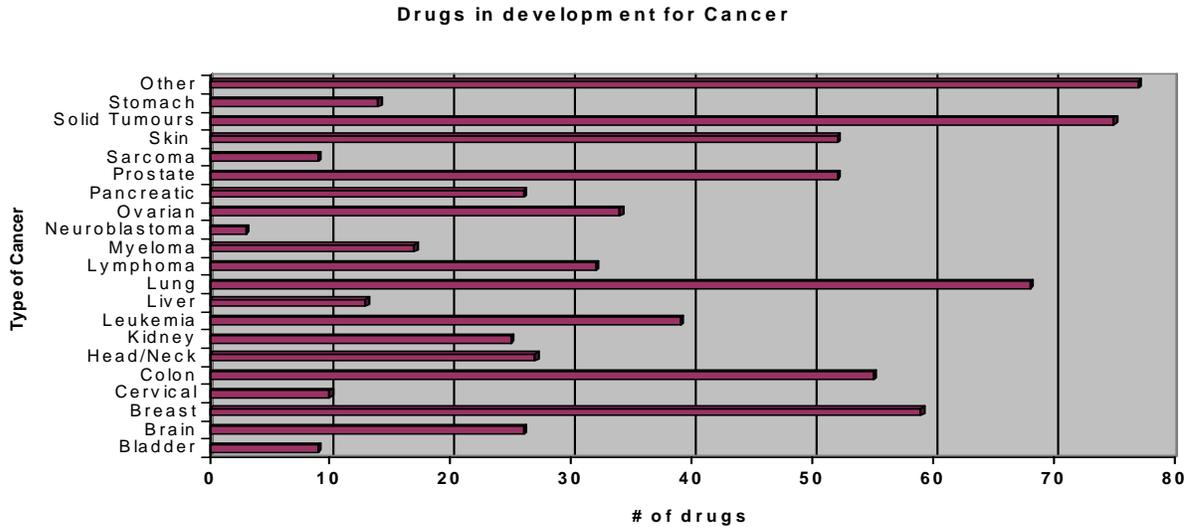
⁶⁷ Based on an opportunity cost gain of \$1.2 million USD sales revenue for a drug with potential of over \$250 million USD in its launch year

Therapeutic Focus in clinical trials and Canada's resources:

A survey conducted by the Canadian Institutes of Health Research (CIHR) indicated that there were 645 biopharmaceutical compounds in development at Canadian companies in January 2001.⁶⁸ These compounds cover more than 20 therapeutic areas including cancer (138), central nervous system (66), infectious disease (55) and cardiovascular disease (51).

According to the Pharmaceutical Research Manufacturers of America, there are some 785 drugs in development by their member companies. Of these, the single largest component are drugs for cancer with 402 (the detailed breakout is depicted in the chart below), the next largest investigative group is heart disease/stroke with 122 in development.

As the population ages the proportion of deaths due to cancer is expected to rise. Currently, one in every four deaths in the US is from cancer. As might be expected, the focus of drug development, is shifting to the treatment and prevention of cancer - specifically to breast, prostate, lung and solid tumours.



Source: PhRMA 2001 Survey (Some drugs are being investigated in more than one type of cancer).

The CIHR has published research which shows that Canadian researchers, on a per head basis are more highly published and cited in the field of cancer research than their American counterparts. This makes Canadian research and treatment facilities highly attractive as sites to assess new therapeutic approaches and modalities.

Market Drivers for clinical trials – cost, research productivity and

⁶⁸ Canadian Biopharmaceutical Companies – Status of Research, Development &

The reality is that the market growth is <8%/yr. Firms launch on average 0.5 NCEs/year. R&D costs >\$800 million, and average sales/drug are closer to \$150MM US/year.

biotech :

The “macro” drivers⁶⁹ for drug development in “big pharma” used to be:

- ♣ maintain market growth at > 15%/ year market growth
- ♣ launch 3-5 New Chemical Entities /year
- ♣ cap R&D costs/drug at ~\$500 million
- ♣ find drugs which will generate >\$265MM US sales/year

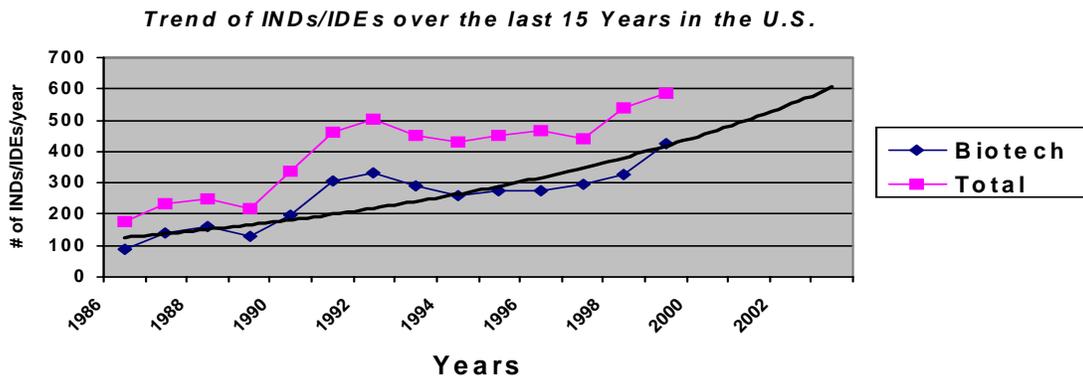
♣ ♣

Over \$30 billion was spent on R&D last year; of which approximately \$13 billion was spent on clinical development.

Industry analysts cite the need for 2-3, billion dollar products per year from each big pharma firm if they are to meet the expectations for growth in value expected from their management and shareholders. The reality is that of the tens of thousands of products on the market today, only 44 achieved sales exceeding \$1 billion per year. Furthermore, the top 10 products accounted for over 70% of sales overall for the top 10 pharma companies.

Reality has also “updated” the often quoted figure of \$500 million US of the cost to research, test and bring a drug to market. The actual cost, as has been cited earlier in this report is somewhere between \$659⁷⁰ and \$800⁷¹ million US.

The trend to a greater number of INDs (Investigational New Drug Submissions) and IDEs (Investigational Device Exemptions) continues unabated. The source of the increased submissions appears to be the biotech industry, not big pharma as first may have been thought. (please see chart below)



⁶⁹ Price Waterhouse Coopers , Dr. Jeff Handen, August 2001

⁷⁰ Boston Consulting Group

⁷¹ Probabilized spend by phase. Source: Eli Lilly Business Development Group.

Although biotech companies may be driving the process of generating new agents or therapeutic approaches to disease it will still be “big pharma” who will complete the process of development and bring the resulting drugs to market.

Operational Planning for a Clinical Trial:

Whether it is an early stage biotech company looking to carry out a proof-of-concept study for its lead compound in an early phase II trial, or a “big pharma” firm about to take a candidate drug into clinical development, the issues to be considered when planning a clinical trial are very similar and are outlined in the following pages.

Later on in this report, three trials are described in detail in as much as their costing is concerned - one is for a medical device in orthopaedics (a very hot area for acquisitions lately), and other two are for cancer (one each in solid tumour and blood borne cancer). The trials have been chosen so as to highlight the cost benefit of using Canadian sites and/or Canadian Clinical trial organisations to carry out pivotal trials for the North American market.

Decision framework to conduct a clinical trial, Key Issues:

- Therapeutic area – based upon properties/positioning of the drug and marketing/regulatory strategy
- Availability of the “right sort” of patients
- Demographics of the site and region
- History of recruitment rates (# of patients recruited per site)
- Performance – recruitment speed (speed at which appropriate patients are recruited over all the sites)
- PI⁷²s and study sites which are GCP⁷³ compliant and have had positive experience in collecting data and closing trials
- Design of the trial with definition of primary and secondary endpoints
- Design, testing and validation of Case Report Forms (CRF).
- Inclusion and exclusion criteria for patients to enter into the trial
- Number of sites – primary care or academic centers
- Location of sites i.e. proximity to hospitals for diagnostic procedures
- Choice of going it alone or with a CRO/ partitioning of responsibilities and objectives
- Duration of trial
- Strategic plan – for “big pharma”, is this part of a global clinical development program? If biotech, is this part of a partnering strategy?
- History of IRB reviews for the institutions being considered
- Quality assurance and routine audits of the sites

⁷² Primary Investigators

⁷³ Good Clinical Practice – A set of guidelines and standards to guide personnel in the management and monitoring of clinical trials.

Unique Implications by Therapeutic Area

- type of cancer to do efficacy trials (e.g. lead with a form of cancer where it might be possible to get orphan drug status and then pursue trials later in the primary more prevalent form of cancer).
- availability of patients with certain particular characteristics (renally compromised, certain genetic predispositions such as hyperlipoproteinemia, hypertriglyceridemia)
- patients who have not been exposed to certain immunologic agents etc..
- standards of care (the art in medicine) and prevalence of certain pharmacotherapeutic practices (e.g. more aggressive use of beta blockers and calcium antagonists by French physicians than their North American counterparts)
- best clinical practices and use of comparators which would be considered unethical to not employ – this is where Canada and the US are very similar

Unique Implications by Geographic Area (Canada vs. the U.S.)

- availability of certain best clinical practice comparators which are influenced by regional differences e.g. cylindrical spinal implants used in Europe versus rectangular ones employed in North America
- Institutional Review Board (IRB) timing for approval which varies by Institution and within geographic area
- although ICH guidelines are meant theoretically to provide international harmonisation of data across most countries in the world, this is not the case in practice. And consequently, Canada (HPB) and the US (FDA) share more common views and exchange information more freely
- overhead costs charged by the institution for trials done within their facilities and with their staff – this can be anywhere from 20-40% for certain Canadian sites but can run as high as 70 -100% for US sites.
- use of indirect institutional services within the protocol e.g. blood chemistry, virology, diagnostic microbiology, etc.. which is not directly billed back to the sponsor. Many Canadian sites (hospitals) offer this added benefit through indirect subsidization by the various provincial health plans.
- SOPs⁷⁴ are more likely to be similar between Canada and the US, than say between Europe, Eastern Europe or Japan and the U.S.
- training of clinicians and accepted clinical practice is much the same between Canada and the U.S.
- common language and philosophy to medical practice
- attitude to work, timelines, commitment to completion, deadlines and monitoring activities are analogous

⁷⁴ Standard Operating Procedures

Checklist of key components which drive the costing of a clinical trial

Key Activity	Responsibility Cost⁷⁵	Comments
Identification, vetting & Negotiation with clinical sites i.e. drafting Clinical Trial Agreements	Sponsor/ CRO	Identify hospitals and appropriate clinicians at appropriate clinical sites ~ 15 = <i>a</i> days; Establish contact person at each of 15 sites; letter to each site, arrange meetings, telephone follow-up = <i>b</i> days; Visit 10 sites do GCP audit and follow-up documentation = <i>c</i> days; Finalize negotiations, with 5-7 sites = <i>d</i> days; Total <i>a</i> + <i>b</i> + <i>c</i> + <i>d</i> days @ \$1500.00/CAD/day. Travel to be billed directly to Sponsor
Setting up, choosing members establishing SOPs for Data Monitoring Committee	Sponsor/ CRO	Preparation = <i>e</i> days; Establish SOPs = <i>f</i> days; Establish compensation, Identify 5 members and Chairman = <i>g</i> days; Meet and vet members = <i>h</i> days; Review SOPs, set up schedule for meetings = <i>i</i> days. Total <i>e</i> + <i>f</i> + <i>g</i> + <i>h</i> + <i>i</i> days @ \$1500.00/day. Travel to be billed directly to Sponsor.
Validation of Trial Design	Sponsor/ CRO	Selection, vetting and engagement of Statistical Consultant = <i>j</i> days.
Study Protocol Review and Critique	Stat Consultant \$?	Study design, validation and plan for the collection of clinical data to meet endpoints and meet regulatory guidelines for approval
Recruiting of Monitors	CRO	
Organize Investigators' Meeting	CRO	Attendance at meeting by Sponsor's personnel, <i>k</i> days Travel to be billed directly to Sponsor
Design, Validation, of CRF ⁷⁶ s	Sponsor/ CRO	Part of EDC solutions -
Trial Monitoring	CRO	EDC ⁷⁷ will reduce significantly the frequency and nature of trial monitoring..
Project Management	Sponsor/ CRO	<i>l</i> days/ month x <i>m</i> months = <i>n</i> days @ \$1500.00/day
Arrange for IRB ⁷⁸	Sponsor/ CRO	Central IRB in Canada and the U.S. Regional IRB approvals for <i>o</i> sites. <i>p</i> days @ \$1500.00/site
Data Collection and Data Management	Sponsor/ CRO \$?	Cost to identify and vet an EDC provider and negotiate the appropriate cost model to meet Sponsor's short and long term needs <i>q</i> days @ \$1500.00/day = <i>r</i> \$
Identify, assess and negotiate for central blood and/or diagnostic Analysis at a site in Canada. Establish a total budget.	Sponsor/ CRO	<i>s</i> days @ \$1500.00/day .
Prep and attendance to FDA	Sponsor/ CRO	

⁷⁵ Subject to final review and requires detailed quote from EDC supplier

⁷⁶ Case Report Forms

⁷⁷ Electronic Data Capture – Capturing clinical trial data in an electronic medium directly and transmitting it to a central databank for conservation and subsequent analysis.

⁷⁸ Institutional Review Board – each major academic site, hospital, research Institute has one which reviews experimental protocols to ensure the highest ethical standard and protect the rights of the participating subjects.

As pointed out in the Checklist previously; there are a number of factors which are taken into account when costing out a clinical study and deciding where to conduct it. However, cost is not the only issue; although, it is one of the most important.

Following closely behind are such issues as:

- 1) the quality of the sites as measured by level of GCP training,
- 2) characteristics of the patient pool,
- 3) history of patient accruals, and
- 4) prior experience in clinical trials.

Information about the quality of the sites is hard to come by. It is accrued over time by practitioners in the field as well as specialized service providers, and is jealously guarded. It even becomes a key competitive advantage for some service provider organizations.

The above notwithstanding, there are organizations and some information resources, such as Center Watch, which do provide some data about sites and institutions; although its reliability and timeliness is under question.

Having said the above, the primary determinant with few exceptions⁷⁹ for where a trial will be conducted in North America still remains cost.

The table below describes the working cost assumptions which drove the elements of the costing:

Parameter	Assumption
CRF costs	CRF design with several revisions - \$100/CRF page. Printing \$1.25/page. 20% shipping and handling.
Double Data Entry(DDE) & Database Management (DM) Fees	DDE is \$4.00/page. Baseline database development fee adjusted for CRF complexity = \$10,000.00
Review and Query	\$10 - \$14/page
Monitoring, Start-up, Close-Out	These are fixed for all studies and include pre-study visits, initiation visits and closeout visits = \$1500- \$2500U.S/visit and an additional \$500 - \$1000 for related non-visit activity e.g. preparation of reports and site contact re:problem solving
Routine Monitoring, Data Driven Model (DDM)	(DDM) CRA can 100% source document verify 100 CRF pages/day. Cost = \$1500- \$2500U.S/visit and an additional \$500 - \$1000 for related non-visit activity
Routine Monitoring, Visit Frequency Model (VFM)	(VFM) \$1500- \$2500U.S/visit and an additional \$500 - \$1000 for related non-visit activity
Monitoring Model Used	DDM or VFM depending upon the trial

⁷⁹ Exceptions may be for very specialised sites which treat or have access to patients with pancreatic or renal cancer; certain populations of patients who have been exposed to the AIDS virus, Hep B, Hep C, etc...

Case Analyses: Canada vs. the U.S.

The following cases illustrate (please refer to attached spreadsheets), using a detailed cost analysis, a variant of which most biopharma companies would employ to cost out a clinical trial; the obvious advantages to conducting a trial in Canada.

Each cell has embedded within it the elements for that particular cost component of the trial. Consequently, it is possible to use these forms as templates to cost out a variety of clinical trial scenarios. The key variable which determines the value of the cost inputs is geography. And geography also indirectly drives a number of cost elements which are critical to the cost of a clinical trial. These are salaries for research nurses, cost of certain procedures⁸⁰, monitoring costs, lab fees, etc..

The conclusion is clear – there are significant savings to carrying out clinical trials in Canada.

⁸⁰ For example, the median fee charged by a radiologist, under U.S. Medicare, to do an MRI scan of the lumbar spine is \$242.67; compared to the OHIP fee for the same procedure of \$96.35